



**LUCAS DE AZEVEDO SANTOS**

**DESCRIÇÃO ELETRÔNICA DAS LIGAÇÕES DE  
HALOGÊNIO: UMA JORNADA EM BUSCA DE NOVOS  
POTENCIAIS EMPÍRICOS**

**LAVRAS – MG**

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Dissertação apresentada à Universidade Federal de Lavras como parte das exigências do Programa de Pós-Graduação em Agroquímica, área de concentração em Química/Bioquímica, para obtenção do título de Mestre.

Prof. Dr. Teodorico de Castro Ramalho

Orientador

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***ELECTRONIC DESCRIPTION OF HALOGEN BONDS: A JOURNEY  
TOWARDS NEW EMPIRICAL POTENTIALS***

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## RESUMO GERAL

Os efeitos eletrônicos em sistemas supramoleculares são um grande desafio para a química computacional, e a compreensão de interações entre proteínas e seus ligantes dadas por Ligações de Halogênio pode ser limitada pelo ponto de vista da Mecânica Molecular. Este trabalho enfatiza o fato de que Ligações de Halogênio ocorrem graças às interações entre orbitais que envolvem o orbital  $\sigma^*_{C-X}$ . Todavia, foi mostrada a existência da relação direta entre o valor máximo da energia potencial eletrostática no  $\sigma$ -hole e a energia do LUMO do doador da Ligação de Halogênio. Essas evidências ressaltam a importância da descrição adequada da correlação eletrônica nas Ligações de Halogênio. De fato, a correlação eletrônica sempre foi um grande obstáculo para os campos de força tradicionais. Neste cenário, o presente trabalho introduz um novo potencial empírico baseado em parâmetros quânticos apto a descrever sistemas gerais guiados por Ligações de Halogênio. Este novo parâmetro permite que os campos de força percebam variações na estrutura molecular de compostos orgânicos halogenados a fim de aprimorar a descrição dos átomos flúor, cloro e bromo em Ligações de Halogênio.

**Palavras-chave:** Ligação de Halogênio, Campos de Força, Lennard-Jones, Potenciais Empíricos, Análise por Decomposição de Energia, DFT-D3.

## GENERAL ABSTRACT

The electronic effects in supramolecular systems are a great challenge for computational chemistry, and the understanding of ligand-protein interactions driven by Halogen Bonds can be limited by a Molecular Mechanics point of view. Our work enhances the statement that Halogen Bonds are led mainly by orbital interactions via  $\sigma^*_{C-X}$ . Nonetheless, we have pointed a straight relationship between the maximum ESP value on the  $\sigma$ -hole and the LUMO energy levels of the Halogen Bond donor. These evidences highlight the importance of electronic correlation description in Halogen Bonds. In fact, the electronic correlation has been a barrier for classical approaches. In line with this scenario, the current work introduces a new promising empirical potential based on quantum parameterizations able to describe general halogen bonded systems. The new parameters allow force fields to detect variations on the molecular electronic structure of halogenated organic compounds to improve the description of fluorine, chlorine and bromine in Halogen Bonds.

**Keywords:** Halogen Bond, Force Fields, Lennard-Jones, Empirical Potentials, Energy Decomposition Analysis, DFT-D3.

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## PRIMEIRA PARTE

### 1 INTRODUÇÃO

As interações não covalentes exercem um papel importante na química, sendo elas responsáveis por diversos fenômenos (BAUZÁ et al., 2011; KASHIWAGI et al., 2013; MORISAKI et al., 2011; RAMALHO; SANTOS; DA CUNHA, 2013). Um exemplo clássico é a ligação de hidrogênio. Podendo ser observada em diversos ambientes biológicos, é uma das mais fortes interações não ligantes já observadas (DEMIRCIOĞLU; KAŞTAŞ; BÜYÜKGÜNGÖR, 2015; KANAGATHARA et al., 2015). Além da forte atração eletrostática, uma vez que um átomo de hidrogênio esteja ligado a um átomo de alta eletronegatividade, o orbital antiligante correspondente a essa ligação pode se sobrepor a um orbital ligante ou não-ligante de alta energia oriundo de outra espécie (SHERIN PERCY PREMA LEELA et al., 2015; SILLA et al., 2013, 2014).

Por outro lado, interações mais fracas também possuem sua relevância. Relações de energia entre proteína-ligante, a estrutura empacotada do DNA e também o rendimento de células orgânicas fotovoltaicas são situações oriundas de interações fracas (HOPPE; SARICIFTCI, 2004; HUNTER, 1993, 1994; KARTHIKEYAN; NAGASE, 2012; PRAMANIK et al., 2015). Ademais, conformações tri dimensionais de proteínas podem ser influenciadas por interações hidrofóbicas, apesar do solvente exercer um papel importante no enovelamento dessas macromoléculas (BEN-NAIM, 2012; RAMALHO; SANTOS; DA CUNHA, 2013). Nesse contexto, as ligações de halogênio vêm demonstrando sua relevância diante da bioquímica e da química medicinal (LU et al., 2009; METRANGOLO et al., 2005; WU et al., 2013). O reconhecimento molecular de inibidores, propriedade espectroscópicas e conformações no estado sólido podem ser determinadas por essas interações (AUFFINGER et al., 2004; CARTER et al., 2013; POZNAŃSKI; SHUGAR, 2013; RENDINE et al., 2011; WILCKEN et al., 2013).

Sendo uma importante ferramenta no desenvolvimento de fármacos, essa interação, embora fraca, é frequentemente negligenciada e estudada teoricamente em sistemas pequenos. Em sistemas grandes que exigem grande esforço computacional, estas interações são avaliadas por meio de metodologias mais simples, como a Mecânica Molecular (LOERBROKS; HEIMERMANN; THIEL, 2015; PEARLMAN et al., 1995; RAPPÉ et al., 1992; VANOMMESLAEGHE; YANG; MACKERELL, 2015). Os campos de força modelam as

interações de van der Waals através de potenciais empíricos. O modelo mais comum é o de Lennard-Jones 12-6 (LENNARD-JONES, 1931). Sem parâmetros quânticos, modelar interações que envolvem alta correlação eletrônica é claramente uma barreira para os campos de força, levando ao surgimento de novas equações que melhor definem estes fenômenos (KOLÁŘ; HOBZA, 2012). Estudos recentes mostram que estes potenciais podem ser aprimorados através de pequenas modificações a fim atender uma interação específica (SANTOS et al., 2014). Tratando especificamente das ligações de halogênio, existem alguns potenciais propostos que buscam aprimorar sua descrição (DU et al., 2013; SCHOLFIELD et al., 2015). Contudo, eles se baseiam no modelo  $\sigma$ -hole que pode ser duvidoso.

Nesse sentido, o objetivo deste trabalho é buscar correções específicas para as ligações de halogênio a serem aplicadas nos campos de força. É essencial, contudo, que estas correções estejam fundamentadas em conceitos teóricos adequados. Portanto, o auxílio de métodos quânticos é crucial para a construção de parâmetros que aproximem a real natureza das ligações de halogênio aos métodos clássicos.

## **2 REFERENCIAL TEÓRICO**

### **2.1 Química Computacional**

Química é a ciência que foca seus estudos para as transformações e propriedades das moléculas. A química teórica é uma de suas subáreas, a qual é fundamentada nos formalismos matemáticos combinados com os princípios da física clássica e moderna (CRAMER, 2004; JENSEN, 2006).

Moléculas podem ser descritas como entidades formadas por um conjunto de partículas carregadas, cujas cargas positivas são encontradas nos núcleos e as cargas negativas são oriundas da presença de elétrons. Dessa forma, a força Coulômbica exerce uma função fundamental na interação entre essas partículas. A existência de moléculas diferentes consiste basicamente na combinação diversa de núcleos e elétrons por diferentes regiões no espaço. A modelagem molecular pode ser entendida como a descrição matemática de um sistema físico composto por essas partículas (núcleos e elétrons). No entanto, apenas sistemas hidrogenóides, formados por um elétron, possuem solução analítica exata. Dessa forma, soluções numéricas foram empregadas para solucionar sistemas de muitos-corpos através de operações matemáticas complexas. Antes da década de 50, o número de sistemas que se podia obter uma resolução aceitável era limitado. Com o advento dos computadores e a evolução tecnológica, a química

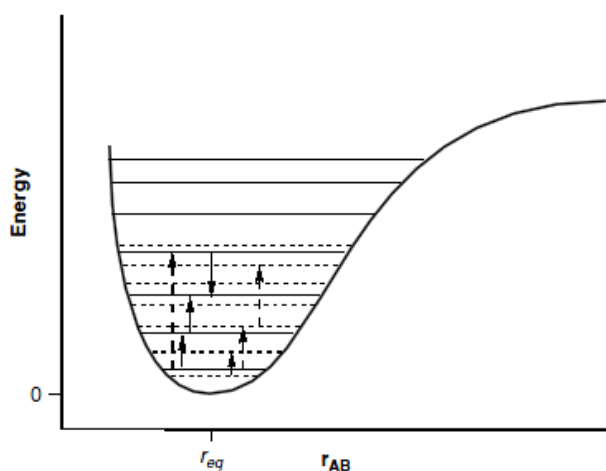
teórica deu um grande salto em prol da contribuição em diversas áreas da ciência, inaugurando um novo ramo na química: a química computacional (CRAMER, 2004; JENSEN, 2006).

Portanto, a química computacional se concentra na solução de problemas químicos, tão como no desenvolvimento de novos conceitos fundamentais desta ciência. O relacionamento entra a química teórica e a química computacional é de fato estreito. O progresso no desenvolvimento de novos modelos teóricos implica na compreensão de novos sistemas que auxiliam na fundamentação da teoria em química. O grande obstáculo na química computacional é a seleção do modelo e nível teórico para a resolução de um dado problema, o que irá afetar diretamente na consistência dos dados obtidos (COHEN; MORI-SÁNCHEZ; YANG, 2012; CRAMER, 2004; JENSEN, 2006; LEVINE, 2001).

## **2.2 Mecânica Molecular**

Através de métodos computacionais, é possível gerar uma Superfície de Energia Potencial (PES) através da variação da energia de uma molécula em estados pontuais. O estudo do espectro vibracional de uma molécula diatômica, por exemplo, pode ser representado por uma PES bidimensional, ou Curva de Energia Potencial (PEC) (Figura, 1). A variação no espectro vibracional ocorre graças a transições quantizadas a nível vibracional de baixa energia que provocam o estiramento da ligação química (CRAMER, 2004).

Figura 1 - Os primeiros sete níveis de energia vibracional de uma molécula diatômica AB. As transições permitidas são indicadas por setas, e as não permitidas estão indicadas por setas tracejadas.



Fonte (CRAMER, 2004)

A diferença nos níveis vibracionais depende da energia potencial associada às respectivas transições eletrônicas. A Figura 1 descreve a aproximação entre os átomos A e B, e a formação da ligação química no ponto  $r_e$  (distância de equilíbrio) correspondente ao mínimo de energia da PEC. Este exemplo é simples, mas para uma estrutura de muitos corpos a energia potencial assume outras variâncias além do estiramento da ligação (JENSEN, 2006). Assim, o estudo computacional através da mecânica molecular, consiste no cálculo da energia potencial obtida de um somatório de termos clássicos denominado Campo de Força (FF):

$$E_{FF} = E_{str} + E_{bend} + E_{tors} + E_{cross} + E_{el} + E_{vdw} \quad (1.1)$$

Pensando em uma molécula tri atômica A-B-C,  $E_{str}$  representa energia de estiramento da ligação química A-B e B-C.  $E_{bend}$  é a energia associada à deformação angular da ligação A-B-C.  $E_{tors}$  é a energia de torção associada à rotação da ligação A-B ou B-C.  $E_{cross}$  é o termo de acoplamento entre as três primeiras energias. Por fim,  $E_{el}$  e  $E_{vdw}$  são os termos que computam a energia das interações não-ligantes. Neste caso, seria a energia envolvida na interação dos átomos não ligados A e C (JENSEN, 2006).



### 2.2.1 Energia de Estiramento (Stretch Energy)

Em uma molécula diatômica AB,  $E_{str}$  é a função de energia que representa uma deformação axial ou o estiramento da ligação A-B. Ela pode ser escrita pela série de Taylor em torno da distância de equilíbrio  $r_{eq}$  (CRAMER, 2004; JENSEN, 2006). Obtendo a expansão de Taylor até a segunda ordem, tem-se que:

$$E_{str}(r^{AB}-r_{eq}^{AB}) = E(0) + \frac{dE}{dr}(r^{AB} - r_{eq}^{AB}) + \frac{1}{2} \frac{d^2E}{dr^2}(r^{AB} - r_{eq}^{AB})^2 \quad (1.2)$$

Por convenção,  $E(0)$  é o ponto zero na escala de energia. Como as derivadas são obtidas em  $r = r_{eq}$ , o segundo termo também é zero, já que  $dE/dr$  é o mínimo da função E.

$$E_{str}(r^{AB}-r_{eq}^{AB}) = \frac{1}{2} \frac{d^2E}{dr^2}(r^{AB} - r_{eq}^{AB})^2 = \frac{1}{2} k^{AB} (\Delta r^{AB})^2 \quad (1.3)$$

A equação final da energia de estiramento assume a forma de um oscilador harmônico (1.3). No entanto, esta aproximação demonstrou diferenças significativas para sistemas grandes quando comparada aos valores experimentais (JENSEN, 2006). Uma forma de melhorá-la foi incluir mais termos na expansão de Taylor:

$$E_{str}(r^{AB}-r_{eq}^{AB}) = \frac{1}{2} k_2^{AB} (\Delta r^{AB})^2 + \frac{1}{2} k_3^{AB} (\Delta r^{AB})^3 + \frac{1}{2} k_4^{AB} (\Delta r^{AB})^4 + \dots \quad (1.4)$$

Entretanto, expansões polinomiais não assumem um comportamento desejado para este fenômeno físico. Constantes  $k$  de ordem ímpar possuem sinal negativo, e as energias tenderão a  $-\infty$  em distâncias grandes se a expansão terminar nessa ordem. Em contrapartida, se truncada na quarta ordem,  $k_4$  é positivo, e as energias tenderão a  $+\infty$  nas mesmas circunstâncias. Outra aproximação foi utilizar o potencial de Morse (MORSE, 1929), que converge através da energia de dissociação:

$$E_{Morse}(\Delta r) = D[1 - e^{\alpha \Delta r}]^2 \quad (1.5)$$

Em (1.5),  $D$  é a energia de dissociação e  $\alpha$  é sua constante de força ( $\alpha = \sqrt{k/2D}$ ). A função de Morse se adequa satisfatoriamente à situação proposta, porém sua convergência é

lenta. Assim, uma estratégia muito utilizada é derivar o potencial de Morse através das respectivas derivadas de ordem  $n$  nas expansões polinomiais. A expressão para uma expansão de quarta ordem é dada por (1.6). Quando comparada com os dados quânticos, a PEC obtida pela equação (1.6) é quase indistinguível em pontos de mais baixa energia (JENSEN, 2006).

$$E_{\text{str}}(\Delta r^{\text{AB}}) = k^{\text{AB}}(\Delta r^{\text{AB}})^2 \left[ 1 - \alpha(\Delta r^{\text{AB}}) + \frac{7}{12}\alpha^2(\Delta r^{\text{AB}})^2 \right] \quad (1.6)$$

Os valores de  $r_{\text{eq}}$ ,  $k^{\text{AB}}$ ,  $\alpha$  e  $D$  são parâmetros determinados experimentalmente para um par de átomos ligados. Em um sistema poliatômico ou molecular, essas constantes assumem valores obviamente distintos e, por isso, a aproximação do oscilador harmônico demonstra ser suficiente para descrever este fenômeno (JENSEN, 2006).

### 2.2.2 Energia de Deformação Angular (Bending Energy)

$E_{\text{bend}}$  é a energia necessária para alterar o ângulo  $\theta$  de uma ligação química envolvendo três átomos A-B-C. Considera-se que A e B estão ligados entre si, assim como os átomos B e C. Dessa forma, B é o átomo central, e A e C não se ligam (JENSEN, 2006).

Assim como a energia de estiramento,  $E_{\text{bend}}$  pode ser obtida através da expansão polinomial de Taylor:

$$E_{\text{bend}}(\theta^{\text{ABC}} - \theta_{\text{eq}}^{\text{ABC}}) = \frac{1}{2}k^{\text{ABC}}(\theta^{\text{ABC}} - \theta_{\text{eq}}^{\text{ABC}})^2 \quad (1.7)$$

O terceiro termo da série também pode ser considerado e, em alguns casos, ele se faz necessário. Para moléculas em que o átomo central é di ou trivalente,  $\theta = \pi$  é um máximo da função, a  $dE/d\theta$  deveria ser zero e  $d^2E/d\theta^2$  deveria ser negativa. A presença do terceiro termo da série ajusta o polinômio nessas circunstâncias (JENSEN, 2006).

### 2.2.3 Energia de Torção (Torsional Energy)

$E_{\text{tors}}$  é a energia associada à variação do ângulo diedro  $\omega$ , formado por uma sequência de quatro átomos ligados A-B-C-D, através da rotação da ligação B-C. Neste caso, a expansão

de Taylor não é capaz de descrever esse efeito, e a  $E_{tors}$  é descrita pela série de Fourier (CRAMER, 2004; JENSEN, 2006).

$$E_{tors}(\omega) = \sum_{n=1} V_n \cos(n\omega) \quad (1.8)$$

Os valores possíveis de  $\omega$  estão compreendidos no intervalo  $[0^\circ, 360^\circ]$ , e  $n$  é o número de rotações.  $V_n$  é a constante que determina a barreira de rotação em torno da ligação B-C (CRAMER, 2004; JENSEN, 2006).

### 2.2.4 Energia Eletrostática

$E_{el}$  é utilizada para descrever a interação não-ligante entre átomos devido a sua carga. Uma forma muito conveniente para descrever a energia eletrostática é através do potencial do Coulomb em função das cargas  $Q$  e das distâncias  $r$  entre os corpos (CRAMER, 2004).

$$E_{el} = \frac{Q^A Q^B}{\epsilon r^{AB}} \quad (1.9)$$

Alguns campos de força acrescentam um termo para descrever interações dipolares em função do momento dipolar  $\mu$  juntamente com (1.9) em  $E_{el}$  (JENSEN, 2006).

$$E_{el}(R^{AB}) = \frac{\mu^A \mu^B}{\epsilon (r^{AB})^3} (\cos \chi - 3 \cos \alpha_A \cos \alpha_B) \quad (1.10)$$

$\chi$ ,  $\alpha_A$  e  $\alpha_B$  são ângulos formados pelos vetores  $\mu$ .

### 2.2.5 Energia de van der Waals

A energia de van der Waals,  $E_{vdw}$ , é utilizada para descrever a repulsão ou atração entre átomos não ligados. Em conjunto com a  $E_{el}$ , ela interpreta as energias das interações não-ligantes. Entretanto,  $E_{vdw}$  envolve interações através de efeitos eletrônicos não-clássicos, não relacionadas com carga, como as interações de orbitais. Contudo, efeitos de dispersão são o maior alvo de interpretação por esses potenciais (JENSEN, 2006).

Diversos potenciais são utilizados para descrever essa modalidade de interação. Além do potencial de Morse (MORSE, 1929), o potencial de Lennard-Jones (LJ) (LENNARD-JONES, 1931) é muito conveniente.

$$E_{LJ}(r) = \varepsilon \left[ \left( \frac{r_{eq}}{r} \right)^{12} - 2 \left( \frac{r_{eq}}{r} \right)^6 \right] \quad (1.11)$$

Em (1.11),  $r_{eq}$  é a distância de equilíbrio e  $\varepsilon$  é o poço da energia potencial. Esta equação é conhecida como LJ 12-6. A parte exponencial 12 descreve a energia de repulsão, enquanto a parte exponencial 6 descreve a atração. Algumas vezes, o mesmo potencial aparece com o expoente 9 ou 10 no termo repulsivo. Existe a forma "Exponencial - 6" (1.12) para o potencial de Lennard-Jones que descreve melhor as energias à longa distância. No entanto, a energia tende a  $-\infty$  quando  $r$  se aproxima de zero (JENSEN, 2006).

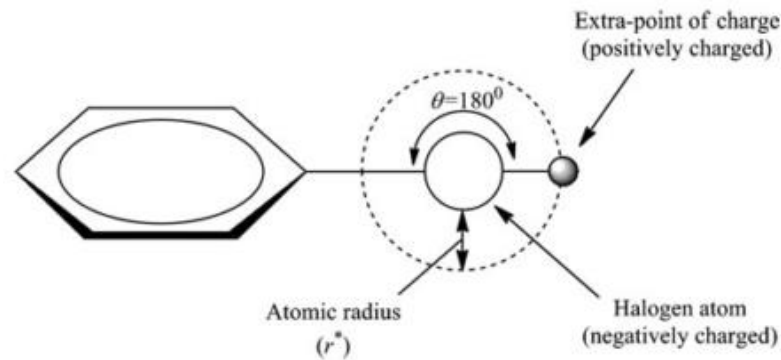
$$E_{vdw}(r) = \varepsilon \left[ \frac{\alpha}{\alpha - 6} e^{\alpha(1-r/r_{eq})} - \frac{\alpha}{\alpha - 6} \left( \frac{r_{eq}}{r} \right)^6 \right] \quad (1.12)$$

Ligações de hidrogênio recebem uma atenção especial, e o potencial de Lennard-Jones se modifica para (1.13).

$$E_{H-bond}(r) = \varepsilon \left[ 5 \left( \frac{r_{eq}}{r} \right)^{12} - 6 \left( \frac{r_{eq}}{r} \right)^{10} \right] \quad (1.13)$$

Para as ligações de Halogênio, existe uma aproximação que recentemente tem sido reportada na literatura chamada de PEP (positive extra point) ou ESH (explicit sigma hole). Ela consiste em representar um ponto de carga no eixo da ligação sigma composta pelo halogênio (Figura 2), simulando a carga do  $\sigma$ -hole (IBRAHIM, 2012b; KOLÁŘ; HOBZA, 2012).

Figura 2 - Representação esquemática do  $\sigma$ -hole na perspectiva da Mecânica Molecular.



Fonte (IBRAHIM, 2012b)

Scholfield et al. determinaram um potencial empírico baseado na aproximação ESH (1.14) (SCHOLFIELD et al., 2015). Ele não considera exatamente a existência de um ponto de carga extra, porém ajusta o raio de van der Waals em função da anisotropia da densidade de carga no halogênio. O termo de ajuste,  $\Delta r_x \cos(\nu\alpha)$ , é usado na parte que descreve a energia de repulsão, diminuindo o raio de van der Waals em função de um ângulo  $\alpha$ . O resultado desta modificação é dar um caráter elíptico ao volume de van der Waals do halogênio, permitindo maior aproximação interatômica e menor repulsão quando houver interação no mesmo sentido do eixo da ligação R-X. Esta equação é bem parametrizada para bases nitrogenadas.

$$E_{LJ}(r) = \sqrt{\epsilon_X \epsilon_A} \left[ \left( \frac{r_{vdw(A)} + \langle r_{vdw(X)} \rangle - \Delta r_x \cos(\nu\alpha)}{r} \right)^{12} - 2 \left( \frac{r_{vdw(A)} + \langle r_{vdw(X)} \rangle}{r} \right)^6 \right] \quad (1.14)$$

## 2.2.6 Universal Force Field (UFF)

O UFF é um campo de força desenvolvido por Rappé e colaboradores em 1992 (RAPPÉ et al., 1992). Ele foi projetado para ser um campo de força universal, parametrizado em toda a tabela periódica, com erros menores que 0,1 Å nas distâncias de ligação e de 5° a 10° nas distorções angulares.

O Universal Force Field adota a forma geral de um campo de força (1.1). Para o estiramento de ligação, é encontrado nele o potencial de Morse (1.5) e a expansão de Taylor (1.3), além de correções para a eletronegatividade. Assim como a torção angular, a distorção angular também é descrita pela série de Fourier (1.8). Nos termos não ligantes, a energia eletrostática é descrita pelo potencial de Coulomb (1.9) e a energia de van der Waals é descrita tanto pela LJ 12-6 (1.11) quanto pela forma Exp.-6 (1.12) (RAPPÉ et al., 1992).

### 2.3 Métodos de Estrutura Eletrônica

A modelagem molecular, no prisma da mecânica de Newton, entende os corpos microscópicos por meio de análogos macroscópicos. Entretanto, sabe-se que ambos se comportam de maneiras distintas, sendo a mecânica clássica apenas um caso restrito da mecânica quântica relativística (CRAMER, 2004).

Na tentativa de compreender os dados incomuns do experimento da radiação do corpo negro, em 1900, Max Planck sugeriu a quantização da energia contrapondo à interpretação clássica, a qual a energia era contínua (CRAMER, 2004; JENSEN, 2006). Os novos conceitos de Planck foram fundamentais para o entendimento de outros fenômenos, como o efeito fotoelétrico, além do aprimoramento de novos modelos teóricos (CRAMER, 2004; JENSEN, 2006).

Outro conceito fundamental na compreensão de sistemas microscópicos foi o da dualidade onda-partícula proposto por de Broglie. Segundo ele, todos os corpos teriam um caráter de onda e partícula ao mesmo tempo, sendo que um deles prevaleceria sobre o outro dependendo do número de onda e de sua massa. Nesse ínterim, Schrödinger desenvolveu a mecânica quântica capaz de descrever micropartículas. A equação postulada por Schrödinger (2.1) entende as partículas leves através de seu comportamento ondulatório. Essa onda, assim como na mecânica clássica, carrega todas as propriedades da partícula leve em questão. Aplicando um operador específico, é possível extrair a energia da partícula através de sua função de onda (CRAMER, 2004; JENSEN, 2006; LEVINE, 2001).

$$\hat{H}\Psi = E\Psi \quad (2.1)$$

Em (2.1),  $\Psi$  é a função de onda da partícula e  $E$  a energia.  $\hat{H}$  é um operador hermitiano conhecido como Hamiltoniano. Através dele, é possível obter a energia total de uma partícula desde que  $\Psi$  seja conhecida. No intuito de extrair a energia total de um átomo, por exemplo, o operador Hamiltoniano pode ser descrito pela equação (2.2) (JENSEN, 2006).

$$\hat{H} = T_e + T_n + V_{ne} + V_{ee} + V_{nn} \quad (2.2)$$

A equação (2.2) é na realidade um somatório de operadores que extraem a energia cinética  $T$  e a potencial  $V$ . Os termos com índice  $n$  se referem ao núcleo, enquanto os índices  $e$  se remetem ao elétron.

$$\hat{H} = - \sum_i \frac{\hbar}{2m_e} \nabla_i^2 - \sum_k \frac{\hbar}{2m_k} \nabla_k^2 - \sum_i \sum_k \frac{e^2 Z_k}{r_{ik}} + \sum_{i<j} \frac{e^2}{r_{ij}} + \sum_{k<l} \frac{e^2 Z_k Z_l}{r_{kl}} \quad (2.3)$$

A equação (2.3) mostra os termos estendidos do operador Hamiltoniano na respectiva ordem de (2.2). Os índices  $i$  e  $j$  se referem ao elétron, enquanto  $k$  e  $l$  se remetem ao núcleo.

Sendo  $\Psi$  pertencente ao conjunto dos números imaginários, é permitido multiplicar (2.1) por  $\Psi^*$ , sendo ela a função antissimétrica de  $\Psi$ . Aplicando a integral no espaço  $dr$  tem-se:

$$\int \Psi_j \hat{H} \Psi_i^* dr = \int \Psi_j E \Psi_i^* dr \quad (2.4)$$

Se  $E$  é uma grandeza escalar, ela é retirada da integral e (2.4) resulta em (2.5):

$$\frac{\int \Psi_j \hat{H} \Psi_i^* dr}{\int \Psi_j \Psi_i^* dr} = E, \quad \int \Psi_j \Psi_i^* dr = \delta_{ij} \quad (2.5)$$

$\delta_{ij}$  é igual a 1 se as funções  $\Psi$  e  $\Psi^*$  forem ortonormais ( $i = j$ ), e igual a 0 em caso contrário ( $i \neq j$ ). Enfim, a equação (2.5) assume um papel fundamental para determinar a energia atômica, desde que  $\Psi$  seja conhecida. Contudo, esta não é uma tarefa simples. Para descobrir  $\Psi$ , é preciso solucionar a equação (2.5). Até então, só se conhece a resolução exata para sistemas hidrogenóides contando com a aproximação de Born-Oppenheimer (CRAMER, 2004).

Em condições normais, as partículas do núcleo também manifestam algum grau de deslocamento, portanto possuem energia cinética. Por um problema de referencial, seria impossível determinar a energia potencial elétron-núcleo se  $r$  sempre for uma variável. De forma sucinta, a aproximação de Born-Oppenheimer considera fixa a posição do núcleo enquanto a localização eletrônica varia. Por consequência, a energia cinética nuclear é zero (CRAMER, 2004).

Lidando com sistemas multieletrônicos, é preciso considerar o spin como um efeito quântico. Elétrons são férmions, ou seja, partículas que possuem spin  $\pm 1/2$ . O princípio de Pauli diz que duas partículas não podem ter todos os quatro números quânticos iguais para que elas

sejam indistinguíveis. Dessa forma, a função de onda multieletrônica total ( $\Phi$ ) deve obedecer ao princípio da antissimetria, respeitando as diferentes coordenadas de cada elétron. Assim, a função de onda eletrônica descrita por  $\Psi$  é acompanhada por outra chama de spinorbital ( $\alpha$  ou  $\beta$ ). A forma matemática para descrever o princípio da antissimetria é através de Determinantes de Slater (SD). Para casos gerais, um sistema com  $N$  elétrons e  $N$  spinorbitais é dado por (JENSEN, 2006):

$$\Phi_{SD} = \frac{1}{\sqrt{N!}} \begin{vmatrix} \Psi_1(1) & \Psi_2(1) & \cdots & \Psi_N(1) \\ \Psi_1(2) & \Psi_2(2) & \cdots & \Psi_N(2) \\ \vdots & \vdots & \ddots & \vdots \\ \Psi_1(N) & \Psi_2(N) & \cdots & \Psi_N(N) \end{vmatrix}, \quad \langle \Psi_i | \Psi_j \rangle = \delta_{ij} \quad (2.6)$$

A teoria de Hartree-Fock escolhe uma única SD para descrever todo o sistema multieletrônico, aplicando a ela o operador de Fock (2.7). Na equação (2.7),  $h_i$  é o operador Hamiltoniano para um elétron e  $J_{ij}$  e  $K_{ij}$  são os operadores de Coulomb e troca, que juntamente descrevem a repulsão elétron-elétron ou correlação eletrônica.

Com estes operadores, um elétron se correlaciona com os outros através de um campo médio. Esse tipo de descrição não é tão refinada, o que dá margem a outros métodos introduzirem modificações para aprimorar a correlação eletrônica (JENSEN, 2006).

$$F_i = h_i + \sum_{ij}^N (J_{ij} - K_{ij}) \quad (2.7)$$

Uma ferramenta matemática extremamente útil para a teoria quântica é o princípio variacional. Assumindo que a função de onda molecular ( $\Phi$ ) seja a combinação linear de funções atômicas ( $\Psi$ ), e que estas funções estejam normalizadas, é possível escrever que:

$$\Phi = \sum_i c_i \Psi_i \quad (2.8)$$

$$\begin{aligned} \int \Phi^2 dr &= 1 = \int \sum_i c_i \Psi_i \sum_j c_j \Psi_j dr \\ &= \sum_{ij} c_i c_j \int \Psi_i \Psi_j dr \end{aligned}$$



$$\begin{aligned}
&= \sum_{ij} c_i c_j \delta_{ij} \\
&= \sum_i c_i^2
\end{aligned} \tag{2.9}$$

tal que  $c_i$  é o coeficiente de contribuição de cada  $\Psi$ , e ambos são desconhecidos (CRAMER, 2004).

Aplicando o operador Hamiltoniano e fazendo a integração para extrair a energia de  $\Phi$ , tem-se que:

$$\begin{aligned}
\int \Phi \hat{H} \Phi \, dr &= \int \left( \sum_i c_i \Psi_i \right) H \left( \sum_j c_j \Psi_j \right) \, dr \\
&= \sum_{ij} c_i c_j \int \Psi_i \hat{H} \Psi_j \, dr \\
&= \sum_{ij} c_i c_j E_i \delta_{ij} \\
&= \sum_i c_i^2 E_i
\end{aligned} \tag{2.10}$$

assumindo que  $\Psi_i$  e  $\Psi_j$  sejam ortonormais. Considerando que  $E_i$  seja um valor de energia qualquer, haverá sempre um mínimo de energia, o estado fundamental  $E_0$ . Considerando  $E_0$  um valor real, multiplicá-lo em (2.9) e subtrair o resultado de (2.10), tem-se que:

$$\int \Phi \hat{H} \Phi \, dr - E_0 \int \Phi^2 \, dr = \sum_i c_i^2 (E_i - E_0) \tag{2.11}$$

Sendo os coeficientes  $c_i$  números reais, o termo  $c_i^2$  deve ser maior ou igual a zero, então:

$$\begin{aligned}
\int \Phi \hat{H} \Phi \, dr - E_0 \int \Phi^2 \, dr &\geq 0 \\
\frac{\int \Phi \hat{H} \Phi \, dr}{\int \Phi^2 \, dr} &\geq E_0
\end{aligned} \tag{2.12}$$

Esta conclusão é extremamente importante. Se  $\Phi$  for normalizada, o denominador é igual a 1. Portanto, para qualquer Hamiltoniano, e para qualquer  $\Phi$ , o resultado da integral no numerador será sempre maior ou igual ao menor valor de energia possível. Ou seja, para um cálculo *ab initio* que obedeça a este princípio, quanto menor o valor de energia obtido, melhor (CRAMER, 2004).

### 2.3.1 Teoria da Perturbação de Møller-Plesset (Møller-Plesset Perturbation Theory)

A teoria da perturbação de Møller-Plesset (MPn) é uma aplicação prática da Teoria da Perturbação de Muitos Corpos (MBPT) de Rayleigh-Schödinger. Segundo esta última, o operador Hamiltoniano é dividido em duas partes (CRAMER, 2004):

$$\hat{H} = \hat{H}_0 + \lambda \hat{H}' \quad (3.1)$$

$\hat{H}_0$  é o operador de referência que irá encontrar os autovalores,  $\hat{H}'$  é o perturbador e  $\lambda$  determina o grau da perturbação. A equação perturbada de Schödinger independente do tempo é (JENSEN, 2006):

$$\hat{H}\Psi = W\Psi \quad (3.2)$$

Nessa nova abordagem, a função de onda  $\Psi$  e a energia  $W$  são descritas através da série de Taylor em função do grau de perturbação (JENSEN, 2006).

$$\begin{aligned} W &= \lambda^0 W_0 + \lambda^1 W_1 + \lambda^2 W_2 + \dots \\ \Psi &= \lambda^0 \Psi_0 + \lambda^1 \Psi_1 + \lambda^2 \Psi_2 + \dots \end{aligned} \quad (3.3)$$

Se  $\lambda = 0$ , então  $\hat{H} = H_0$ ,  $\Psi = \Psi_0$  e  $W = E_0$ . Estas seriam as características de um sistema não perturbado ou correção de ordem zero. Se  $\lambda = 1$  ou  $\lambda = 2$ , obtém-se as correções de primeira e segunda ordem respectivamente, de forma que

$$\begin{aligned} \lambda^0: \hat{H}_0 \Psi_0 &= W_0 \Psi_0 \\ \lambda^1: \hat{H}_0 \Psi_1 + \hat{H}' \Psi_0 &= W_0 \Psi_1 + W_1 \Psi_0 \\ \lambda^2: \hat{H}_0 \Psi_2 + \hat{H}' \Psi_1 &= W_0 \Psi_2 + W_1 \Psi_1 + W_2 \Psi_0 \end{aligned}$$

$$\lambda^n: \hat{H}_0 \Psi_n + \hat{H}' \Psi_{n-1} = \sum_{i=0}^n W_i \Psi_{n-i} \quad (3.4)$$

são as respectivas equações para as correções de zero-, primeira-, segunda, e n-ésima ordem (JENSEN, 2006). Mais além, a energia da n-ésima ordem pode ser obtida multiplicando a equação (3.4) por  $\Psi_0$  e integrando-a:

$$\begin{aligned} \langle \Psi_0 | \hat{H}_0 | \Psi_n \rangle + \langle \Psi_0 | \hat{H}' | \Psi_{n-1} \rangle &= \sum_{i=0}^{n-1} W_i \langle \Psi_0 | \Psi_{n-i} \rangle + W_n \langle \Psi_0 | \Psi_0 \rangle \\ E_0 \langle \Psi_0 | \Psi_n \rangle + \langle \Psi_0 | \hat{H}' | \Psi_{n-1} \rangle &= W_n \langle \Psi_0 | \Psi_0 \rangle \\ W_n &= \langle \Psi_0 | \hat{H}' | \Psi_{n-1} \rangle \end{aligned} \quad (3.5)$$

Na teoria da perturbação de Møller-Plesset (MPn), o operador Hamiltoniano não perturbado é descrito pela soma dos operadores de Fock. No entanto, esta soma conta a repulsão elétron-elétron ( $V_{ee}$ ) duas vezes, fazendo com que a perturbação seja descrita por (3.6) (JENSEN, 2006).

$$\begin{aligned} \hat{H}_0 &= \sum_{i=1}^N F_i = \sum_{i=1}^N \left( h_i + \sum_{j=1}^N (J_{ij} - K_{ij}) \right) = \sum_{i=1}^N h_i + 2 \langle V_{ee} \rangle \\ \hat{H}' &= \hat{H} - \hat{H}_0 = \sum_{j=1}^N (J_{ij} - K_{ij}) - \sum_{i=1}^N \sum_{j=1}^N (J_{ij} - K_{ij}) = V_{ee} - 2 \langle V_{ee} \rangle \end{aligned} \quad (3.6)$$

É notório que se a perturbação não existir (ordem zero), a energia de ordem zero será extraída apenas de  $\hat{H}_0$ , sendo ele o somatório dos operadores de Fock. Pela equação (3.5), nota-se que a energia da primeira ordem será justamente

$$W_1 = \langle \Psi_0 | \hat{H}' | \Psi_0 \rangle = \langle V_{ee} \rangle - 2 \langle V_{ee} \rangle = - \langle V_{ee} \rangle \quad (3.7)$$

e a energia total (soma de  $W_0$  e  $W_1$ ) será exatamente a energia de Hartree-Fock. Portanto, a verdadeira contribuição para o aprimoramento à estimativa da correlação eletrônica será iniciada a partir da correção de ordem dois. A nomenclatura MPn indica a ordem a ser

executada, tal que MP0 corresponde à ordem zero, e MP2 corresponde à ordem 2 (JENSEN, 2006).

O MP2 chega a computar 80~90% da energia de correlação, podendo chegar a até 98% da energia no MP4. Em geral, a teoria da perturbação converge melhor quando a perturbação é menor, por causa da utilização da série de Taylor. Uma característica dos métodos MPn é não obedecer ao princípio variacional, o que torna difícil a comparação entre os dados obtidos. Além disso, isso faz com que, muitas das vezes, o cálculo superestime o valor de energia, sendo ele, praticamente, a correlação eletrônica por causa do operador da perturbação. Ademais, por ser um método truncado, a utilização de funções de base finitas acarreta em um número finito de orbitais virtuais, podendo diminuir a precisão do método (CRAMER, 2004).

### 2.3.2 Teoria do Funcional de Densidade (Density Functional Theory)

A Teoria do Funcional de Densidade (DFT), proposta por Hohenberg e Kohn, consiste em determinar a energia eletrônica através da densidade eletrônica  $\rho$  e não mais diretamente de  $\Phi$ . Entretanto,  $\rho$  aparece sendo diretamente dependente de  $\Phi$ , agregando a aproximação quântica de Schrödinger ao DFT (4.1). A função de onda molecular é obtida por (2.8), e os coeficientes são calculados de modo que a energia provida de  $\rho$  seja a menor possível. Assim, a interpretação física de  $\Phi$  é diferente dos métodos Hartree-Fock (CHERMETTE; BERNARD, 1998; CRAMER, 2004; JENSEN, 2006; KOHN; BECKE; PARR, 1996; MORGON; CUSTODIO, 1995).

$$\rho(r) = \sum_{i=1}^N |\Phi_i(r)|^2 \quad (4.1)$$

Ao longo do tempo, surgiram inúmeras metodologias que abordaram  $\rho$  como fonte da energia molecular, e a DFT é oriunda delas. *A priori*, a tentativa de determinar a energia molecular utilizando a densidade eletrônica veio da teoria de Thomas-Fermi (TF) (4.2). Posteriormente, veio a contribuição de Dirac adicionando o termo de troca  $K_D[\rho]$ , e o modelo ficou conhecido como Thomas-Fermi-Dirac (TFD) (4.3) (JENSEN, 2006).

$$E_{TF}[\rho] = T_{TF}[\rho] + E_{ne}[\rho] + J[\rho] \quad (4.2)$$

$$E_{\text{TFD}}[\rho] = T_{\text{TF}}[\rho] + E_{\text{ne}}[\rho] + J[\rho] + K_{\text{D}}[\rho] \quad (4.3)$$

Nesses modelos,  $T_{\text{TF}}[\rho]$  é a energia cinética,  $E_{\text{ne}}[\rho]$  é a atração elétron-núcleo, e  $J[\rho]$  e  $K[\rho]$  são os termos de correlação e troca respectivamente:

$$\begin{aligned} T_{\text{TF}}[\rho] &= \frac{3}{10} (3\pi^2)^{2/3} \int \rho^{5/3}(\mathbf{r}) d\mathbf{r} \\ E_{\text{ne}}[\rho] &= \sum_a \int \frac{Z_a \rho(\mathbf{r})}{|\mathbf{r}_a - \mathbf{r}|} d\mathbf{r} \\ J[\rho] &= \frac{1}{2} \int \int \frac{\rho(\mathbf{r})\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r} d\mathbf{r}' \\ K_{\text{D}}[\rho] &= -\frac{3}{4} \left(\frac{3}{\pi}\right)^{1/3} \int \rho^{4/3}(\mathbf{r}) d\mathbf{r} \end{aligned} \quad (4.4)$$

Para deduzir a energia cinética e de troca, foi introduzido um sistema fictício chamado 'Jellium'. O Jellium é modelo composto por um número infinito de elétrons se movendo em um espaço infinito com cargas positivas distribuídas uniformemente. Este sistema ficou conhecido como o gás uniforme de elétrons, com densidade constante diferente de zero. Entretanto, esta abordagem contém margens de erros inaceitáveis no ponto de vista energético, além da incapacidade de prever ligações químicas. Vários aprimoramentos foram propostos desde então, permitindo até mesmo a existência de moléculas no ponto de vista do gás uniforme de elétrons. Não obstante, os resultados obtidos ainda não se comparavam aos outros métodos de estrutura eletrônica (CRAMER, 2004).

Nesse ínterim, Kohn e Sham (KS) introduziram os orbitais no formalismo de Thomas-Fermi. Seu principal problema era a representação muito pobre da energia cinética. Logo, o formalismo de KS introduz o funcional da energia cinética exata,  $T_{\text{S}}$ , calculada a partir dos orbitais  $\phi$  (JENSEN, 2006).

$$T_{\text{S}} = \sum_{i=1}^N \langle \phi_i | -\frac{1}{2} \nabla^2 | \phi_i \rangle \quad (4.5)$$

A teoria KS para o cálculo da energia cinética assume que os elétrons não interagem, similar à ideia de Hartree-Fock. Na realidade, os elétrons interagem, e, por isso, a equação (4.5)

prevê cerca de 99% da energia cinética real. A energia restante é interpretada pelo termo de troca e correlação  $E_{XC}$  (JENSEN, 2006). A equação geral da energia DFT é dada por:

$$E_{DFT}[\rho] = T_S[\rho] + E_{ne}[\rho] + J[\rho] + E_{XC}[\rho] \quad (4.6)$$

O último termo é separado em duas partes: pura troca  $E_x$  e a correlação  $E_c$ . Cada um desses termos são descritos em função das energias por partícula (densidade de energia),  $\epsilon_X$  e  $\epsilon_C$  (JENSEN, 2006).

$$E_{XC}[\rho] = E_X[\rho] + E_C[\rho] = \int \rho(r)\epsilon_X[\rho(r)]dr + \int \rho(r)\epsilon_C[\rho(r)]dr \quad (4.7)$$

Pensando em encontrar orbitais  $\phi$  que minimizem o valor de energia, é necessário que um problema de auto-valor seja solucionado (JENSEN, 2006).

$$h_{KS}\phi_i = \epsilon_i\phi_i \quad (4.8)$$

O operador Kohn-Sham (KS) monoelétrônico é definido por

$$h_i^{KS} = -\frac{1}{2}\nabla_i^2 - \sum_k^{\text{nuclei}} \frac{Z_k}{|r_i - r_k|} + \int \frac{\rho(r')}{|r_i - r'|} dr' + V_{XC} \quad (4.9)$$

e o potencial  $V_{XC}$  é obtido pela derivada da energia em relação à densidade eletrônica (JENSEN, 2006).

$$V_{XC}(r) = \frac{\partial E_{XC}[\rho]}{\partial \rho(r)} = \epsilon_{XC}[\rho(r)] + \rho(r) \frac{\partial \epsilon_{XC}(r)}{\partial \rho} \quad (4.10)$$

Se a energia encontrada em (4.6) for a energia exata, os orbitais encontrados em (4.7) proverão densidades muito próximas das reais. Contudo, se a  $E_{XC}[\rho]$  exata for conhecida, seria possível obter a energia total exata, contabilizando a correlação eletrônica, através do método DFT. Entretanto, solucionar essas equações é tão complicado quanto encontrar a solução analítica da equação de Schrödinger. Não obstante, é possível calcular a energia de troca e correlação através de funcionais específicos. A diferença entre os métodos DFT é exatamente

a escolha dos funcionais, e cada funcional é desenvolvido a fim de atender determinadas situações. De forma geral, o DFT é um método variacional. Portanto, é conveniente comparar sua eficiência de acordo com este princípio. Porém, há funcionais que incorporam parâmetros empíricos e, por esse fator, podem resultar em energias menores que a energia real. Ademais, é usual utilizar dados experimentais ou métodos de mecânica quântica de alto nível como meio de comparação para selecionar o funcional mais adequado (CRAMER, 2004; JENSEN, 2006; LEVINE, 2001)

### 2.3.3 Funcionais de correlação e troca

A busca por encontrar a energia de correlação e troca através da ideia dos funcionais DFT resultou em uma gama de tentativas que atendessem a necessidade de vários sistemas químicos. Na *Local Density Approximation* (LDA), foi adotada a abordagem do gás uniforme de elétrons e a energia de troca é obtida da mesma forma proposta por Dirac (eq. 4.4). Esta aproximação é usual para sistemas que variam pouco sua densidade. No entanto, alguns sistemas possuem as densidades de spin  $\alpha$  e  $\beta$  diferentes. Isso culminou em uma aproximação mais adequada, a *Local Spin Density Approximation* (LSDA), que adiciona a dependência das diferentes densidades em relação ao spin. Caso as densidades em  $\alpha$  e  $\beta$  forem iguais, a LSDA se torna exatamente igual à LDA (CRAMER, 2004; JENSEN, 2006).

$$E_X^{\text{LSDA}}[\rho] = -2^{1/3} \frac{3}{4} \left(\frac{3}{\pi}\right)^{1/3} \int [\rho_\alpha^{4/3} + \rho_\beta^{4/3}] dr$$

$$\epsilon_X^{\text{LSDA}}[\rho] = -2^{1/3} \frac{3}{4} \left(\frac{3}{\pi}\right)^{1/3} [\rho_\alpha^{1/3} + \rho_\beta^{1/3}] \quad (4.10)$$

A consideração do gás uniforme ainda era um problema, pois apenas a expansão de Taylor não conduzia a resultados convincentes. Então, alguns aprimoramentos nesse sentido fizeram com que a energia de correlação e troca não dependesse apenas da densidade eletrônica, mas também de seu gradiente. Isso permitia a variação da densidade eletrônica através de suas derivadas. Tais métodos são conhecidos como *Generalized Gradient Approximation* (GGA) (JENSEN, 2006).

O funcional de Perdew e Wang (PW86) (PERDEW; BURKE; WANG, 1996) adiciona modificações na densidade de energia LSDA utilizando o conceito GGA. Em (4.11), a, b e c são constantes. Expressões para  $\alpha$  e  $\beta$  são implicitamente contabilizadas.

$$\begin{aligned}\varepsilon_X^{\text{PW86}} &= \varepsilon_X^{\text{LDA}}(1 + ax^2 + bx^4 + cx^6)^{1/15} \\ x &= \frac{|\nabla\rho|}{\rho^{4/3}}\end{aligned}\quad (4.11)$$

Becke (BECKE, 1988), assim como Lee, Yang e Parr (LEE; YANG; PARR, 1988) propuseram funcionais famosos conhecidos como B88 e LYP respectivamente. O funcional LYP é relacionado à energia de correlação. Ambos possuem constantes parametrizadas experimentalmente (JENSEN, 2006).

$$\begin{aligned}\varepsilon_X^{\text{B88}} &= \varepsilon_X^{\text{LDA}} + \Delta\varepsilon_X^{\text{B88}} \\ \Delta\varepsilon_X^{\text{B88}} &= -\beta\rho^{1/3} \frac{x^2}{1 + 6\beta x \sin h^{-1} x}\end{aligned}\quad (4.12)$$

$$\begin{aligned}\varepsilon_C^{\text{LYP}} &= -a \frac{\gamma}{(1 + d\rho^{-1/3})} \\ &\quad - ab \frac{\gamma e^{-c\rho^{-1/3}}}{9(1 + d\rho^{-1/3})\rho^{8/3}} \left[ 18(2^{2/3})C_F(\rho_\alpha^{8/3} + \rho_\beta^{8/3}) - 18\rho t_W \right. \\ &\quad + \rho_\alpha(2t_W^\alpha + \nabla^2\rho_\alpha) \\ &\quad + \rho_\beta(2t_W^\beta \\ &\quad \left. + \nabla^2\rho_\beta) \right]\end{aligned}\quad (4.13)$$

Há funcionais que vão ainda mais além e não dependem apenas do gradiente da densidade eletrônica. É acrescentada, então, a dependência da densidade de energia cinética  $\tau$  no potencial de troca e correlação, e  $\phi$  são os orbitais KS. Tais funcionais são conhecidos como meta-GGA e, comparado aos funcionais GGA, são geralmente mais precisos (CRAMER, 2004).

$$\tau(r) = \sum_1^{\text{occupied}} \frac{1}{2} |\nabla\phi_i(r)|^2 \quad (4.14)$$

Contudo, levando em conta a possibilidade de os elétrons não interagirem, o funcional de correlação e troca seria reduzido ao potencial de troca apenas. Dessa forma, ele poderia ser



estipulado através da teoria de Hartree-Fock. Se os orbitais KS forem idênticos aos orbitais HF, a troca exata seria estimada de forma semelhante ao método HF. Ademais, pode-se atribuir ao potencial de correlação e troca total a contribuição de outros funcionais. Esse modelo de cálculo é conhecido como métodos híbridos. Um exemplo de funcional híbrido é o B3LYP, que conta com a contribuição dos funcionais de Becke, LYP, da troca exata de HF, entre outros (JENSEN, 2006).

$$E_{XC}^{B3LYP} = (1 - a)E_X^{LSDA} + aE_X^{HF} + b\Delta E_X^B + (1 - c)E_C^{LSDA} + cE_C^{LYP} \quad (4.15)$$

As constantes  $a$ ,  $b$  e  $c$  são parâmetros otimizados de acordo com dados experimentais (JENSEN, 2006). Funcionais híbridos mais modernos contam com a aproximação meta-GGA e são conhecidos como meta-híbridos. O pacote de Funcionais de Minnesota (M05, M06,...) é um exemplo recente (ZHAO; TRUHLAR, 2007).

### 2.3.4 Correções de dispersão (DFT-D)

Apesar da grande complexidade que teoria DFT agregou, ainda restou um problema: a dificuldade de descrever interações eletrônicas de longo alcance, responsáveis pelas forças de dispersão de van der Waals. Este problema se torna mais grave para os funcionais que utilizam a troca exata de HF, onde se exclui a correlação eletrônica. Pela grande importância dos efeitos dispersivos na interação das moléculas, principalmente em sistemas biológicos, Grimme criou correções empíricas capazes de balancear tais efeitos, incorporando tais funções em funcionais conhecidos, além de propor o funcional B97-D. Esta metodologia é conhecida como DFT-D (GRIMME, 2006).

$$E_{DFT-D} = E_{KS-DFT} + E_{disp}$$

$$E_{disp} = -s_6 \sum_{i=1}^{N_{at}-1} \sum_{j=i+1}^{N_{at}} \frac{C_6^{ij}}{R_{ij}^6} f_{dmp} \quad (4.16)$$

Em (4.16),  $N_{at}$  representa o número de átomos,  $s_6$  é um fator de escala global dependente do funcional utilizado,  $C_6$  denota o coeficiente de dispersão e  $R_{ij}$  são as distâncias interatômicas. Contudo, a correção para as energias de dispersão conta com um termo chave,  $f_{dmp}$ .

$$f_{\text{dmp}} = \frac{1}{1 + e^{-d(R_{ij}/R_r - 1)}} \quad (4.17)$$

A equação (4.17) mostra a Damping Function usada por Grimme. Percebe-se que  $E_{\text{disp}}$  tende a infinito se  $R \rightarrow 0$  (4.16). Essas funções são essenciais para corrigir algumas singularidades a curtas distâncias e evitar dupla-contagem da correlação eletrônica em distâncias intermediárias.

A princípio, o DFT-D ainda contava com muitas parametrizações empíricas, e apenas poucos elementos eram considerados (H, C-Ne). Não obstante, os resultados eram promissores e as energias obtidas eram muito inferiores aos métodos não dispersivos (GRIMME, 2006). Conseqüentemente, Grimme publicou novos trabalhos que diminuiriam o grau empírico das parametrizações, otimizando constantes de modo *ab initio*. Além disso, as correções foram expandidas para vários elementos da tabela periódica, incluindo metais. O funcional B97-D evoluiu para o então B97-D3, e as novas correções também podem ser aplicadas a outros funcionais (GRIMME et al., 2010). Posteriormente, foram incorporadas ao DFT-D3 as Damping Functions de Becke-Johnson (4.18), a fim de aprimorar a descrição das interações de curto alcance (BECKE; JOHNSON, 2005; GRIMME; EHRLICH; GOERIGK, 2011; JOHNSON; BECKE, 2005, 2006).

$$f_{\text{dmp}} = \frac{\kappa C_{6,ij}}{E_{c,ij}} \quad (4.18)$$

Em (4.18),  $E_c$  é a soma das energias de correlação dos átomos livres e  $\kappa$  é uma constante universal na ordem de 1000. Ao utilizar (4.18), a equação (4.16) irá manter a forma  $C_6/R^6$  para interações de longo alcance, mas irá tender à  $E_c/\kappa$  se  $R \rightarrow 0$ .

### 2.3.5 Funções de base

A tarefa de solucionar a equação de Schrödinger exige a consideração de diferentes aproximações. Uma delas é a introdução do conceito de funções de base. Função de base é um conjunto de funções matemáticas com as quais a função de onda é construída. Isso implica que um número infinito de funções pode ser empregado, o que é imensurável para os cálculos atuais. Na teoria HF, os orbitais moleculares (OM) são representados como uma combinação linear de funções de base (eq. 2.8). Quanto maior o número de funções utilizadas, melhor será a

representação dos OM. Dessa forma, a escolha das funções de base influenciará diretamente na precisão dos cálculos quânticos (CRAMER, 2004; JENSEN, 2006).

A única função de onda analiticamente ou numericamente conhecida, a hidrogenóides, é computacionalmente inviável. Isto exigia uma nova aproximação que abordaria outros tipos de funções para substituí-la. As funções mais comumente encarregadas dessa tarefa são as gaussianas ou Gaussian Type Orbitals (GTO) (JENSEN, 2006).

$$\chi_{\zeta,n,l,m}(r, \theta, \varphi) = N Y_{l,m}(\theta, \varphi) r^{(2n-2-l)} e^{-\zeta r^2} \quad (5)$$

Ainda restava saber o número adequado de funções a serem utilizadas para descrever os orbitais. O aprimoramento em questão veio com a ideia de dobrar, triplicar ou quadruplicar o número de funções de base, gerando as Double Zeta (DZ), Triple Zeta (TZ) ou Quadruple Zeta (QZ) Type Orbitals (CRAMER, 2004; JENSEN, 2006). Com certeza, esta aproximação melhorava a descrição eletrônica de sistemas com muitos elétrons. No entanto, uma ligação química, por exemplo, ocorre entre os orbitais de valência. Apenas dobrando as funções para os orbitais mais internos não iriam atender a descrição do ambiente químico em questão. Assim surgiu uma variação que apenas dobrava o número dos orbitais de valência, Split Valence Basis. Para funções do tipo DZ, denominava-se então VDZ para a nova consideração. Quando os efeitos de polarização são considerados, adicionam-se novas funções ao conjunto de base (funções-p para hidrogênios e funções-d para átomos pesados). Acrescentando-as nas funções DZ, originam-se as DZP (Double Zeta plus Polarization). Dunning-Huzinaga utilizaram desses conceitos para criar suas funções de base que otimizam o número de funções contraídas, além de usar técnicas empíricas que extrapolam o limite de convergência (Complete Basis Set - CBS). Um exemplo de suas funções são as cc-PVDZ ou cc-PVTZ (correlation-consistent Polarized Valence Double/Triple Zeta) (CRAMER, 2004; JENSEN, 2006).

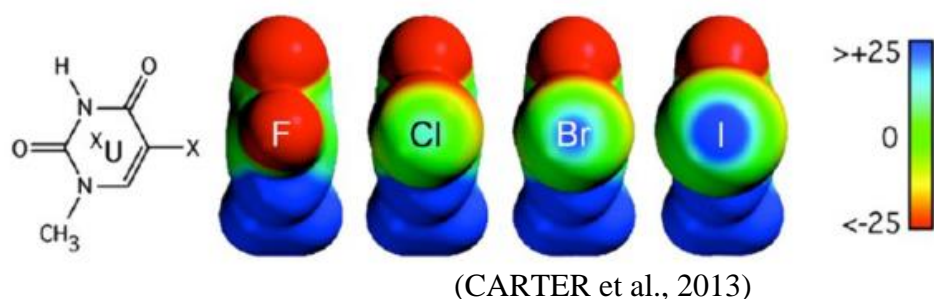
Outro tipo de funções de bases, mais econômicas, porém não piores, são das de Pople. Para estas, há um mínimo de funções a serem utilizadas e subdivisões adequadas para descrever os OM. As funções de Pople são do tipo Split Valence, cuja fórmula padrão é k-nlmG. A letra k corresponde ao número de funções gaussianas que descrevem os orbitais internos e as letras nlm correspondem aos orbitais de valência. Os orbitais de valência podem ser divididos em duas (nl) ou três partes (nlm) de funções n, l e m. Critérios de difusão e polarização são considerados para as bases de Pople. A indicação por '+' corresponde a funções difusas s e p para átomos pesados, e o mesmo ocorre com os hidrogênios quando '++' é utilizado. A

polarização é indicada entre parênteses, especificando os orbitais polarizados. A base 6-311+(d,p), por exemplo, possui funções de polarização para os orbitais *d* e *p*. A notação (d,p) pode ser substituída por \*\* (JENSEN, 2006).

## 2.4 Ligação de Halogênio

Por definição, ligação de halogênio é a interação entre um aceptor (A), frequentemente uma base de Lewis, e um doador (D) que possua ao menos um halogênio em sua composição, que será o vetor da aproximação com (A) (CAVALLO et al., 2016; POLITZER; MURRAY; CLARK, 2013). Inicialmente, acreditava-se que as ligações de halogênio eram possíveis graças ao efeito anisotrópico da ligação  $\sigma$  em átomos do Grupo VII (CLARK et al., 2007; NZIKO; SCHEINER, 2016; POLITZER; MURRAY; CLARK, 2013). Anisotropia é a dependência de determinada propriedade em relação à direção. No caso, a polarização de carga se concentra ao longo da ligação covalente, o que induz uma deficiência eletrônica do lado oposto. A região positiva formada é chamada de  $\sigma$ -hole (CLARK et al., 2007; POLITZER et al., 2007). A Figura 3 ilustra o  $\sigma$ -hole na molécula de Uracila substituída. O aparecimento do  $\sigma$ -hole é diretamente proporcional ao volume do halogênio, sendo ele maior para o iodo e quase inexistente para o flúor. Neste contexto, a ligação de halogênio teria um caráter eletrostático e direcional significativo (THIRMAN; HEAD-GORDON, 2015; WU et al., 2014).

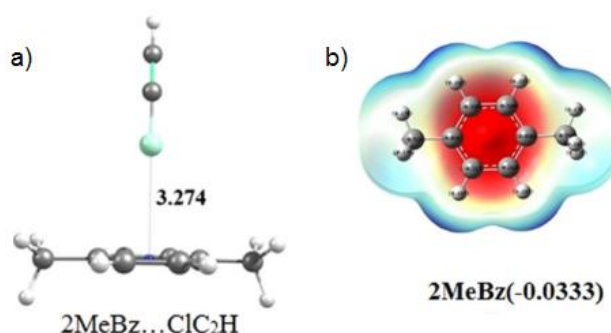
Figura 3 - Superfície eletrostática da base Uracila halogenada. Regiões positivas em azul e negativas em vermelho, de -25 a 25 kcal.mol<sup>-1</sup>. A comparação é feita a partir da substituição na ligação C-X (X = F, Cl, Br, I).



Embora alguns autores defendam o modelo  $\sigma$ -hole, trabalhos recentes demonstram que as interações entre orbitais sejam aquelas que verdadeiramente determinam o aparecimento das ligações de halogênio (WOLTERS et al., 2014; WOLTERS; BICKELHAUPT, 2012; WOLTERS; SMITS; GUERRA, 2015). O modelo  $\sigma$ -hole falha ao explicar as ligações que

envolvem o átomo de flúor como doador, já que este não possui qualquer região de energia potencial eletrostática positiva. A teoria do orbital molecular, por sua vez, pode racionalizar perfeitamente esta interação como sendo produto de combinações entre o HOMO (highest occupied molecular orbital – orbital molecular ocupado de mais alta energia) do acceptor e o LUMO (lowest unoccupied molecular orbital – orbital molecular desocupado de mais baixa energia) do doador (WOLTERS; BICKELHAUPT, 2012).

Figura 4 - Ligação de halogênio na forma T-Shaped: a) Estrutura otimizada em MP2/cc-pVTZ do complexo 1,4-dimetilbenzeno e cloroacetileno; b) Superfície eletrostática do 1,4-dimetilbenzeno.



(KARTHIKEYAN; LEE, 2014)

Além dos pares de elétrons, anéis benzênicos também podem agir como base de Lewis para a ligação de halogênio, como mostra a Figura 4b. A ligação de halogênio será direcionada para o centro do anel aromático, assumindo a forma T-Shaped (Figura 4a). Dessa forma, substituintes no anel aromático influenciam diretamente na energia de interação. Grupos doadores como CH<sub>3</sub>, NH<sub>2</sub> e OH tendem a intensificar a interação, enquanto grupos retiradores de elétrons, como NO<sub>2</sub>, CN, Br, Cl e F, tendem a enfraquecê-la (KARTHIKEYAN; LEE, 2014).

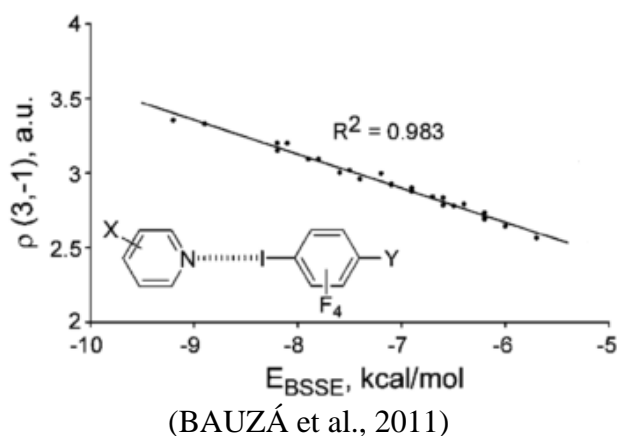
Há ainda outros aspectos relevantes para as ligações de halogênio. A presença de grupos doadores e retiradores de elétrons nos doadores de ligação de halogênio também afetam a energia de interação. Neste caso, os grupos retiradores potencializam a interação, enquanto os doadores a enfraquecem. Em bases de Lewis como a piridina, por exemplo, é possível notar o efeito inverso. Grupos doadores e retiradores intensificam e enfraquecem a ligação de halogênio, respectivamente. Apesar disso, o efeito da ressonância não influencia a força de interação, uma vez que não há preferência quanto à posição dos substituintes (BAUZÁ et al., 2011; ESRAFILI; SOLIMANNEJAD, 2013; SOLIMANNEJAD; MALEKANI, 2013). Ademais, metais do bloco d contribuem ainda mais que os grupos doadores para a energia de

interação nas ligações de halogênio, graças ao alto potencial de polarização das cargas negativas nos pares de elétrons da base de Lewis (WU et al., 2014).

A termodinâmica das ligações de halogênio possui detalhes interessantes. Em uma interação, é de se esperar que ocorra um efeito chamado de compensação entropia-entalpia. Isto é, quanto mais negativo for a variação entálpica ( $\Delta H$ ), mais negativa também será a variação entrópica ( $\Delta S$ ). A compreensão deste efeito torna-se bem clara quando se percebe a diminuição do grau de liberdade de uma molécula conforme a força de interação se intensifica. Para as interações com  $\sigma$ -hole, isto não é diferente. Sendo as ligações de halogênio interações fracas, observam-se muitas das vezes valores de  $\Delta G$  positivos. No entanto, a energia livre de Gibbs pode atingir valores negativos em fase gasosa quando o acceptor da ligação de halogênio for iônico (POLITZER; MURRAY; CLARK, 2013).

Como visto anteriormente, a energia de interação diminui com o aumento do volume do halogênio. Entretanto, a energia livre de Gibbs nem sempre segue a mesma lógica. Por exemplo, a entalpia de interação para a ligação de halogênio segue a ordem  $I < Br < Cl < F$ . Não obstante, se esta interação ocorre dentro de uma cavidade enzimática, átomos muito volumosos afetarão o  $\Delta S$  fazendo com que a energia livre aumente. Dessa forma, irá existir um halogênio ótimo que apresentará o menor  $\Delta G$ , mas não necessariamente terá o maior volume (CARTER et al., 2013).

Figura 5 - Regressão linear da densidade eletrônica no ponto crítico da ligação de halogênio versus a energia de interação.



A metodologia AIM (Atoms In Molecules) pode ser eficiente para a caracterização das ligações de halogênio. A Figura 5 mostra como a densidade eletrônica no ponto crítico varia com a energia de interação. Mudando os substituintes em X e Y, varia-se a energia de interação. Sendo a densidade eletrônica linearmente proporcional à força da interação, é possível

categorizar e qualificar as ligações de halogênio por meio dos pontos críticos de ligação (BAUZÁ et al., 2011).

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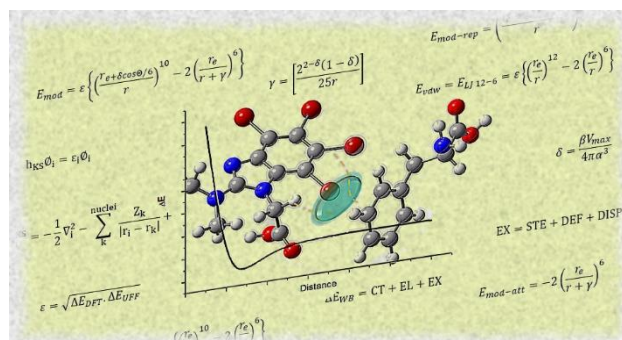
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## SEGUNDA PARTE



**Artigo - Towards the Classical Description of Halogen Bonds: A Quantum Based Generalized Empirical Potential for Fluorine, Chlorine and Bromine.**

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## Abstract

The electronic effects in supramolecular systems are a great challenge for computational chemistry, and the understanding of ligand-protein interactions driven by Halogen Bonds can be limited by Molecular Mechanics point of view. In fact, the variations of the Halogen Bond acceptors, such as an aromatic ring and electrons lone pairs, restrict the classical approximations even more. Our work enhances the statement that Halogen Bonds are led mainly by orbital interactions via  $\sigma^*_{C-X}$ . Nonetheless, we have pointed a straight relationship between the maximum ESP value on the  $\sigma$ -hole and the LUMO energy levels of the Halogen Bond donor. In line with this scenario, the current work introduces a new promising empirical potential based on quantum parameterizations able to describe general halogen bonded systems. The new parameters allow force fields to detect variations on the molecular electronic structure of halogenated organic compounds to improve the description of fluorine, chlorine and bromine in Halogen Bonds.



## 1. INTRODUCTION

In recent decades, Halogen Bonds have emerged as an important tool in several fields of science and the understanding of these interactions has produced many contributions to materials science, organic, medical and biochemistry fields<sup>1-12</sup>. For instance, investigating the mechanism of ligand-protein interactions via halogen bonds and its influence on structural parameters of the ligand/protein complex can be a crucial factor to preview and design more efficient lead-molecules<sup>13-18</sup>.

Halogen bonds are non-covalent interactions between an acceptor (A), often Lewis base like electron lone pairs, and a halogenated molecule acting as a donor (D), which has a positive electrostatic region on the halogen (X) of D – X bond called  $\sigma$ -hole<sup>19-22</sup>. However, recent works have shown strong evidences that orbital interactions lead the formation of halogen bonded systems, putting in doubt if the  $\sigma$ -hole model are robust enough to describe these interactions by itself<sup>23-25</sup>.

In fact, the accurate description of the electronic structure of halogen bonds is highly necessary<sup>26-28</sup>. However, it should be kept in mind that large systems are still a great challenge to electronic structure methods, leading us to use simpler techniques such as molecular mechanics force fields<sup>29-33</sup>.

In this sense, the way in which force fields will describe the charge anisotropy in  $\sigma$  halogen covalent bonds or their orbital interactions has been a real challenge for empirical potentials<sup>33-37</sup>. These potentials often use the Lennard-Jones 12-6 (1) potential to describe general non-bonded interactions<sup>38-40</sup>. Some works have shown good progress in the classical description of Halogen Bonds, simulating the  $\sigma$ -hole by a punctual charge<sup>34,35,37</sup>. Albeit this strategy ignores the orbital nature of these interactions, it shows very good results to specific systems<sup>34,41</sup>. Thus, it would be very interesting to have parameters that describes the real electronic nature of Halogen Bonds.

$$E_{vdw} = E_{LJ\ 12-6} = \varepsilon \left\{ \left( \frac{r_e}{r} \right)^{12} - 2 \left( \frac{r_e}{r} \right)^6 \right\} \quad (1)$$

In view of this scenario, the goal of this work is to improve the MM description of fluorine, chlorine and bromine in Halogen Bonds by empirical potentials considering their electronic nature. To get more insights of the electronic behaviour in Halogen bonds, we will use an energy decomposition analysis approach over the reaction coordinates through potential energy curves (PEC). Furthermore, this work will clarify which quantum properties correlated

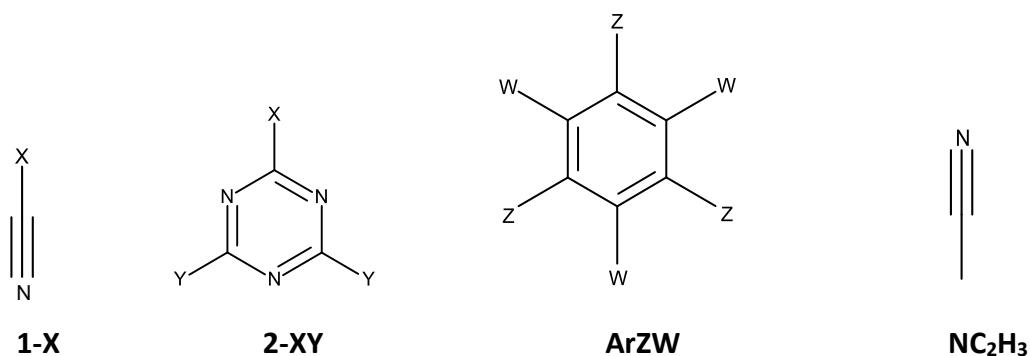
to Halogen Bonds can be used as parameters that will be introduced into classical equations based on the  $\sigma$ -hole model and the molecular orbital point of view.

## 2. METHODOLOGY

### 2.1. Computational details

To validate an appropriate theory level, the DFT-D3 functionals study was carried out using the Gaussian 09 software Revision D.01<sup>42</sup> following the dimer illustrated in Figure S4, an example of aromatic halogen bond in T-Shaped conformation. The dimer is composed of Compound **1** interacting with **Ar** (Figure 1). Two hybrid functionals (M062X and B3LYP) were selected and one pure GGA functional (B97-D3) with 6-31+G\*\* and aug-cc-pVTZ basis sets. The BJ-damping functions were used for B3LYP-D3 and B97-D3 in cases they are assigned as D3BJ. All minimum search calculations were driven by the Counterpoise corrections<sup>43,44</sup> to estimate the BSSE. Our results were compared with those already reported by Forni et al<sup>45</sup> at CCSD(T)/CBS1 level through the equation (2), that can measure the difference between the tested level and the benchmark, to finally elect the best method.

$$d_{\text{CCSD(T)}} = (\Delta E_{\text{CCSD(T)/CBS1}} - \Delta E_{\text{Method}})^2 \quad (2)$$



**Figure 1.** Structures of Halogen Bonded donors (**1** and **2**) and Halogen Bonded acceptors (**Ar** and **NC<sub>2</sub>H<sub>3</sub>**). X = Br, Cl and F; Y = NO<sub>2</sub>, NH<sub>2</sub> and H; W and Z = OH, F and H.

To conceive parameters that can describe the electronic behaviour of Halogen Bonds, their nature in different situations needs to be clarified. The energy decomposition analysis (EDA) was carried out using the software NBO 6.0<sup>46</sup> through Del calculations to obtain the

charge transfer (CT) and NCE analysis to obtain the coulombic contribution (EL) as shown in equation (3).

$$\Delta E_{WB} = CT + EL + EX \quad (3)$$

The equation 3 needs the interaction energy without the BSSE corrections which can be obtained by (4).  $E_{AB}$  is the complex energy single point from the BSSE corrected geometry and the energy of the monomers are  $E_A$  and  $E_B$ .

$$\Delta E_{WB} = E_{AB} - (E_A + E_B) \quad (4)$$

The steric repulsion is obtained by (5). For this, the calculation of DEF<sup>47</sup> and DISP are needed. The last is obtained applying the dispersion corrections D3 and D3BJ<sup>48,49</sup>.

$$EX = STE + DEF + DISP \quad (5)$$

The EDA calculations were carried out in the training set. The interaction between **2** and **ArZW** or **NC<sub>2</sub>H<sub>3</sub>** molecules (Figure 1) was studied following the scheme showed in Figure S5. **ArZW** or **NC<sub>2</sub>H<sub>3</sub>** molecules represents two different groups of Lewis Bases for Halogen Bond acceptors. The **NC<sub>2</sub>H<sub>3</sub>** structure was selected to evoke the Lone Pair (LP)  $\rightarrow \sigma^*_{C-X}$  contribution and the electrostatic attraction between  $N^{\delta-}$  and the  $\sigma$ -hole. The **ArZW** was chosen to act as a  $\pi$  donor to the halogen bond and for being able to perform electrostatic interactions as well.

The LUMO levels that contains the  $\sigma^*_{C-X}$  orbitals and the HOMO levels were identified via NBO 6.0<sup>46</sup> software. The ESP (electrostatic potential) was obtained through the ChelpG model. The energy decomposition analysis results were reported through potential energy curves (PEC) varying the substituents X, Y, Z and W (Figure 1), the interaction distance  $r$  and the interaction angle  $\Theta$  (Figure S5).

## 2.2 Empirical Potential Function Formulation

The best quantum level of theory was chosen to act as a benchmark for the molecular mechanics (MM) techniques in this work. The Universal Force Field (UFF) was chosen to perform the calculations at the MM level. This Force Field mostly uses the LJ 12-6 potential

(1). The MM results were compared with the quantum mechanics (QM) calculations through PEC and Potential Energy Surfaces (PES) generated by Single Point calculations varying  $r$  and  $\Theta$  in order to detect the traditional empirical potential drawbacks.

Well-consisted and strategic modifications on Lennard-Jones potentials were applied to fit the MM techniques to the QM benchmark. The new empirical function was tested into the studied models and real systems to validate its ability to describe the nature of general halogen bonds. The iodine atom is not present in this paper due to relativistic effects<sup>50,51</sup>. Distinct behaviour of the inner electrons would lead to different interpretations that could misjudge the conclusions over the remaining halogens. A proper analysis over how the relativistic effects can affect our parameters will be done in the future.

### 3. RESULTS AND DISCUSSION

#### 3.1 DFT-D3 Functionals Study – Method Validation Analysis

The new empirical potential must always be compared with trustworthy methods, which will act as benchmarks<sup>45,52–54</sup>. At first sight, CCSD(T) and MP2 methods can be suitable but too expensive for large systems. In this stream of thought, DFT functionals with Third-Order Grimme's Dispersion corrections (D3)<sup>49</sup> and Becke-Johnson damping functions (BJ)<sup>48</sup> seem to be a great candidate to benchmark these interactions.

Our analysis leads the conclusion that B3LYP-D3BJ/aug-cc-pVTZ level is appropriate for further studies (further discussion in supporting information). Furthermore, for optimization calculations, the 6-31+G\*\* seems to be enough, albeit the aug-cc-pVTZ basis sets is more reliable dealing with this energy decomposition analysis method.

#### 3.2 $\sigma$ -Hole and LUMO relationship

As mentioned before, the origin of halogen bonds was given initially by the existence of  $\sigma$ -Hole<sup>19</sup>. In other words, attractive electrostatic interactions would lead the system to an energy minima point. Nevertheless, recent findings have shown that orbital interactions actually also play a crucial role to stabilize halogen bonded complexes<sup>24,25</sup>.

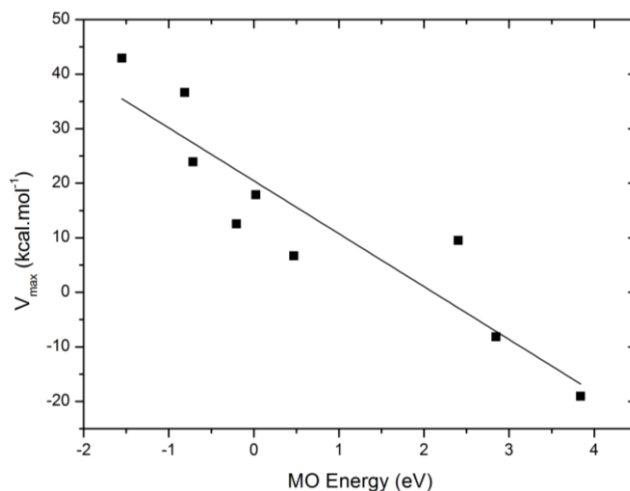
In this sight, our results highlight the importance of charge transfer to the strength of halogen bonds (see supporting information). These outcomes are in line with other works<sup>23–25</sup> that use different EDA methods, which make the theoretical approach used in this paper

trustworthy. Our findings have also shown that the electrostatic component was that most responsible for the  $\Delta E$  difference between **1-Br\_Ar** and **1-Cl\_Ar** (see supporting information). It is not an easy task to translate the orbital description to the classical point of view, but the electrostatic effects are simpler.

Delving deeper into this topic, several structural changes in **2-XY** molecule (Figure S1) have been made to observe the variations in the  $\sigma$ -Hole maximum ESP value ( $V_{\max}$ ). If charge transfer is present in these interactions, the halogen bond donor will act as an electron acceptor. In this sense, there should be an unoccupied molecular orbital, with high participation of the  $\sigma^*_{C-X}$  orbital, that will lead this interaction<sup>55</sup>.

For this study, we have opted for the **2-XY** model (Figure 1), which is able to add substituents at hydrogen positions. Figure S3 indicates the straight relationship between  $\Delta E$  and  $V_{\max}$ , as well as between  $\Delta E$  and the halogen bond donor LUMO level.  $\Delta E$  is the complexation energy of **2-XY...Ar** interaction shown in Table S7 and all values of correspondent **2-XY** molecule are shown Table S1. Withdrawing groups can enforce the charge anisotropy enlarging the  $\sigma$ -hole (Figure S1) and increasing  $V_{\max}$ . For instance, the  $V_{\max}$  on **2-F** electrostatic potential surface is  $-8.17 \text{ kcal.mol}^{-1}$ , but it is increased to  $9.52 \text{ kcal.mol}^{-1}$  for  $Y = \text{NO}_2$ . Electron donor groups cause an opposite effect decreasing  $V_{\max}$  to  $-19.04 \text{ kcal.mol}^{-1}$  for  $Y = \text{NH}_2$ . Nevertheless, electron donor and withdrawing groups will also modify the MO energy levels. The orbital energies of **2-FNH<sub>2</sub>**, **2-F** and **2-FNO<sub>2</sub>** are 3.84 eV, 2.85 eV and 2.40 eV respectively. Thus,  $\text{NO}_2$  groups will intensify orbital interactions and  $\text{NH}_2$  groups will interfere on it.

The natural order of halogen bond force is to grow from F to Br, and it can also be observed for **2-X...Ar** interaction (Table S7). However, our findings highlight the importance of surrounded atoms in the halogen bond energy order. In fact, Table S7 shows that **2-CINO<sub>2</sub>...Ar** interaction are stronger than **2-BrNH<sub>2</sub>...Ar** ( $-3.08 \text{ kcal.mol}^{-1}$  and  $-2.17 \text{ kcal.mol}^{-1}$  respectively). These results are in line with  $V_{\max}$  and orbital energy values, which are respectively  $36.63 \text{ kcal.mol}^{-1}$  and  $-0.81 \text{ eV}$  for **2-CINO<sub>2</sub>**, and  $12.54 \text{ kcal.mol}^{-1}$  and  $-0.20 \text{ eV}$  for **2-BrNH<sub>2</sub>**. Indeed, Figure 2 suggests the existence of a synergy between orbital interactions and electrostatic attraction in halogen bonds by the  $V_{\max}$  and LUMO energy straight relationship. The halogen bond strength can be affected by  $V_{\max}$  and the  $\sigma^*_{C-X}$  energy, but both are depended of the same substituent effect. In other words,  $V_{\max}$  and the  $\sigma^*_{C-X}$  energy have a common origin. In this sight, a parameter that can describe  $V_{\max}$  will also describe the orbital interactions.



**Figure 2.** MO Energy versus  $V_{\max}$  linear regression for 2-XY molecules (X = F, Cl or Br; Y = H, NO<sub>2</sub> or NH<sub>2</sub>).  $R^2 = 0.8451$ ,  $a = 20.4465$  and  $b = -9.6978$ .

### 3.3 PEC approach in EDA

Our results have shown that CT is very important to describe Halogen Bonds and how  $V_{\max}$  can be a descriptor to classical approaches. Therefore, it would be interesting investigate how CT, EL, DISP and STE react along the interaction to understand the traditional empirical potentials drawbacks. This time, the fluorine will be considered, although being often ignored among the halogen bond donors. As we have also shown, the level B3LYP-D3BJ<sup>β</sup> will be very useful to compute all energy components (see the session 2, page S6, in supporting information).

Previously, we have shown that CT was the most active component to stabilize the halogen bonded dimers. In addition, DISP was predominant over EL as well. In such a way, Figure S6 confirms that with different donors and acceptors this same pattern can be observed and reproduced for fluorine. For all PECs, the component responsible for reducing the high steric repulsion, mainly at low range interactions, is the CT component (see the further discussion in the supporting information). Secondly, there is the dispersion energy which is not much higher than electrostatic energy. However, at 2.0 Å their contribution is negligible to decrease the steric repulsion.

Orbital interactions are known to be highly directional depended in contrast to typical electrostatic interactions. On the other hand, in halogen bonds, the electrostatic attraction is strongly correlated to the  $\sigma$ -hole, which is a directional property<sup>56</sup>. Thus, the interaction angle ( $\Theta$ ) can be an important variable to CT and EL components.

In **2-XY<sub>2</sub>Ar** PECs, EL reaches its minimum at 180° whereas its maximum lies at 90° and 270° (Figure S7). Nonetheless, the reason for this is still unclear. Even the halogen negative surface as the s-triazine nitrogen approximation could be responsible for some electrostatic repulsion. The  $\Delta E$  PEC profile resembles the STE curves. Indeed, the most important role of  $\Theta$  in **2-XY<sub>2</sub>Ar** interactions is to avoid the steric repulsions.

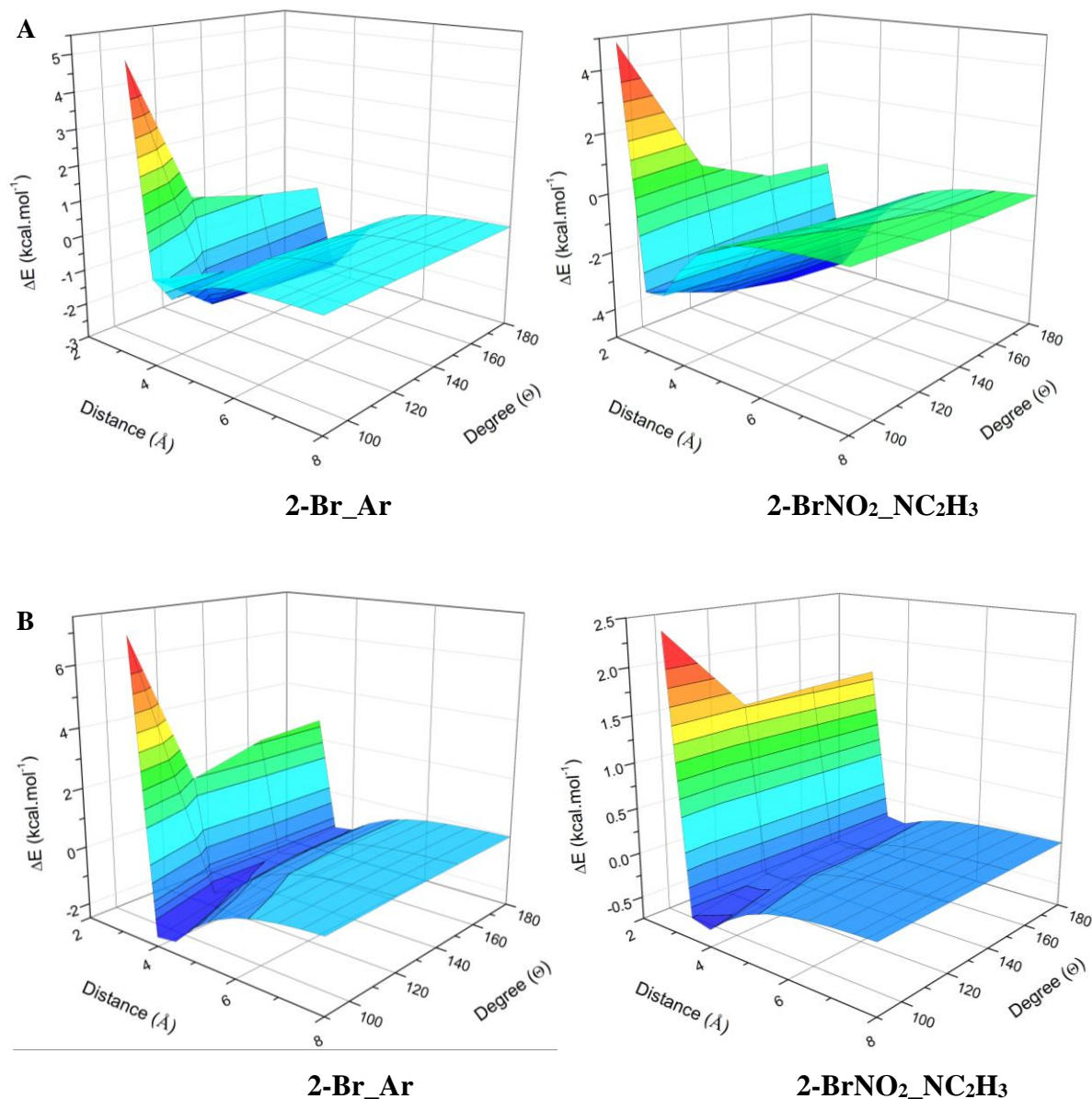
Summarizing, the charge transfer is the main responsible to decrease the steric repulsion over the  $\Theta$  and  $r$  paths. The potential depths of  $\Delta E$  tend to have the same depth of CT. Furthermore, the dispersion can slightly help to stabilize these complexes mainly when benzene is the halogen bond acceptor. These outcomes reinforce even more the importance to describe correctly the orbital interactions.

### 3.4 Insights from the potential energy surface: MM vs QM

The molecular mechanics approach is essential to study large systems. Nevertheless, before extending to macromolecular systems, the MM approach should be able to describe minor systems. With the insights of quantum description of the electronic properties in mind, will molecular mechanics be able to depict the halogen bonds? In order to answer that question, the B3LYP-D3BJ/aug-cc-pVTZ level was used as benchmark to potential energy surfaces (PES) calculated by Universal Force Field (UFF)

Figure 3A shows the PES of **2-Br<sub>2</sub>Ar** interaction predicted by the QM method, whose potential depth lies at 3.5 Å and  $\Theta = 180^\circ$  with  $\Delta E = -2.76$  kcal.mol<sup>-1</sup>. Figure 3B shows the PES from the same interaction predicted by UFF. The interaction energy at the potential depth is almost the same, -2.18 kcal.mol<sup>-1</sup>, but it lies at 4.0 Å and  $\Theta = 90^\circ$ . In fact, the low range energies are highly overestimated (Figure S12) and  $\Theta = 180^\circ$  is a point of maximum (Figure S13) in UFF calculations. The difference between QM and MM methods are attenuated when the halogen series goes from bromine to fluorine.

Figure 3A also shows the PES of **2-BrNO<sub>2</sub>NC<sub>2</sub>H<sub>3</sub>** interaction predicted by the QM method. The potential depth lies at 3.0 Å and  $\Theta = 180^\circ$  with  $\Delta E = -4.75$  kcal.mol<sup>-1</sup>. Even with a different system, the UFF have predicted the potential depth at 4.0 Å and  $\Theta = 90^\circ$  with  $\Delta E = -0.56$  kcal.mol<sup>-1</sup> (Figure 3B). With the lone pair halogen bond donor, the UFF trends to overestimate the low range energies as well and misses the  $r_e$  (Figure S12). For QM curves, the  $r_e$  for **2-Cl<sub>2</sub>NC<sub>2</sub>H<sub>3</sub>** and **2-Br<sub>2</sub>NC<sub>2</sub>H<sub>3</sub>** are both at 3.0 Å, but at 3.5 Å and 4.0 Å for MM curves respectively (Figure S12). In contrast to MM, the QM method does not predict a potential depth for **2-F<sub>2</sub>NC<sub>2</sub>H<sub>3</sub>** interaction as aforementioned.



**Figure 3.** Potential Energy Surfaces of 2-Br $\cdots$ Ar and 2-BrNO $_2\cdots$ NC $_2$ H $_3$  interactions calculated by B3LYP-D3BJ/ug-cc-pVTZ (A) and UFF (B).

Our findings have shown that structural modifications in the halogenated molecule, such as the addition of electron donating or withdrawing groups, affect the interaction energy through EL component. To achieve our goal, it is important to investigate how MM techniques will react to variations in the molecular electronic structure. The PECs of **2-XY $\cdots$ Ar** interaction with different substituent in **Y** calculated by QM (A) and MM (B) methods can be seen in Figure S12. The QM curves can detect that NO $_2$  groups enforce the interaction energy and NH $_2$  groups weakens the **2-XY $\cdots$ Ar** interaction. The MM cannot predict the energy variations by



changing Y. For **2-FY**⋯**Ar** in particular, the  $r_e$  varies with Y (Table S7), but the MM calculations predict all of them at 3.0 Å.

The same is observed for **2-XY**⋯**NC<sub>2</sub>H<sub>3</sub>** interactions and there are no energy variations changing Y for MM calculations (Figure S15). Besides that, the  $r_e$  for QM calculations trends to be close to 3.0 Å (Table S8), but for MM calculations it is at 4.0 Å for **2-BrY** and at 3.5 Å for **2-ClY** and **2-FY**. It is important to highlight that for QM calculations, **2-FY**⋯**NC<sub>2</sub>H<sub>3</sub>** interactions have a potential depth only when Y = NO<sub>2</sub>.

It is worth noticing that the MM curves in Figures S12 and S13 are very close to STE curves in Figures S6 and S7. Moreover, the PEC ranges from 120° to 240° (Figure S13) and fits exactly with the DISP curves in Figure S7. Indeed, the traditional force field empirical potentials are very well parameterized to provide a good response to spatial repulsions and dispersion interactions, but not to describe high correlated electronic effects. For UFF calculations in Figure S13, the energy reaches its minimum at 120° and 240°. The trend would lead the energy minima to 90° if the steric energy were lower. Thus, the molecular mechanics calculations force longer equilibrium distances to avoid the repulsion (Figure 3B). Based on the quantum mechanics calculations, this angular prediction is correct only for **2-F**⋯**Ar** interactions where the halogen  $V_{\max}$  is negative (Figure S13). For all other interactions, the energy minima are in 180°.

In a previous work, we showed that orbital interactions can play a crucial role in non-covalent hydrophobic interactions and the traditional empirical potentials are not able to describe them<sup>52,57</sup>. As demonstrated in the previous sections, the orbital interactions are the driving force to stabilize the steric repulsion and not the  $\sigma$ -hole interactions. However, the electrostatic component is the most sensitive to the structural modifications in the halogenated molecule, significantly changing the  $\Delta E$  along  $r$ . An ideal empirical potential for general halogen bonds should be sensible to the energy variations due to structural modifications and correctly describe the orbital interactions.

### 3.5 Towards a new empirical potential

According to our findings, we have reached important conclusions regarding the halogen bonded systems: substituents in the halogenated molecule play a strong influence at the  $\sigma^*_{C-X}$  orbital level and at the  $V_{\max}$ ; the LUMO containing  $\sigma^*_{C-X}$  orbital and the  $V_{\max}$  properties are in synergy; the electrostatic is the weakest component to stabilize the interaction energy, although it is very responsible for the energy variations with different substituents; the

charge transfer is the strongest component to stabilize the interaction energy and it is highly necessary to soften the destabilization at low range due to the steric repulsion; the energy minima trends to  $\Theta = 180^\circ$  when halogen's  $V_{\max}$  is positive and to  $\Theta = 90^\circ$  when halogen's  $V_{\max}$  is negative; the behaviour of halogen bonds depends on the halogen bond acceptor; the traditional force fields fail in all these aspects.

In fact, UFF uses the Lennard-Jones 12-6 empirical potential (1) to describe non-covalent interactions which has no parameters for the charge anisotropy and predicts high energy values at low range distances<sup>38,39</sup>. An alternative to soften these high energies is to use the 10-6 potential (6), but the charge anisotropy is still missing<sup>35</sup>.

$$E_{vdw} = E_{LJ\ 10-6} = \varepsilon \left\{ \left( \frac{r_e}{r} \right)^{10} - 2 \left( \frac{r_e}{r} \right)^6 \right\} \quad (6)$$

$\Theta$  and  $r_e$  will be badly predicted by the traditional force fields without parameters for specific orbital interactions. All drawbacks of Lennard-Jones potentials to describe halogen bonds could be fixed by introducing new parameters able to read the electronic structure of halogenated molecules. To achieve our goal, these new parameters should be general and sensitive enough, so they can fit into several systems. As a starting point, we have considered the LJ 10-6 potential without  $\varepsilon$ , that will be named as  $E_{st}$  (7).

$$E_{st} = \left\{ \left( \frac{r_e}{r} \right)^{10} - 2 \left( \frac{r_e}{r} \right)^6 \right\} \quad (7)$$

The  $E_{st}$  potential, as well as LJ 10-6, is divided into two parts: the repulsive (S3) and the attractive functions (S4) (see supporting information). In accordance to our findings, the corrections should be applied in order to decrease the low range energies. In other words, reduce the excessive repulsion due to the absence of the orbital interactions. Nevertheless, it was also shown that  $V_{\max}$  is highly correlated to LUMO levels. Thus, here we introduce a new parameter,  $\delta$ , which is a quantum parameter in function of three variables:  $V_{\max}$ , the halogen van der Waals radii ( $\alpha$ ) and an empirical constant ( $\beta$ ) depending on the halogen bond acceptor (S7) (see supporting information).

The van der Waals radii values were selected following the determination of Mantina and co-workers<sup>58</sup>, which are 0.147 nm, 0.175 nm and 0.183 nm for fluorine, chlorine and bromine respectively. Thus, this yields the modified repulsion function,  $E_{mod-rep}$  (8).

$$E_{mod-rep} = \left( \frac{r_e + \delta \cos \Theta / 6}{r} \right)^{10} \quad (8)$$

In (8),  $\delta$  is related to  $\Theta$ , which will mould its magnitude. It is worth noticing that (8) will be a point of minimum when  $\Theta = 180^\circ$  if  $\delta$  is positive and a point of maximum if  $\delta$  is negative. This will help to lead  $\Theta$  into the correct potential depth for different interactions such as **2-F**···**Ar** and **2-BrNO<sub>2</sub>**···**Ar**.  $\delta$  is nullified when  $\Theta = 90^\circ$  and (8) becomes identical to LJ 10-6 repulsive function.

The modifications in the repulsive function have turned  $E_{st}$  into a dysfunctional potential, thus it must be repaired modifying the attractive function as well.

$$E_{mod-att} = -2 \left( \frac{r_e}{r + \gamma} \right)^6 \quad (9)$$

The adjustment on the attractive function was carried out introducing another empirical parameter,  $\gamma$ . It is worth noticing the dependence of  $r$  in  $\gamma$ , which means the adjustment will be increased with the approximation of two molecules (see supporting information). How  $\gamma$  modifies the attractive function (increasing or decreasing) will depend on the signal and magnitude of  $\delta$  – The modulus of  $E_{mod-att}$  will be lower than  $E_{att}$  if  $\delta < 1$  and higher than  $E_{att}$  if  $\delta > 1$ .

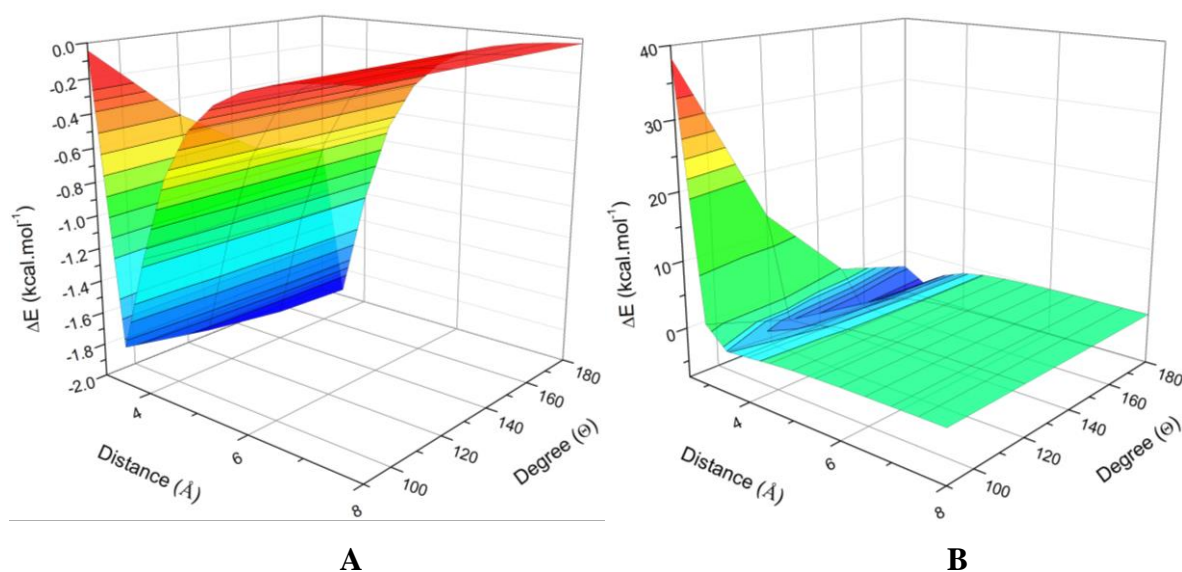
The sum of modified functions (8) and (9) yields (10) (see supporting information).  $E_{mod}$  is a new potential fitted to describe general halogen bonds with aromatic and lone pair acceptors. It was developed in order to attend several systems and different molecules based on how  $V_{max}$  varies in every compound.

$$E_{mod} = \varepsilon \left\{ \left( \frac{r_e + \delta \cos \Theta / 6}{r} \right)^{10} - 2 \left( \frac{r_e}{r + \gamma} \right)^6 \right\} \quad (10)$$

The core of all applied modifications is around  $\delta$ , which will exist only for halogens. For all other atoms  $\delta$  will be zero. This is an interesting feature of  $E_{mod}$ , since all parameters are

nullified when  $\delta = 0$  and (10) becomes the traditional LJ 10-6 (6). Otherwise,  $E_{mod}$  will recognize different halogenated species through  $\delta$ . Another principle of this potential is the maintenance of the previous force field  $r_e$  parameter. Actually, all the new parameters were developed based on UFF parameters using B3LYP-D3BJ curves as benchmark.

The PES plotted only with  $E_{mod}$  are already much more reliable than the surfaces obtained by UFF. Figure 4 shows these results for **2-Br\_Ar** and **2-BrNO<sub>2</sub>\_NC<sub>2</sub>H<sub>3</sub>**, in which  $r_e$  and  $\Theta$  are the same as B3LYP-D3BJ. All parameters are reported in Table S10 and S11.



**Figure 4.** Potential Energy Surfaces plotted for  $E_{mod}$  of 2-Br $\cdots$ Ar (A) and 2-BrNO<sub>2</sub> $\cdots$ NC<sub>2</sub>H<sub>3</sub> (B) interactions.

Moreover, a comparison among UFF, LJ 12-6, LJ 10-6 and  $E_{mod}$  have been made (Figures S16, S17 and S18, see supporting information). The curves were plotted using only the potentials, without the other force field elements. It should be kept in mind that the Coulombic energy is the only one which will vary with  $r$  in the MM calculations, besides the van der Waals term. Being generated by single point calculations, all the bonded terms will be cancelled along the curve. To get more accuracy to determine the  $r_e$  of UFF, we have varied  $r$  in 0.25 Å next to the equilibrium point. Notice that  $\epsilon$  was not really parameterized in this work. We have estimated this parameter from Eq. S10 to equalize all the potentials, in order to make their comparison possible. Thus, the same  $\epsilon$  has been used for all potentials (Table S10 and S11).

In Figures S16, S17 and S18 we have confirmed the aforementioned notes about the Lennard-Jones potentials. The LJ 12-6 indeed results in high low range energies and LJ 10-6 already gives better results. Nevertheless, the  $E_{mod}$  potential also smooths the low range

energies. It is important to highlight the difference between LJ 12-6 and UFF curves, which means that the Coulombic term is also important to provide better energy values, mainly at low range. Besides that,  $E_{mod}$  has shown excellent progress fixing  $r_e$  taking into account the different  $\mathbf{Y}$ . The previous errors, that could be approximately 0.75 Å, were reduced to less than 0.25 Å with the new potential (Table S10 and S11).

Regarding  $\Theta$ ,  $E_{mod}$  has shown very promising results (Figures S19 and S20). Positive  $\delta$  will lead the PEC to  $\Theta = 180^\circ$  in order to maximize the  $\sigma$ -hole and orbital interactions, as quantum techniques have shown (Figure S7). Negative  $\delta$ , which is valid for **2-F** and **2-FNH<sub>2</sub>** like species, trends to lead the PEC to  $\Theta = 90^\circ$ . This trend for **2-F** and **2-FNH<sub>2</sub>** like species was already observed in UFF calculations, but with overestimated repulsion at  $\Theta = 180^\circ$  now softened by  $E_{mod}$ .

Figure S15 shows that MM techniques cannot properly predict the energy variations with different substituents in  $\mathbf{Y}$ . In Figure S21 how  $E_{mod}$  varies in function of  $\delta$  due to  $\mathbf{Y}$  is revealed. Indeed,  $\Delta E_{mod}$  varies with  $\delta$  and not because of  $\epsilon$ , as LJ potentials (Table S10 and S11). The interaction becomes strong as  $\delta$  grows. For **2-F** and **2-FNH<sub>2</sub>** interactions that do not have a potential depth, the  $\Delta E$  was highly decreased and  $r_e$  has been elongated to guarantee that  $\Theta = 180^\circ$  will not be a global minimum (Table S10 and S11).

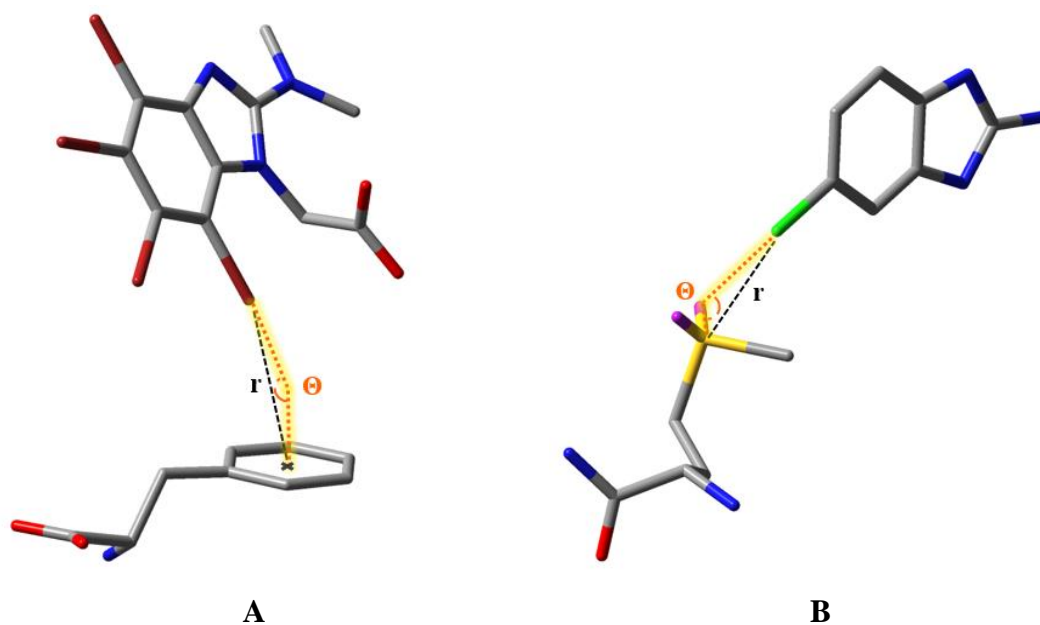
### 3.6 Insights from a study case

In order to illustrate our findings and evidence the new developed empirical potential ( $E_{mod}$ ) performance out of our training set, we have evaluated the halogen bond interactions of real systems represented in Figure 5.

Figure 5A shows the interaction between 2-dimethylamino-4,5,6,7-tetrabromobenzimidazol-1-yl-acetic acid (K66) and the Phe113 residue in CK2 kinase alpha subunit [PDB code: 3KXH]. The strict connection between cancer cells and CK2, whose  $\alpha$  subunit activity is higher in these cells, is already known<sup>59,60</sup>. In this sense, the development of CK2 inhibitors has been a challenging task<sup>61,62</sup>. The strong contribution of hydrophobic and van der Waals interactions to the energy stabilization in the CK2 active site in complex with tetrabromobenzimidazol analogues has also been reported<sup>63,64</sup>. Therefore, the aromatic halogen bond can play an important role in this system.

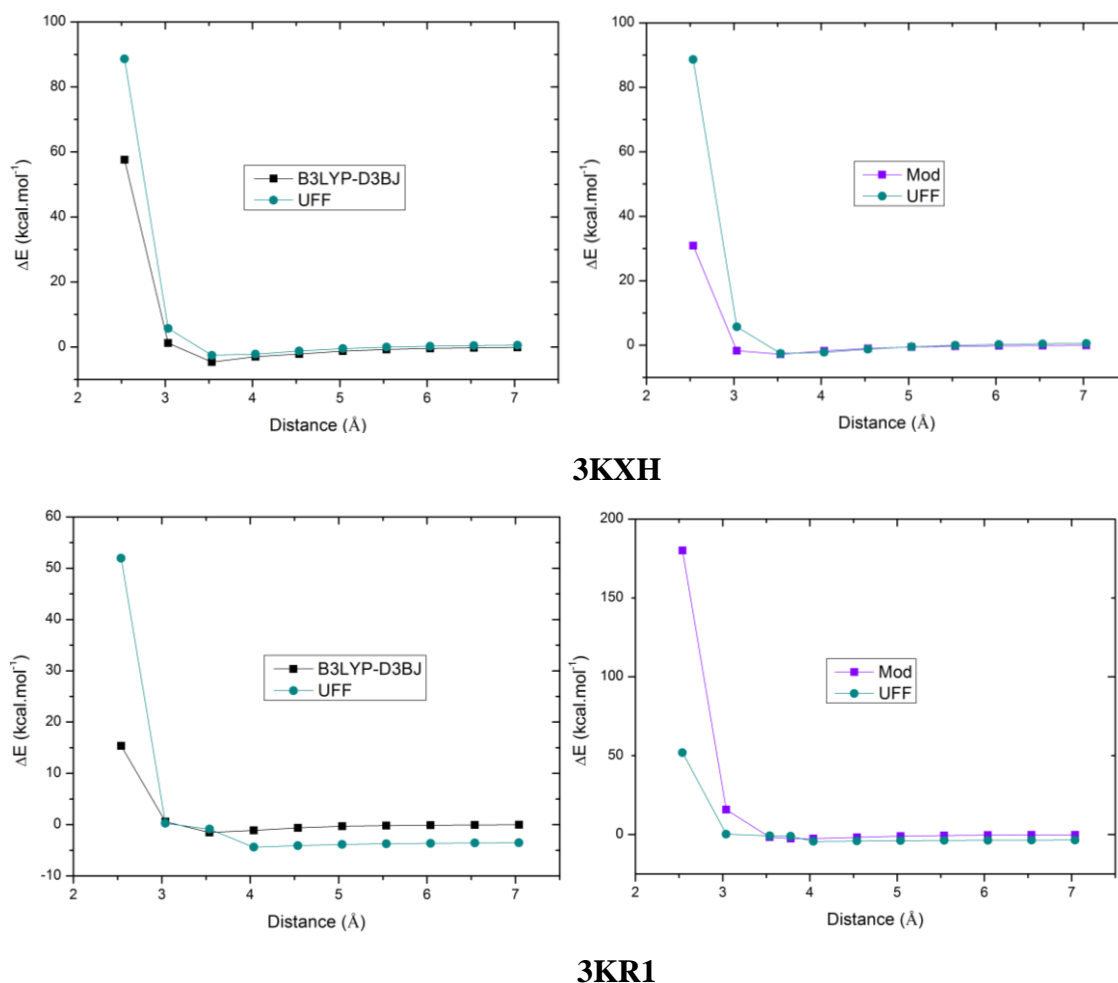
Figure 5B illustrates the interaction between 2-amino-5(6)-chloro-benzimidazole and the Met258 residue in phenylethanolamine N-methyltransferase (PNMT) [PDB code: 3KR1]. The halogenated compound is an inhibitor with high affinity to PNMT, which is responsible

for the methylation of noradrenaline in the final step in adrenaline biosynthesis<sup>14</sup>. The Halogen Bond between Cl $\cdots$ S was identified as a driving force for the approximation of these molecules, being a good example for lone pair acceptors<sup>13</sup>.



**Figure 5.** Protein Data Bank systems for the application of  $E_{mod}$  in Halogen Bonds: 3KXH (A) and 3KR1 (B). Color code: carbon in grey, nitrogen in blue, oxygen in red, bromine in dark red, chlorine in green, sulfur in yellow, representation of sulfur lone pairs in purple, the interaction distance ( $r$ ) in black and the interaction angle ( $\Theta$ ) in orange.

The evidence in Figure 6 reinforces the MM technique drawbacks to describing Halogen Bonds when compared to QM methods. Moreover, the same patterns observed in our training sets have been noticed in Figure 5. The UFF tends to elongate  $r_e$  when the halogen bond acceptors interact through electron lone pairs, but not for aromatic ring acceptors. Nonetheless, the overestimation of low range energies is still observed in all cases.



**Figure 6.** Potential Energy Curves plotted by QM, MM and  $E_{mod}$  3KXH and 3KR1 Halogen Bond interactions.

The parameters used to plot the  $E_{mod}$  are reported in Table 1. The  $E_{mod}$  potential have demonstrate a great performance to describe these interactions fitting the trend of the benchmark level, improving the  $r_e$  prediction. The high energy at 2.0 Å of  $E_{mod}$  in 3KR1 is due to the high  $\Delta E_{UFF}$  value, which was considered to calculate  $\epsilon$  (Eq. S10, see supporting information). The LJ 12-6 potential would certainly have higher  $\Delta E$  values at 2.0 Å with the same  $\epsilon$ , as we have shown in Figure S17.

**Table 1.**  $E_{mod}$  parameters of Figure 6 PECs. Energies,  $\delta$  and  $\epsilon$  in kcal.mol<sup>-1</sup>,  $\Theta$  in degrees and distances in Å.

| PDB<br>Code | $\delta$ | $\epsilon$ | $\Theta$ | $r_e$ | $r_e$ | $r_e$ | $\Delta E_{UFF}$ | $\Delta E_{DFT}$ | $\Delta E_{Mod}$ |
|-------------|----------|------------|----------|-------|-------|-------|------------------|------------------|------------------|
|             |          |            |          | UFF   | DFT   | Mod   |                  |                  |                  |
| 3KR1        | 0.22508  | 2.59668    | 122.80   | 4.04  | 3.54  | 3.78  | -4.40            | -1.53            | -2.61            |
| 3KXH        | 0.20307  | 3.44766    | 151.11   | 3.53  | 3.53  | 3.53  | -2.55            | -4.66            | -3.29            |

These results highlight the prediction ability of  $E_{mod}$  in systems out of our training set, that could be promising to describe other Halogen Bonded complexes. It is worth noting that the only difference in  $E_{mod}$  among all plotted PECs was the  $\delta$  parameter. In a practical implementation, standard parameterizations on  $\delta$  could be done but also allowing the possibility to input  $V_{max}$  from a previous calculation to obtain  $\delta$  with more accuracy.

## CONCLUSIONS

The Halogen Bonds are electronic dependent interactions usually reported in biological environments<sup>13,29,65</sup>. Their description from a supramolecular point of view must be conducted by Force Fields that cannot consider the electron correlation properly. This conjuncture gets even more complicated with the variation of the electron donor.

The molecular orbital theory is extremely relevant to explain these interactions, which could not be interpreted only by the  $\sigma$ -hole model. The electrostatic component can be important and reflects the molecular structure variations in the Halogen Bond strength, but it is no more than a coadjutant. In fact, we have shown that LUMO levels and the  $\sigma$ -hole charge acts synergistically due to the substituent effects, thus they have a common origin. That can explain why the  $\sigma$ -hole model can work in some cases. This feature can be used to build new empirical force field parameters, but it should be kept in mind that the orbital interactions concerning  $\sigma^*_{C-X}$  are the leading figure to these Halogen Bonds.

In this sense, we have shown that simple and strategic modifications in LJ potentials can improve the MM description of Halogen Bonds. The  $E_{mod}$  potential have demonstrate to be consistent under different molecular structures to describe Halogen Bonds compared to trustful QM methods for fluorine, chlorine and bromine. Our parameterizations have been done for lone pairs and aromatic acceptors only. In fact, the greatest contribution of this potential is to use the halogen electrostatic potential to describe the orbital interactions instead of the  $\sigma$ -hole model. The  $E_{mod}$  was formulated based on general parameters enabling its application to several systems leading us to believe in its promising potential to be helpful in molecular engineering.

Our parameterizations do not consider relativistic effects, which is essential for iodine. The next step is to expand this study to the iodine atom, considering the relativistic effects and how to embrace them into empirical potentials. We strongly feel, then, that the present study might be helpful for putting forth new insights into how force fields could be improved. If appropriate force fields are used for larger systems, where *ab initio* calculations are highly computational-demanding, great advances can, in principle, be achieved.



## Supporting Information

Electrostatic potential surfaces, ESP and orbital analysis data, halogen bonded complex scheme, comparison between CCSD(T) level and several DFT-D3 functionals and basis set combination, further energy decomposition analysis discussion, detailed  $E_{mod}$  description and calculated parameters for  $E_{mod}$ . This material is available free of charge via the Internet at <http://pubs.acs.org>.

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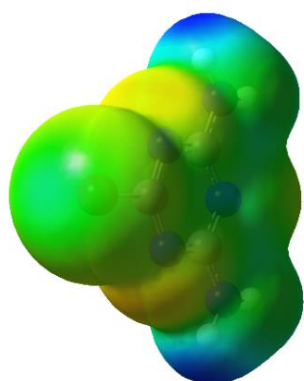
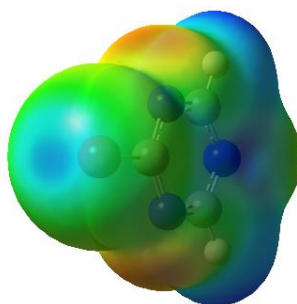
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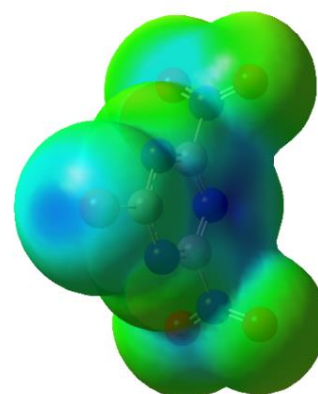
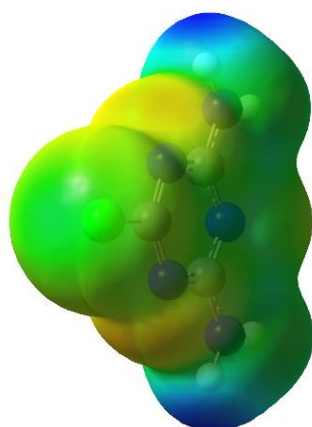
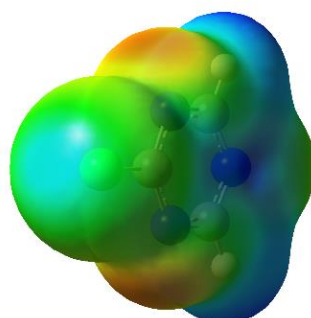
## APÊNDICE – SUPPORTING INFORMATION

## 1. Geometries, electrostatic potential surfaces and electronic information of studied monomers

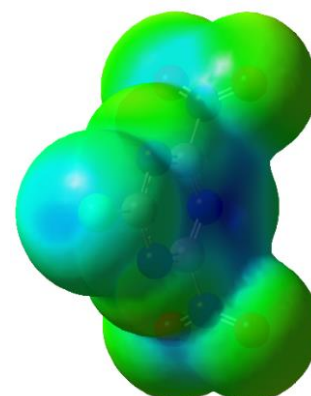
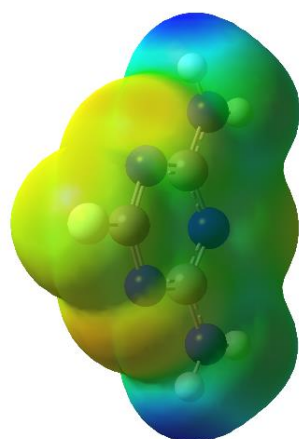
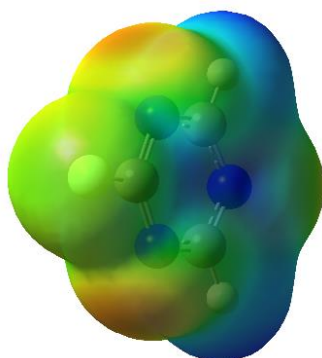
-6.029x10  6.029x10

2-BrNH<sub>2</sub>

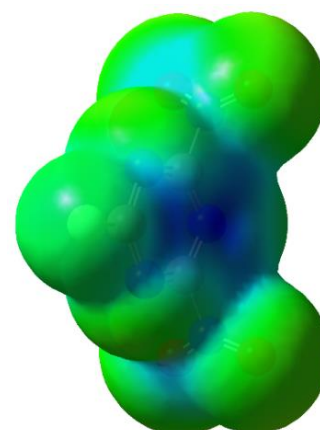
2-Br

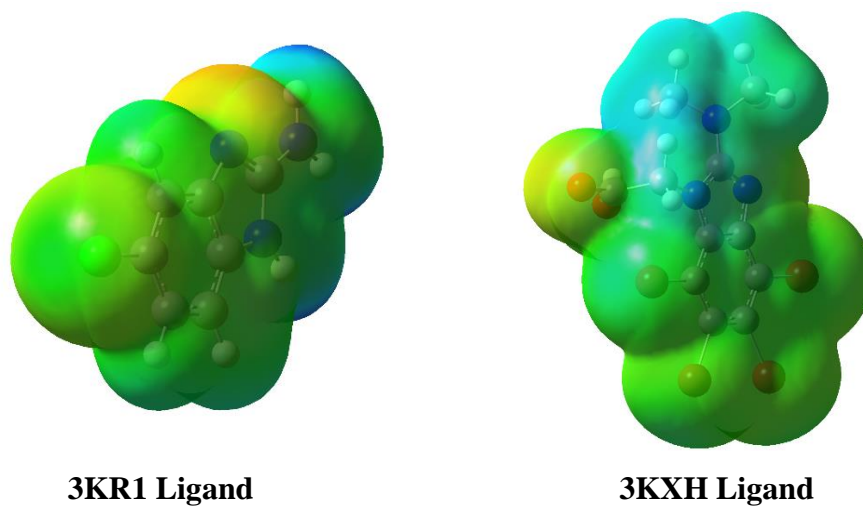
2-BrNO<sub>2</sub>2-ClNH<sub>2</sub>

2-Cl

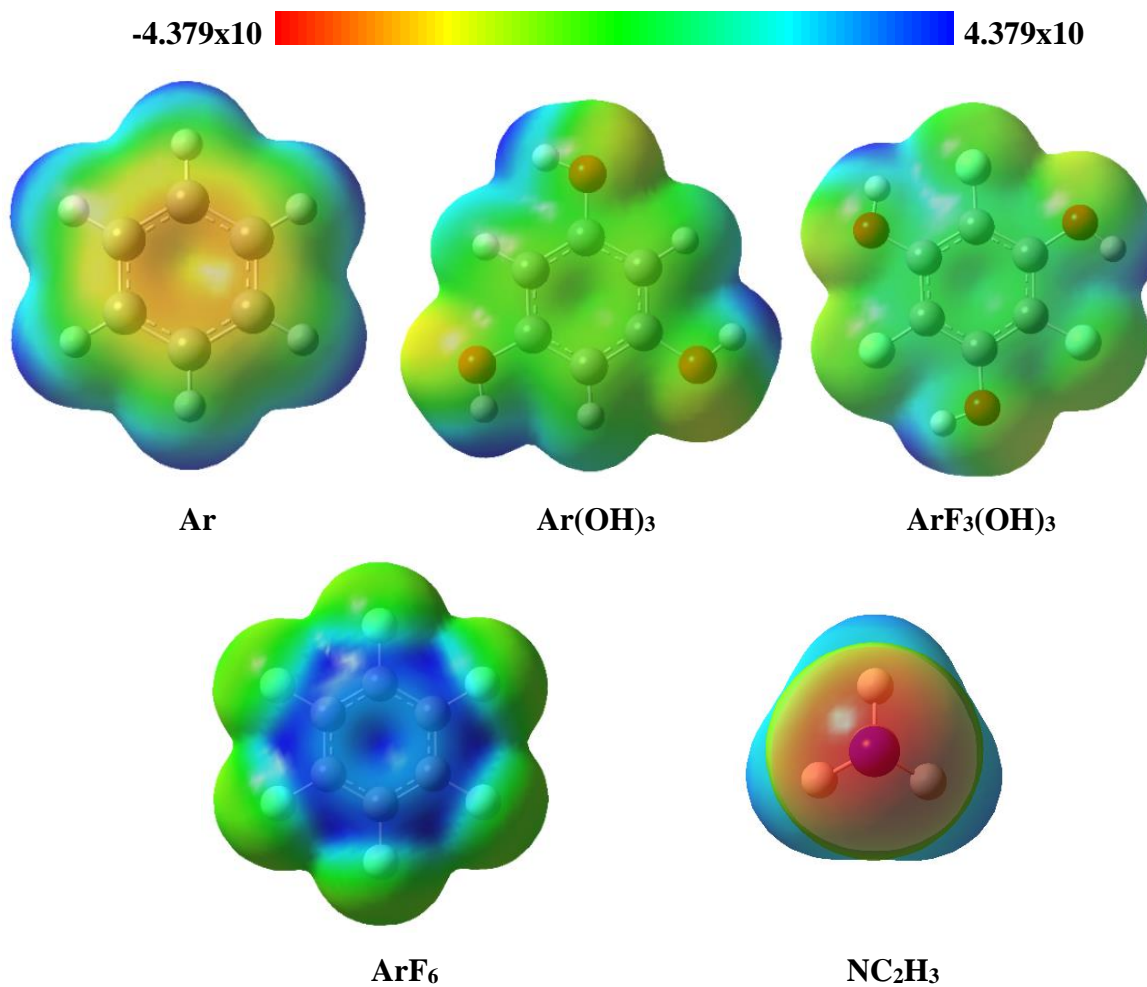
2-ClNO<sub>2</sub>2-FNH<sub>2</sub>

2-F

2-FNO<sub>2</sub>



**Figure S1.** Optimized geometries and Electrostatic Potential Surface in kcal.mol<sup>-1</sup> of Halogen Bond donors.

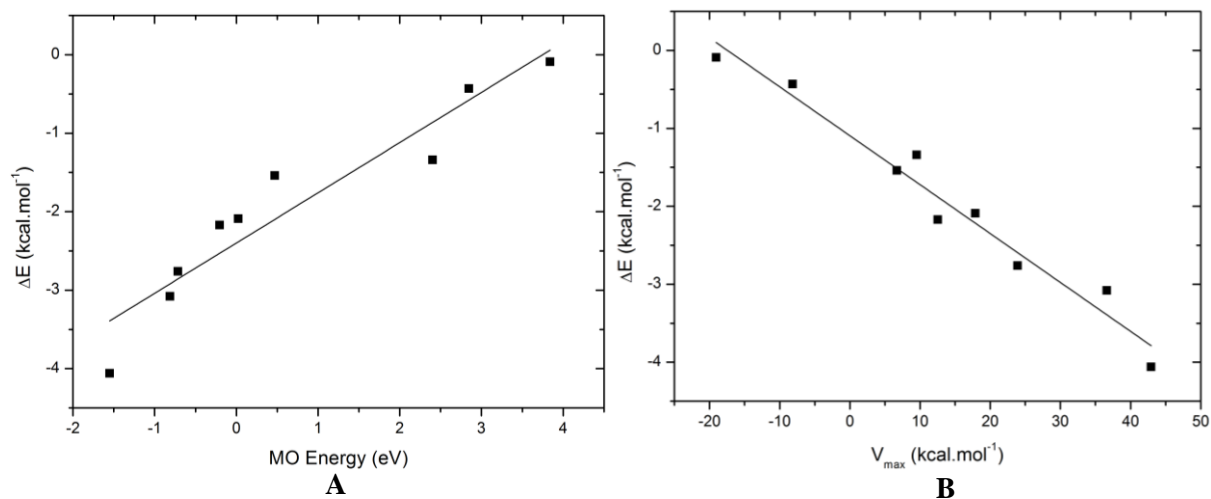


**Figure S2.** Optimized geometries and Electrostatic Potential Surface in kcal.mol<sup>-1</sup> of Halogen Bond acceptors.

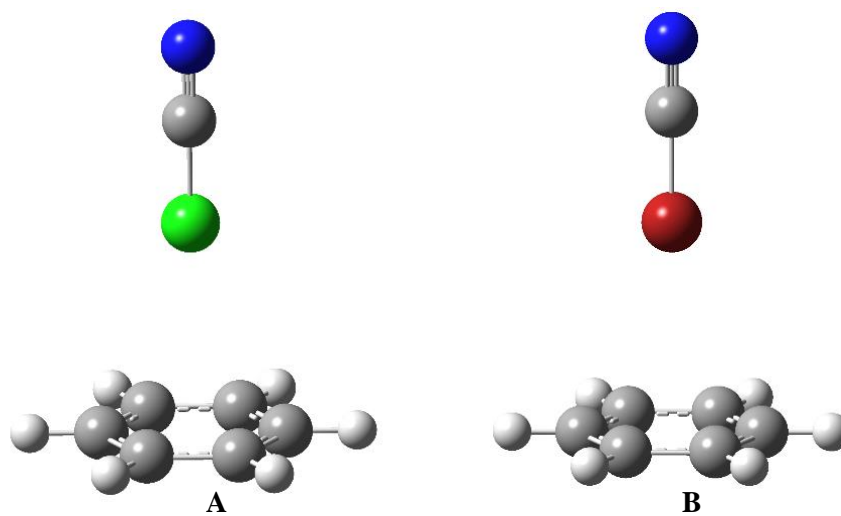
**Table S1.  $\sigma$ -Hole maximum charge, ring center charge or  $\sigma$ -axis nitrogen charge ( $V_{\max}$ ) and energy of related halogen bond orbital.**

| Molecule                           | $V_{\max}$ (kcal.mol <sup>-1</sup> ) | Orbital Energy (eV) | Orbital Level |
|------------------------------------|--------------------------------------|---------------------|---------------|
| Ar                                 | -10.76                               | -7.09               | Homo          |
| ArF <sub>3</sub> (OH) <sub>3</sub> | 8.98                                 | -6.65               | Homo          |
| ArF <sub>6</sub>                   | 26.26                                | -7.84               | Homo          |
| Ar(OH) <sub>3</sub>                | -7.08                                | -6.25               | Homo          |
| NC <sub>2</sub> H <sub>3</sub>     | -43.78                               | -10.08              | Homo-2        |
| 2-F                                | -8.17                                | 2.85                | Lumo+15       |
| 2-FNO <sub>2</sub>                 | 9.54                                 | 2.40                | Lumo+16       |
| 2-FNH <sub>2</sub>                 | -19.04                               | 3.84                | Lumo+24       |
| 2-Cl                               | 17.88                                | 0.02                | Lumo+3        |
| 2-ClNO <sub>2</sub>                | 36.63                                | -0.81               | Lumo+4        |
| 2-ClNH <sub>2</sub>                | 6.70                                 | 0.47                | Lumo+5        |
| 2-Br                               | 23.92                                | -0.71               | Lumo+2        |
| 2-BrNO <sub>2</sub>                | 42.94                                | -1.55               | Lumo+4        |
| 2-BrNH <sub>2</sub>                | 12.54                                | -0.20               | Lumo+4        |
| 3KR1 Ligand                        | 3.80                                 | -                   | -             |
| 3KXH Ligand                        | 22.72                                | -                   | -             |

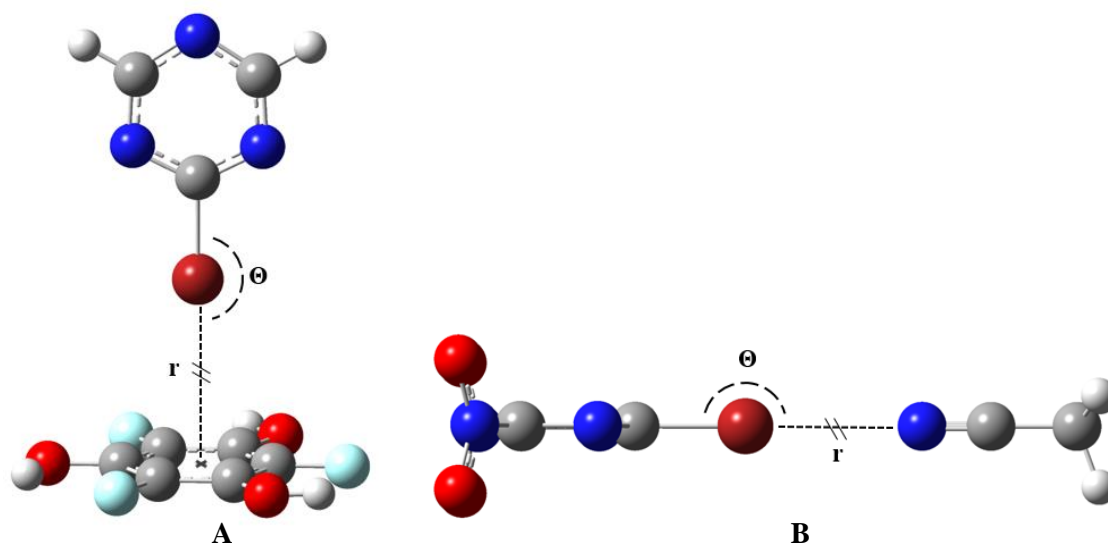




**Figure S3.** Linear Regression of 2-XY...Ar interaction. MO Energy versus  $\Delta E$  (A):  $R^2 = 0.8996$ ,  $a = -2.3989$  and  $b = 0.6399$ .  $V_{\max}$  versus  $\Delta E$  (B):  $R^2 = 0.9622$ ,  $a = -1.0941$  and  $b = -0.0627$ .



**Figure S4.** Optimized geometries of 1-X...Ar interaction: 1-Cl\_Ar (A) and 1-Br\_Ar (B).



**Figure S5.** Structural models of 2-XY...ArZW and 2-XY...NC<sub>2</sub>H<sub>3</sub> interactions: 2-Br-ArF<sub>3</sub>(OH)<sub>3</sub> (A) and 2-BrNO<sub>2</sub>-NC<sub>2</sub>H<sub>3</sub> (A).  $\Theta$  is the interaction angle and  $r$  is the interaction distance.

## 2. DFT-D3 Functionals Study – Method Validation Analysis

Table S2 shows the **1-Br-Ar** complex results. In general, the DFT-D3 functionals have shown an acceptable performance compared to the CCSD(T) calculations (Table S2). By looking at the previous interaction energy ( $\Delta E$ ) results, B97-D/aug-cc-pVTZ was the closest level to CCSD(T), with  $d_{\text{CCSD(T)}} = 0.01 \text{ kcal}^2.\text{mol}^{-2}$ . Nevertheless, M062X-D3/aug-cc-pVTZ calculations are close to CCSD(T) with  $d_{\text{CCSD(T)}} = 0.00 \text{ kcal}^2.\text{mol}^{-2}$ . Notwithstanding, the same functional with 6-31+G\*\* basis set has resulted in a deviation of  $0.02 \text{ kcal}.\text{mol}^{-1}$ .

On the other hand, the accuracy to predict the equilibrium distance ( $r_e$ ) is also important. In this regard, our results were quite accurate with no more than  $0.05 \text{ \AA}$  of difference to CCSD(T)  $r_e$ . Despite this, the B3LYP-D3 or B3LYP-D3BJ results are not far from the best, with  $d_{\text{CCSD(T)}} = 0.12 \text{ kcal}^2.\text{mol}^{-2}$ . It is important to highlight the deviation without the dispersion corrections that is  $8.47 \text{ kcal}^2.\text{mol}^{-2}$ .

**Table S2. 1-Br\_Ar complex interaction energies ( $\Delta E$ ), equilibrium distances ( $r_e$ ) and the deviation from CCSD(T) energies ( $d_{\text{CCSD(T)}}$ ). The energy unit is kcal.mol<sup>-1</sup> and  $r_e$  is in Å.**

| Method            | 6-31+G** |            |                      | aug-cc-pVTZ     |            |                      |
|-------------------|----------|------------|----------------------|-----------------|------------|----------------------|
|                   | $r_e$    | $\Delta E$ | $d_{\text{CCSD(T)}}$ | $r_e$           | $\Delta E$ | $d_{\text{CCSD(T)}}$ |
| B97-D3BJ          | 3.381    | -4.48      | 0.23                 | 3.389           | -4.31      | 0.10                 |
| B97-D3            | 3.336    | -4.38      | 0.14                 | 3.346           | -4.21      | 0.04                 |
| B3LYP-D3BJ        | 3.369    | -4.37      | 0.14                 | 3.363           | -4.34      | 0.12                 |
| B3LYP-D3          | 3.352    | -4.38      | 0.14                 | 3.348           | -4.35      | 0.12                 |
| M062X-D3          | 3.305    | -4.13      | 0.02                 | 3.234           | -3.98      | 0.00                 |
|                   |          | $r_e^{45}$ |                      | $\Delta E^{45}$ |            | $d_{\text{CCSD(T)}}$ |
| B97-D/aug-cc-pVTZ |          | 3.364      |                      | -3.91           |            | 0.01                 |
| M062X/aug-cc-pVTZ |          | 3.249      |                      | -3.84           |            | 0.03                 |
| B3LYP/aug-cc-pVTZ |          | 3.757      |                      | -1.09           |            | 8.47                 |
| MP2/aug-cc-pVDZ   |          | 3.369      |                      | -4.37           |            | 0.14                 |
| MP2/aug-cc-pVTZ   |          | 3.280      |                      | -4.78           |            | 0.61                 |
| CCSD(T)/CBS1      |          | 3.350      |                      | -4.00           |            | -                    |

The **1-Cl\_Ar** complex results can be seen in Table S3. In energetic terms, the B97-D/aug-cc-pVTZ level can describe halogen bonds involving bromine atoms (Table S2) very well, but it fails for chlorine (Table S3). In the first case,  $d_{\text{CCSD(T)}} = 0.01$  kcal<sup>2</sup>.mol<sup>-2</sup>, while  $d_{\text{CCSD(T)}} = 0.42$  kcal<sup>2</sup>.mol<sup>-2</sup> for the NCCl-Ar complex. The best DFT functional was M062X with aug-cc-pVTZ basis set,  $d_{\text{CCSD(T)}} = 0.06$  kcal<sup>2</sup>.mol<sup>-2</sup>. The MP2/aug-cc-pVDZ method gives good results as well, with  $d_{\text{CCSD(T)}} = 0.09$  kcal<sup>2</sup>.mol<sup>-2</sup>. For sure, the DFT-D3 calculations were more promising.

Considering the aug-cc-pVTZ basis set, B97-D3BJ, B3LYP-D3BJ and B3LYP-D3 functionals pointed out the best results for this interaction. It is worth noticing the differences in B3LYP calculations with and without the D3 and BJ corrections here as well. Without these corrections, the B3LYP deviation from CCSD(T) result is equal to 6.30 kcal<sup>2</sup>.mol<sup>-2</sup>. The deviation decreases to 0.00 kcal<sup>2</sup>.mol<sup>-2</sup> with D3 corrections and to 0.01 kcal<sup>2</sup>.mol<sup>-2</sup> with BJ damping functions. It is possible to decrease the computational cost using the 6-31+G\*\* basis set. For B97-D3BJ and B3LYP-D3BJ,  $d_{\text{CCSD(T)}}$  is equal to 0.01 kcal<sup>2</sup>.mol<sup>-2</sup> virtually with the same accuracy of aug-cc-pVTZ basis.

These results would already represent good progress in the study of chlorine compounds compared to MP2 methods regarding the computational cost. The accurate estimation of  $\Delta E$  and  $r_e$  by B3LYP-D3BJ will be very convenient in the following sections.

**Table S3. 1-Cl<sub>2</sub>Ar complex interaction energies ( $\Delta E$ ), equilibrium distances ( $r_e$ ) and the deviation from CCSD(T) energies ( $d_{\text{CCSD(T)}}$ ). The energy unit is kcal.mol<sup>-1</sup> and  $r_e$  is in Å.**

| Method            | 6-31+G** |            |                      | aug-cc-pVTZ     |            |                      |
|-------------------|----------|------------|----------------------|-----------------|------------|----------------------|
|                   | $r_e$    | $\Delta E$ | $d_{\text{CCSD(T)}}$ | $r_e$           | $\Delta E$ | $d_{\text{CCSD(T)}}$ |
| B97-D3BJ          | 3.340    | -3.25      | 0.01                 | 3.311           | -3.36      | 0.00                 |
| B97-D3            | 3.283    | -3.06      | 0.08                 | 3.268           | -3.17      | 0.03                 |
| B3LYP-D3BJ        | 3.314    | -3.26      | 0.01                 | 3.291           | -3.42      | 0.01                 |
| B3LYP-D3          | 3.286    | -3.19      | 0.03                 | 3.268           | -3.37      | 0.00                 |
| M062X-D3          | 3.299    | -3.06      | 0.08                 | 3.178           | -3.13      | 0.05                 |
|                   |          | $r_e^{45}$ |                      | $\Delta E^{45}$ |            | $d_{\text{CCSD(T)}}$ |
| B97-D/aug-cc-pVTZ |          | 3.409      |                      | -2.70           |            | 0.42                 |
| M062X/aug-cc-pVTZ |          | 3.177      |                      | -3.11           |            | 0.06                 |
| B3LYP/aug-cc-pVTZ |          | 3.728      |                      | -0.84           |            | 6.30                 |
| MP2/aug-cc-pVDZ   |          | 3.311      |                      | -3.65           |            | 0.09                 |
| MP2/aug-cc-pVTZ   |          | 3.208      |                      | -4.02           |            | 0.45                 |
| CCSD(T)/CBS1      |          | 3.250      |                      | -3.35           |            | -                    |

In addition to selecting a good benchmark method to formulate an empirical potential for halogen bonds, it is important to understand what electronic effects conduct these phenomena attempting to find the best parameters for their classical description. Thus, the Energy Decomposition Analysis (EDA) is an useful tool to obtain insights on the nature of molecular interactions and has to be done carefully(LAO; HERBERT, 2016; PHIPPS et al., 2015; THIRMAN; HEAD-GORDON, 2015). We have pointed DFT-D3 suitable functionals to proceed halogen bonded systems calculations and two promising basis sets. It is always tempting to use a smaller basis sets due to their low computational demanding, but how 6-31+G\*\* and aug-cc-pVTZ will respond to the EDA approach?

Tables S4 and S5 give the full EDA calculations data. It should be kept in mind that NBO calculations do not support the counterpoise corrections. In fact, quantum calculations using finite basis sets are susceptible to basis set superposition error (BSSE). In this way, the

BSSE can become an important factor to be analyzed to judge the most reliable component energies.  $\Delta E$  is the total energy with counterpoise corrections and  $\Delta E_{\text{WB}}$  is the total energy without BSSE (4).

**Table S3. 1-Br\_Ar energy decomposition analysis. All energy values are in kcal.mol<sup>-1</sup> and  $r_e$  is in Å.  $\alpha = 6\text{-}31\text{+G}^{**}$  and  $\beta = \text{aug-cc-pVTZ}$ .**

| Method                                    | $\Delta E$ | BSSE | $\Delta E_{\text{WB}}$ | CT    | EL    | EX   | $r_e$ |
|---|------------|------|------------------------|-------|-------|------|-------|
| B97-D3BJ <sup><math>\alpha</math></sup>   | -4.48      | 3.13 | -7.61                  | -4.42 | -3.55 | 0.36 | 3.381 |
| B97-D3BJ <sup><math>\beta</math></sup>    | -4.31      | 0.14 | -4.43                  | -6.73 | -2.82 | 5.12 | 3.389 |
| B3LYP-D3BJ <sup><math>\alpha</math></sup> | -4.37      | 3.20 | -7.57                  | -4.51 | -3.58 | 0.52 | 3.369 |
| B3LYP-D3BJ <sup><math>\beta</math></sup>  | -4.34      | 0.14 | -4.46                  | -7.22 | -2.88 | 5.64 | 3.363 |
| M062X-D3 <sup><math>\alpha</math></sup>   | -4.13      | 3.20 | -7.33                  | -4.62 | -3.75 | 1.04 | 3.305 |
| M062X-D3 <sup><math>\beta</math></sup>    | -3.98      | 0.21 | -4.18                  | -7.80 | -3.20 | 6.82 | 3.234 |

The energy components and BSSE calculation results of the **1-Br\_Ar** dimer are shown in Table S4. It is very clear that the 6-31+G\*\* basis set gives the highest BSSE error values for the **1-Br...Ar** interaction. In these calculations,  $\Delta E_{\text{WB}}$  is about 3 kcal.mol<sup>-1</sup> lower than  $\Delta E$ . It also reflects on the CT outcomes, that tend to be higher with the 6-31+G\*\* basis set. This fact also holds some influence on the EX, which depends on CT (Eq. 3).

**Table S4. 1-Cl\_Ar energy decomposition analysis. All energy values are in kcal.mol<sup>-1</sup> and  $r_e$  is in Å.  $\alpha = 6\text{-}31\text{+G}^{**}$  and  $\beta = \text{aug-cc-pVTZ}$ .**

| Method                                    | $\Delta E$ | BSSE | $\Delta E_{\text{WB}}$ | CT    | EL    | EX   | $r_e$ |
|---|------------|------|------------------------|-------|-------|------|-------|
| B97-D3BJ <sup><math>\alpha</math></sup>   | -3.25      | 0.26 | -3.51                  | -2.58 | -2.80 | 1.87 | 3.340 |
| B97-D3BJ <sup><math>\beta</math></sup>    | -3.36      | 0.11 | -3.46                  | -6.99 | -2.33 | 5.86 | 3.311 |
| B3LYP-D3BJ <sup><math>\alpha</math></sup> | -3.26      | 0.30 | -3.55                  | -2.75 | -2.79 | 1.99 | 3.314 |
| B3LYP-D3BJ <sup><math>\beta</math></sup>  | -3.42      | 0.13 | -3.55                  | -7.41 | -2.31 | 6.17 | 3.291 |
| M062X-D3 <sup><math>\alpha</math></sup>   | -3.06      | 0.23 | -3.29                  | -2.69 | -2.78 | 2.17 | 3.299 |
| M062X-D3 <sup><math>\beta</math></sup>    | -3.13      | 0.22 | -3.35                  | -7.91 | -2.50 | 7.06 | 3.178 |

The BSSE values with the 6-31+G\*\* basis set are not so far from the aug-cc-pVTZ results for the **1-Cl...Ar** interaction (Table S5). Notwithstanding, CT values show the same trend noticed for the **1-Br...Ar** interaction, leading us to believe that the difference among these basis sets in the energy components results is not due to the BSSE phenomena.

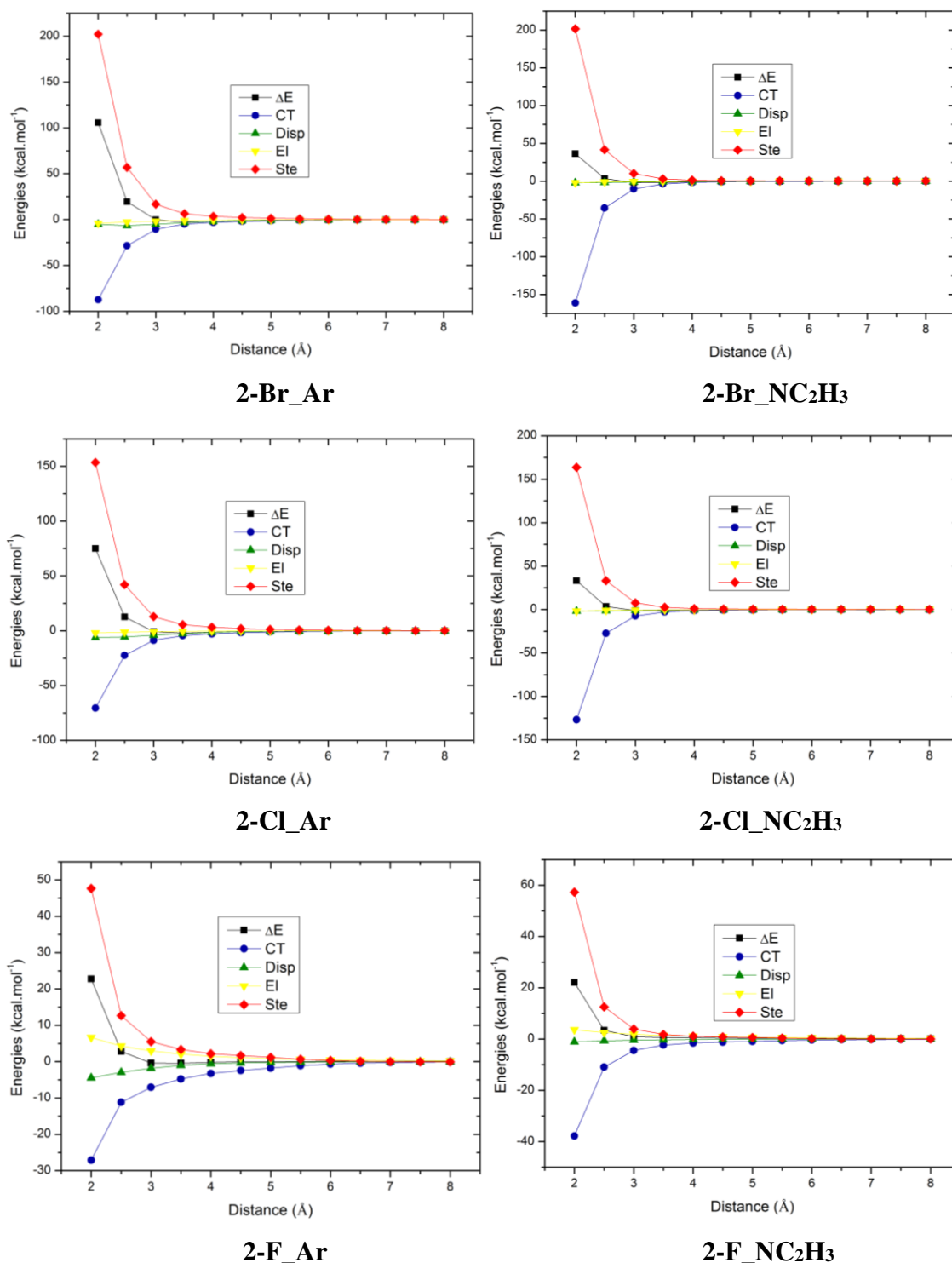
For NCE calculations (Table S4 and S5), EL in the **1-Br...Ar** interaction was lower than in **1-Cl...Ar**, as expected, since the  $\sigma$ -hole size in bromine is larger than in chlorine<sup>(ESRAFI; AHMADI, 2012)</sup>.

The energy contributions to deformation and dispersion effects are inside EX (5), where STE, DEF and DISP are the steric repulsion, the deformation energy and the dispersion energy, respectively. As we can see in Table S6, the DEF is the component least important to the proposed interactions. Acting as a stabilizing energy, the DISP is quite important to both complexes. However, it is important to emphasize that only the B3LYP-D3BJ calculations provide the real dispersion energy. Unlike the B3LYP, the M062X and B97-D functionals have dispersion terms already included. Thus, the DISP component in B97-D3BJ and M062X-D3 calculations can be understood as the corrected dispersion energy over the previous dispersion terms used.

**Table S5. Decomposition of EX component for 1-Br\_Ar (left) and 1-Cl\_Ar (right) in the equilibrium distance. All energy values are in kcal.mol<sup>-1</sup>.  $\beta$  = aug-cc-pVTZ.**

| Method                                   | EX   |      | DEF  |      | DISP  |       | STE  |      |
|--|------|------|------|------|-------|-------|------|------|
| B97-D3BJ <sup><math>\beta</math></sup>   | 5.12 | 5.86 | 0.02 | 0.03 | -0.39 | -0.68 | -    | -    |
| B3LYP-D3BJ <sup><math>\beta</math></sup> | 5.64 | 6.17 | 0.01 | 0.01 | -3.74 | -3.03 | 9.37 | 9.19 |
| M062X-D3 <sup><math>\beta</math></sup>   | 6.82 | 7.06 | 0.10 | 0.08 | -0.15 | -0.18 | -    | -    |

### 3. Potential Energy Curves in Energy Decomposition Analysis



**Figure S6.** Energy decomposition analysis of substituted s-Triazine...acceptor (2-XY\_Acceptor) interaction PEC for  $\Theta = 180^\circ$  and  $Y = H$ .  $\Delta E$  curves are the same as reported in Figure S12.

Tables S7 and S8 show the PECs information at their equilibrium distances. **2-XY...Ar** interactions are highly dominated by CT and DISP, in which the first term always holds the highest values (Table S7). Comparing the molecules with Br and Cl, it is possible to see that CT decreases from Br to Cl in  $0.50 \text{ kcal.mol}^{-1}$  and STE decreases in  $1.02 \text{ kcal.mol}^{-1}$ . Even though, it is not enough to justify the  $\Delta E$  increases of  $0.67 \text{ kcal.mol}^{-1}$ . Looking at the other components, DISP decreases from Br to Cl in  $0.82 \text{ kcal.mol}^{-1}$  and EL also decreases in  $0.49 \text{ kcal.mol}^{-1}$ . Indeed, bromine is more polarizable than Cl. Albeit less than all other components, the variation in EL is not unimportant.

**2-F...Ar** interaction is quite different from the others. With  $\Delta E$  equal to  $-0.43 \text{ kcal.mol}^{-1}$ , it is characterized by low DISP and STE. Despite its lesser steric repulsion, the repulsive electrostatic interactions ( $2.05 \text{ kcal.mol}^{-1}$ ) highly increases  $\Delta E$  in comparison with **2-Br** and **2-Cl** dimers. In fact, this highlights that the nature of fluorine halogen bonds is different. But does it stand for different acceptors?

The behaviour of  $\text{NC}_2\text{H}_3$  PECs is very similar to Ar PECs. However, looking at the potential depth some differences can be found. Besides the equilibrium distance shifts from  $3.5 \text{ \AA}$  to  $3.0 \text{ \AA}$  with  $\text{NC}_2\text{H}_3$  acceptor for **2-Br** and **2-Cl**, the DISP contribution has dramatically decreased and so does the variation of EL (Table S8).  $\text{NC}_2\text{H}_3$  is less polarizable than benzene, so it makes sense. But it is surprising to have less EL energies since  $V_{\text{max}}$  in  $\text{NC}_2\text{H}_3$  is more negative than in Ar (Table S1). Perhaps it can be understood by the electrostatic potential surface area, which is greater in Ar. There are negative charges distributed on the whole ring centre in benzene, but, in  $\text{NC}_2\text{H}_3$ , the negative charges are all concentrated on a unique point – the nitrogen atom.

Short equilibrium distances will also lead to better orbital overlaps, and CT component is higher than in **2-XY...Ar** interactions. However, it will increase the steric repulsion as well. It is worth noticing that CT almost nullifies STE by itself. For instance, in **2-Br\_NC2H3** CT is  $-10.30 \text{ kcal.mol}^{-1}$  and STE is  $10.15 \text{ kcal.mol}^{-1}$ . In **2-Cl\_NC2H3** CT is  $-7.34 \text{ kcal.mol}^{-1}$  and STE is  $7.70 \text{ kcal.mol}^{-1}$ . Moreover, **2-F\_NC2H3** has even more differences. The PEC for this dimer has no depth. In other words, this interaction may not happen by the electronic energy. Comparing with **2-F\_Ar** (Tables S7 and S8), **2-F\_NC2H3** has less electrostatic repulsion and is less stabilized by dispersion. In addition, the charge transfer has decreased by  $2.60 \text{ kcal.mol}^{-1}$ , which is highly correlated with orbital energy levels of both acceptors ( $-7.09 \text{ eV}$  for Ar and  $-10.08$  for  $\text{NC}_2\text{H}_3$ ) (Table S1).

We have shown that electron withdrawing and donating groups affects  $V_{\text{max}}$ , the  $\sigma^*_{\text{C-X}}$  molecular orbital energy and  $\Delta E$ . If  $\Delta E$  is different, the energy components should be affected



as well. Figures S8 and S9 shows the PECs of **2-XNO<sub>2</sub>** and **2-XNH<sub>2</sub>** with **Ar** and **NC<sub>2</sub>H<sub>3</sub>** respectively. All the patterns remain as before (Figure S6) with high CT values at low range interactions nulling STE while DISP and EL are almost ineffective.

Adding NO<sub>2</sub> groups to **2-XY** complexed with **Ar**, the CT contribution increases just around 0.4 kcal.mol<sup>-1</sup>, but EL is intensified by 1.90 kcal.mol<sup>-1</sup> for **2-BrNO<sub>2</sub>**, 1.56 kcal.mol<sup>-1</sup> for **2-ClNO<sub>2</sub>** and it is 1.49 kcal.mol<sup>-1</sup> less repulsive for **2-FNO<sub>2</sub>**. In **NC<sub>2</sub>H<sub>3</sub>** dimers it is even more expressive. EL becomes 2.73 kcal.mol<sup>-1</sup> more negative for **2-BrNO<sub>2</sub>**, 1.84 kcal.mol<sup>-1</sup> more negative for **2-ClNO<sub>2</sub>** and 1.65 kcal.mol<sup>-1</sup> less positive for **2-FNO<sub>2</sub>**, while CT increases just around 0.2 kcal.mol<sup>-1</sup>. In this sight, EL is much more sensitive to substituents than CT in halogen bonds. These findings show that EL plays an important role at  $r_e$  in order to lead halogen bonds to better energy states regarding the atomic environment.

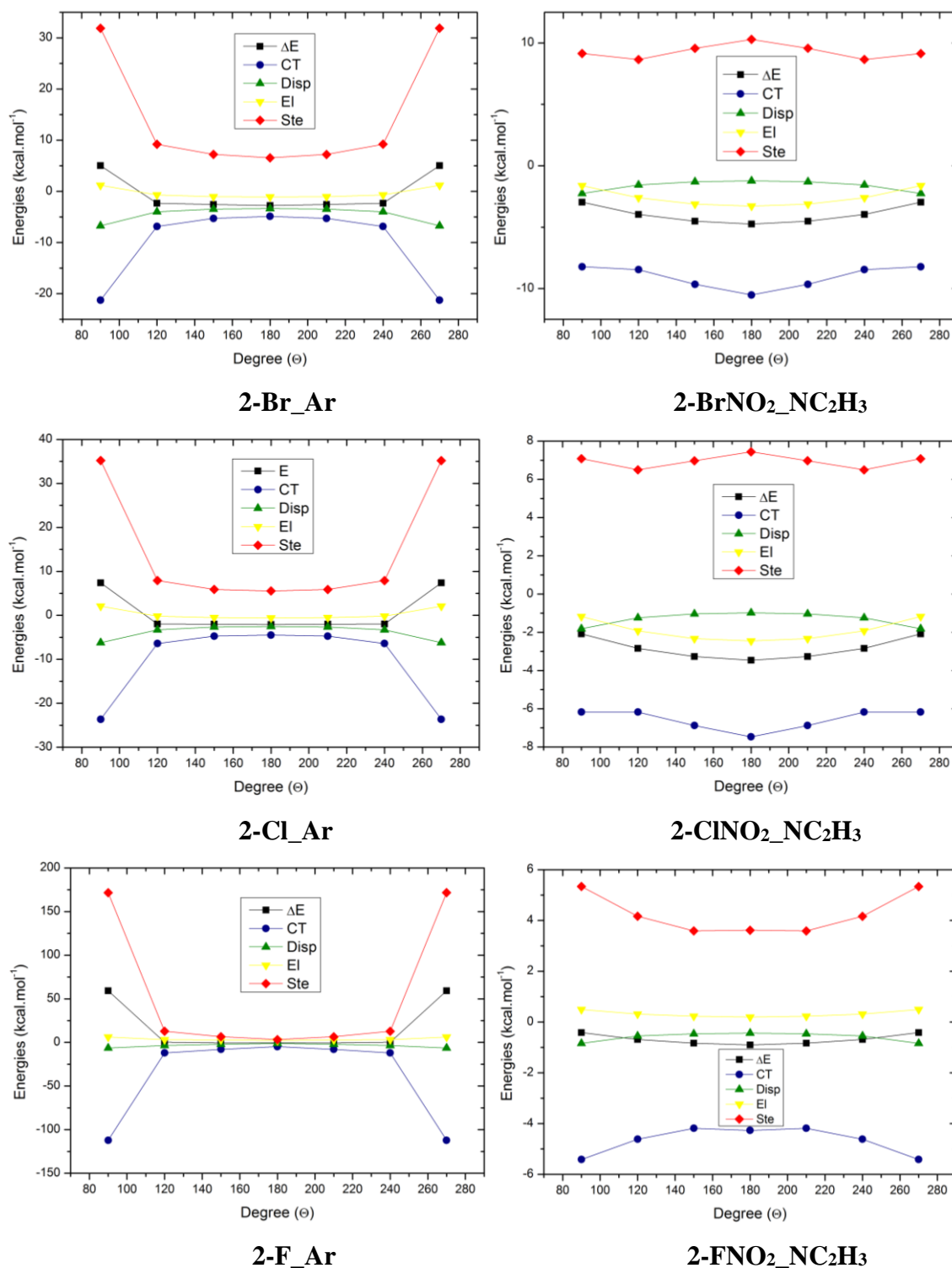
Moreover, Figures S10 and S11 highlight the real nature of halogen bonds. Herein, **ArF<sub>3</sub>(OH)<sub>3</sub>** and **ArF<sub>6</sub>** were used as acceptors. Both have positive  $V_{\max}$  (Table S1) and lead to positive EL along the PECs. However, our results show that **2-XY...Ar** interactions are stronger than **2-XY...ArF<sub>6</sub>**, but weaker than **2-XY...ArF<sub>3</sub>(OH)<sub>3</sub>** (see Table S7 and S9). These results are compatible with their HOMO energy levels which are -6.65 eV, -7.09 and -7.84 for **ArF<sub>6</sub>**, **Ar** and **ArF<sub>3</sub>(OH)<sub>3</sub>** respectively. The **2-XY...ArF<sub>3</sub>(OH)<sub>3</sub>** interactions become even stronger when Y = NO<sub>2</sub>. In these complexes, EL becomes more positive, whereas CT is intensified. Herein, the LUMO energy level, the halogen donor  $V_{\max}$  and  $\Delta E$  have conserved their straight relationship.

Orbital interactions are known to be highly directional depended in contrast to typical electrostatic interactions. On the other hand, in halogen bonds, the electrostatic attraction is strongly correlated to the  $\sigma$ -hole, which is a directional property (KOLÁŘ; HOSTAŠ; HOBZA, 2014). Thus, the interaction angle ( $\Theta$ ) can be an important variable to CT and EL components. Figure S7 shows how the energy components vary with  $\Theta$ .

In the first place, it is important to highlight that the potential depth lies at 180°, which was already expected as the ideal direction of orbital overlap and  $V_{\max}$  interactions between the monomers take place. Thus, CT and EL curves should have their potential depth at 180° as well. However, this feature is not observed in all cases.

Starting with **2-XY-Ar** PECs, the hydrogens in Y were chosen to allow the dimer to be in  $\Theta = 90^\circ$  without atoms superposition (Figure S7). In CT PECs of these dimers, 180° is the point of maximum energy. In fact, this is occurring due to approximation of triazine's nitrogen lone pairs to **Ar**  $\pi^*$  and  $\sigma^*_{C-H}$  orbitals when  $\Theta$  tends towards 90° or 270°. Despite that, CT stays negative and the highest stabilizing component in all points.

In **2-XY\_Ar** PECs, EL reaches its minimum at 180° whereas its maximum lies at 90° and 270°. Nonetheless, the reason for this is still unclear. Even the halogen negative surface as the s-triazine nitrogen approximation could be responsible for some electrostatic repulsion. Leaving this discussion for a later time, it is worth noticing STE. The  $\Delta E$  PEC profile resembles the STE curves. Indeed, the most important role of  $\Theta$  in **2-XY...Ar** interactions is to avoid the steric repulsions. For **2-XY\_NC<sub>2</sub>H<sub>3</sub>** dimers (Figure S7), the nitro groups in Y were chosen to intensify the electrostatic interactions. Here, the **2-FNO<sub>2</sub>...NC<sub>2</sub>H<sub>3</sub>** interaction has a different behaviour from the others.



**Figure S7.** Energy decomposition analysis of substituted s-Triazine...acceptor (2-XY\_Acceptor) interaction PEC for  $r = r_e$  (see Table S7 and S8).  $\Delta E$  curves are the same as reported in Figure S13.

**Table S6. Energy Decomposition Analysis at PECs equilibrium distances for Ar acceptor and  $\Theta = 180^\circ$ . Energies in kcal.mol<sup>-1</sup> and distances in Å.**

| Dimer                   | $r_e$            | $\Delta E$ | CT    | DISP  | EL    | STE  |
|-------------------------|------------------|------------|-------|-------|-------|------|
| 2-Br_Ar                 | 3.5              | -2.76      | -4.89 | -3.37 | -1.07 | 6.55 |
| 2-BrNO <sub>2</sub> _Ar | 3.5              | -4.06      | -5.24 | -3.40 | -2.97 | 7.55 |
| 2-BrNH <sub>2</sub> _Ar | 3.5              | -2.17      | -4.91 | -3.38 | -0.26 | 6.38 |
| 2-Cl_Ar                 | 3.5              | -2.09      | -4.49 | -2.55 | -0.58 | 5.53 |
| 2-ClNO <sub>2</sub> _Ar | 3.5              | -3.08      | -4.80 | -2.58 | -2.14 | 6.44 |
| 2-ClNH <sub>2</sub> _Ar | 3.5              | -1.54      | -4.57 | -2.57 | 0.26  | 5.34 |
| 2-F_Ar                  | 3.5              | -0.43      | -4.78 | -1.04 | 2.05  | 3.33 |
| 2-FNO <sub>2</sub> _Ar  | 3.5 <sup>a</sup> | -1.34      | -4.74 | -1.08 | 0.56  | 4.11 |
| 2-FNH <sub>2</sub> _Ar  | 3.5              | -0.09      | -4.70 | -1.06 | 2.64  | 3.03 |

<sup>a</sup> The real equilibrium distance has shifted to 3.0 Å.

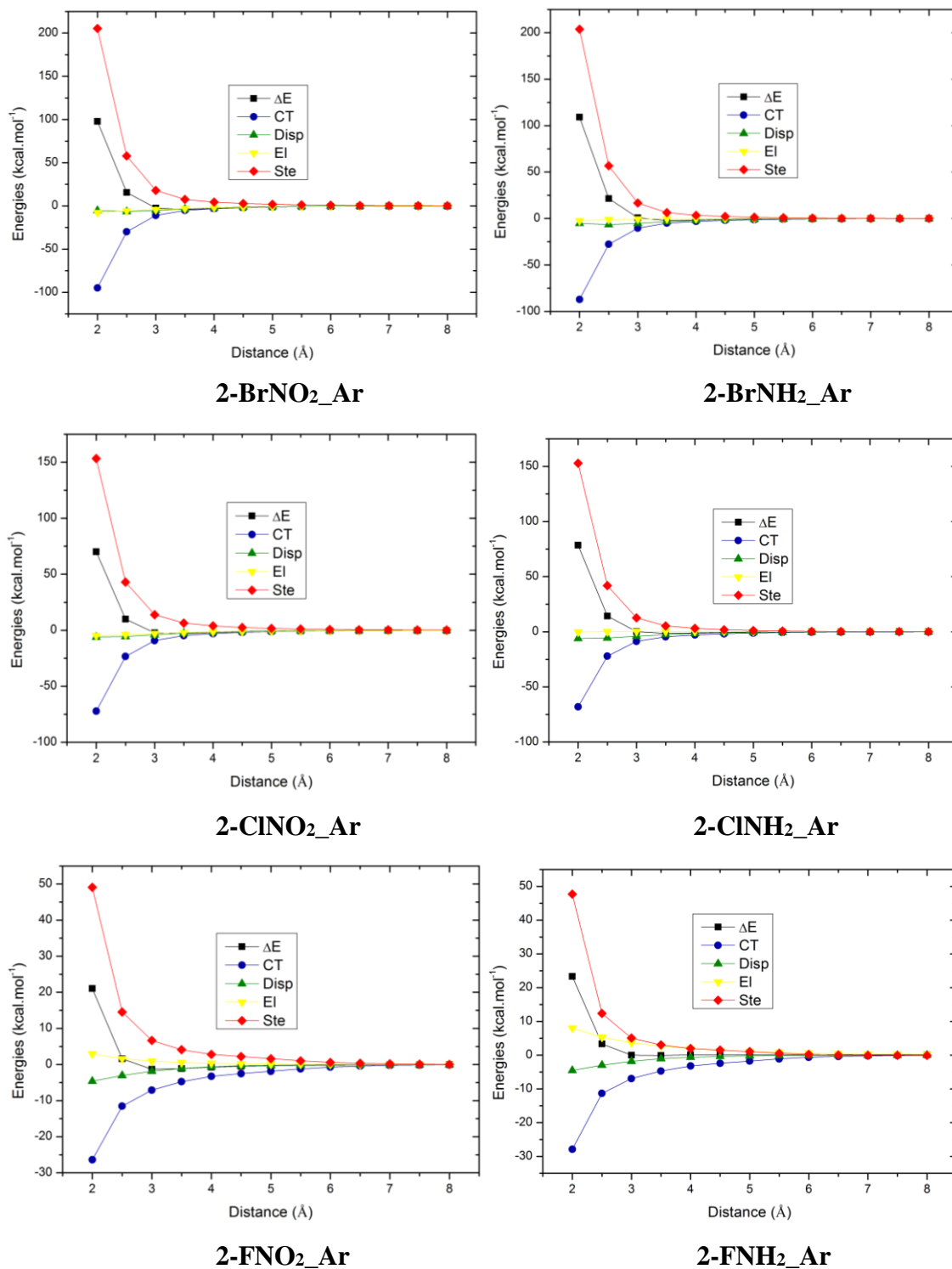
**Table S7. Energy Decomposition Analysis at PECs equilibrium distances for NC<sub>2</sub>H<sub>3</sub> acceptor and  $\Theta = 180^\circ$ . Energies in kcal.mol<sup>-1</sup> and distances in Å.**

| Dimer   | $r_e$            | $\Delta E$ | CT     | DISP  | EL    | STE   |
|---|------------------|------------|--------|-------|-------|-------|
| 2-Br_NC <sub>2</sub> H <sub>3</sub>                 | 3.0              | -1.92      | -10.30 | -1.22 | -0.55 | 10.15 |
| 2-BrNO <sub>2</sub> _NC <sub>2</sub> H <sub>3</sub> | 3.0              | -4.75      | -10.52 | -1.23 | -3.28 | 10.29 |
| 2-BrNH <sub>2</sub> _NC <sub>2</sub> H <sub>3</sub> | 3.0 <sup>a</sup> | -0.46      | -10.15 | -1.23 | -0.22 | 11.14 |
| 2-Cl_NC <sub>2</sub> H <sub>3</sub>                 | 3.0              | -1.22      | -7.34  | -0.97 | -0.61 | 7.70  |
| 2-ClNO <sub>2</sub> _NC <sub>2</sub> H <sub>3</sub> | 3.0              | -3.47      | -7.47  | -0.98 | -2.45 | 7.44  |
| 2-ClNH <sub>2</sub> _NC <sub>2</sub> H <sub>3</sub> | 3.0 <sup>a</sup> | 0.21       | -7.28  | -0.98 | 0.31  | 8.16  |
| 2-F_NC <sub>2</sub> H <sub>3</sub>                  | 3.0 <sup>b</sup> | 0.88       | -4.46  | -0.43 | 1.84  | 3.92  |
| 2-FNO <sub>2</sub> _NC <sub>2</sub> H <sub>3</sub>  | 3.0              | -0.90      | -4.27  | -0.44 | 0.19  | 3.61  |
| 2-FNH <sub>2</sub> _NC <sub>2</sub> H <sub>3</sub>  | 3.0 <sup>b</sup> | 1.92       | -4.28  | -0.44 | 2.48  | 4.15  |

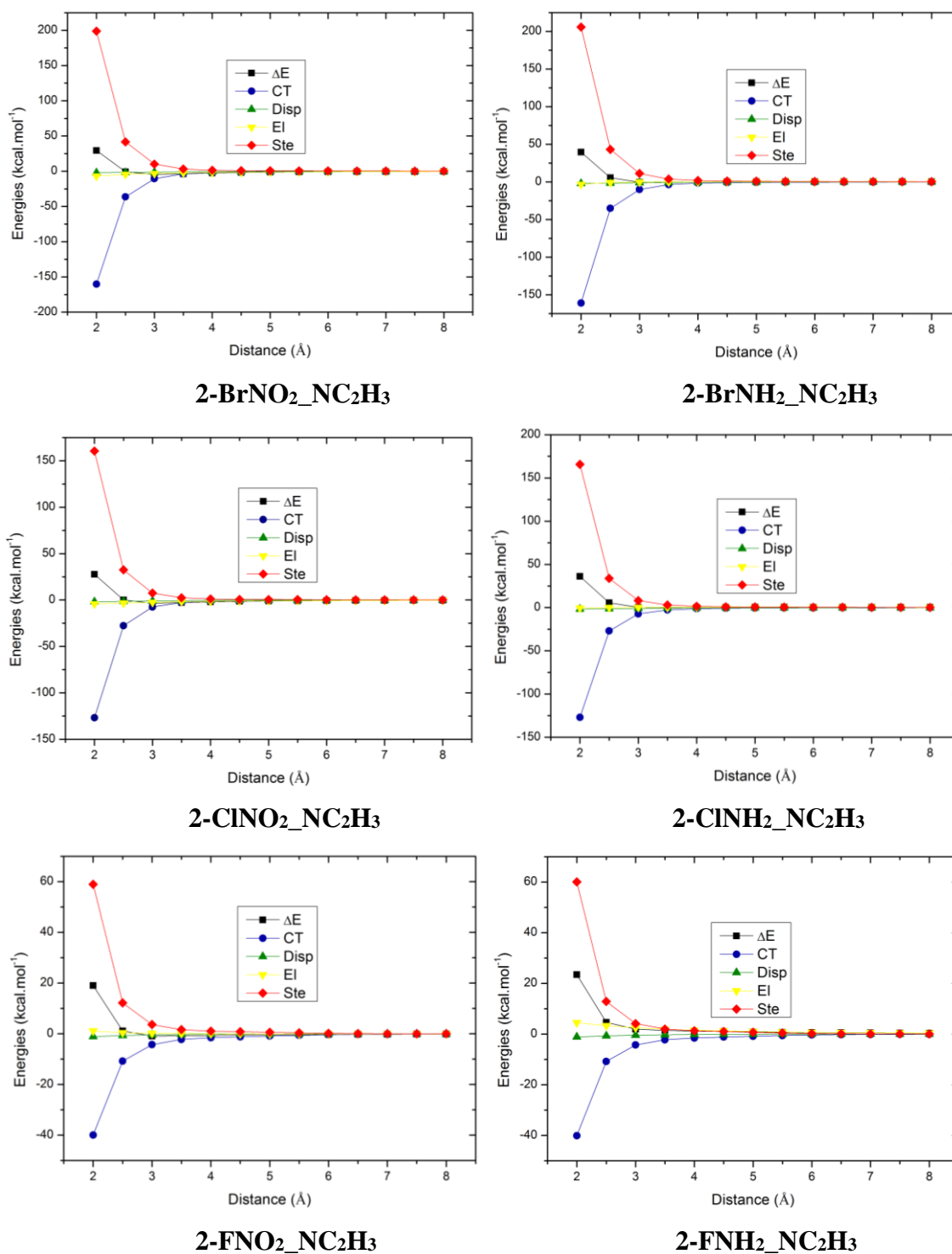
<sup>a</sup> The real equilibrium distance has shifted to 3.5 Å; <sup>b</sup> The PEC has no equilibrium distance.

**Table S8. Energy Decomposition Analysis at PECs equilibrium distances for ArZW acceptors and  $\Theta = 180^\circ$ . Energies in kcal.mol<sup>-1</sup> and distances in Å.**

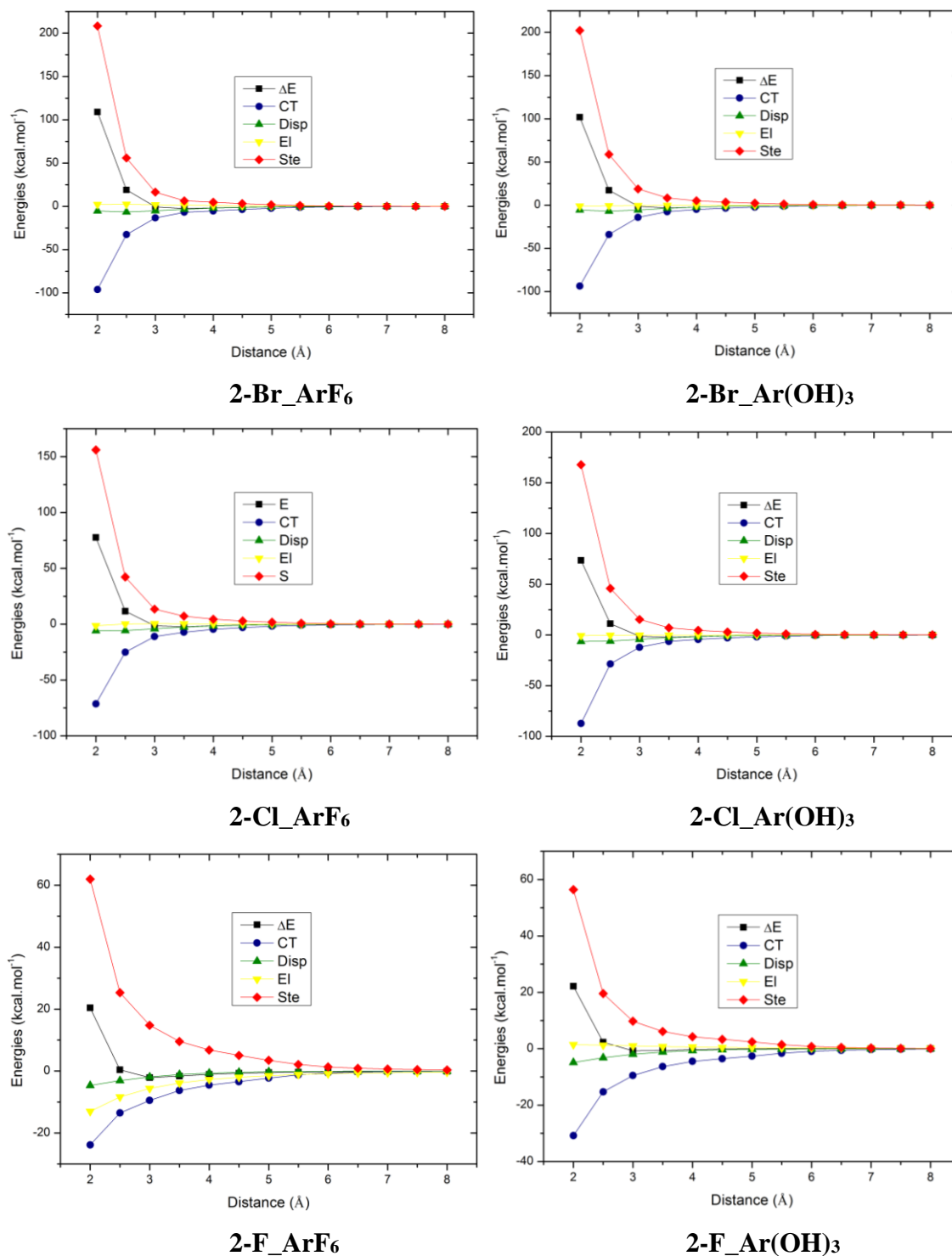
| <b>Dimer</b>  | <b>r<sub>e</sub></b> | <b>ΔE</b> | <b>CT</b> | <b>DISP</b> | <b>EL</b> | <b>STE</b> |
|---|----------------------|-----------|-----------|-------------|-----------|------------|
| 2-Br_ArF <sub>6</sub>                                   | 3.5                  | -2.69     | -6.84     | -3.47       | 1.26      | 6.37       |
| 2-Br_Ar(OH) <sub>3</sub>                                | 3.5                  | -3.20     | -7.56     | -3.63       | -0.34     | 8.33       |
| 2-Br_ArF <sub>3</sub> (OH) <sub>3</sub>                 | 3.5                  | -3.10     | -9.53     | -3.68       | 0.93      | 9.18       |
| 2-BrNO <sub>2</sub> _ArF <sub>3</sub> (OH) <sub>3</sub> | 3.5                  | -3.35     | -10.11    | -3.71       | 2.61      | 7.86       |
| 2-Cl_ArF <sub>6</sub>                                   | 3.5                  | -2.27     | -7.18     | -2.64       | 0.35      | 7.20       |
| 2-Cl_Ar(OH) <sub>3</sub>                                | 3.5                  | -2.35     | -6.47     | -2.76       | -0.15     | 7.03       |
| 2-Cl_ArF <sub>3</sub> (OH) <sub>3</sub>                 | 3.5                  | -2.43     | -8.09     | -2.79       | 0.38      | 8.07       |
| 2-ClNO <sub>2</sub> _ArF <sub>3</sub> (OH) <sub>3</sub> | 3.5                  | -2.60     | -8.37     | -2.83       | 1.96      | 6.65       |
| 2-F_ArF <sub>6</sub>                                    | 3.0                  | -2.12     | -9.46     | -1.90       | -5.58     | 14.82      |
| 2-F_Ar(OH) <sub>3</sub>                                 | 3.0                  | -0.74     | -9.49     | -1.98       | 0.98      | 9.75       |
| 2-F_ArF <sub>3</sub> (OH) <sub>3</sub>                  | 3.0                  | -1.55     | -11.25    | -2.01       | -3.28     | 14.99      |
| 2-FNO <sub>2</sub> _ArF <sub>3</sub> (OH) <sub>3</sub>  | 3.0                  | -1.54     | -11.30    | -2.08       | -1.33     | 13.16      |



**Figure S8.** Energy decomposition analysis of substituted s-Triazine...Benzene (2-XY<sub>Ar</sub>) interaction potential curve, when Y = NO<sub>2</sub> or NH<sub>2</sub>.

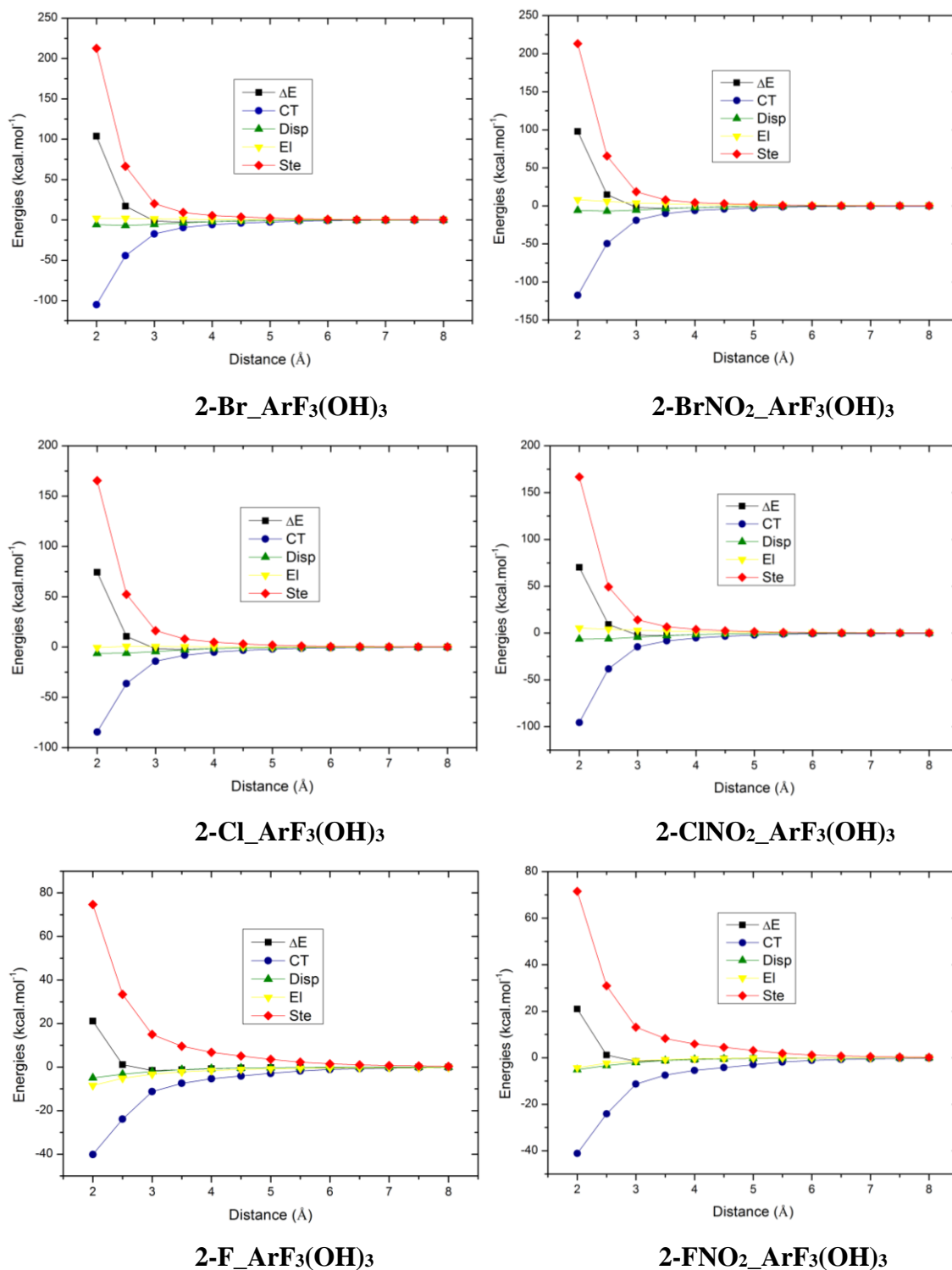


**Figure S9.** Energy decomposition analysis of substituted s-Triazine...NC<sub>2</sub>H<sub>3</sub> (2-XY\_NC<sub>2</sub>H<sub>3</sub>) interaction potential curve, when Y = NO<sub>2</sub> or NH<sub>2</sub>.



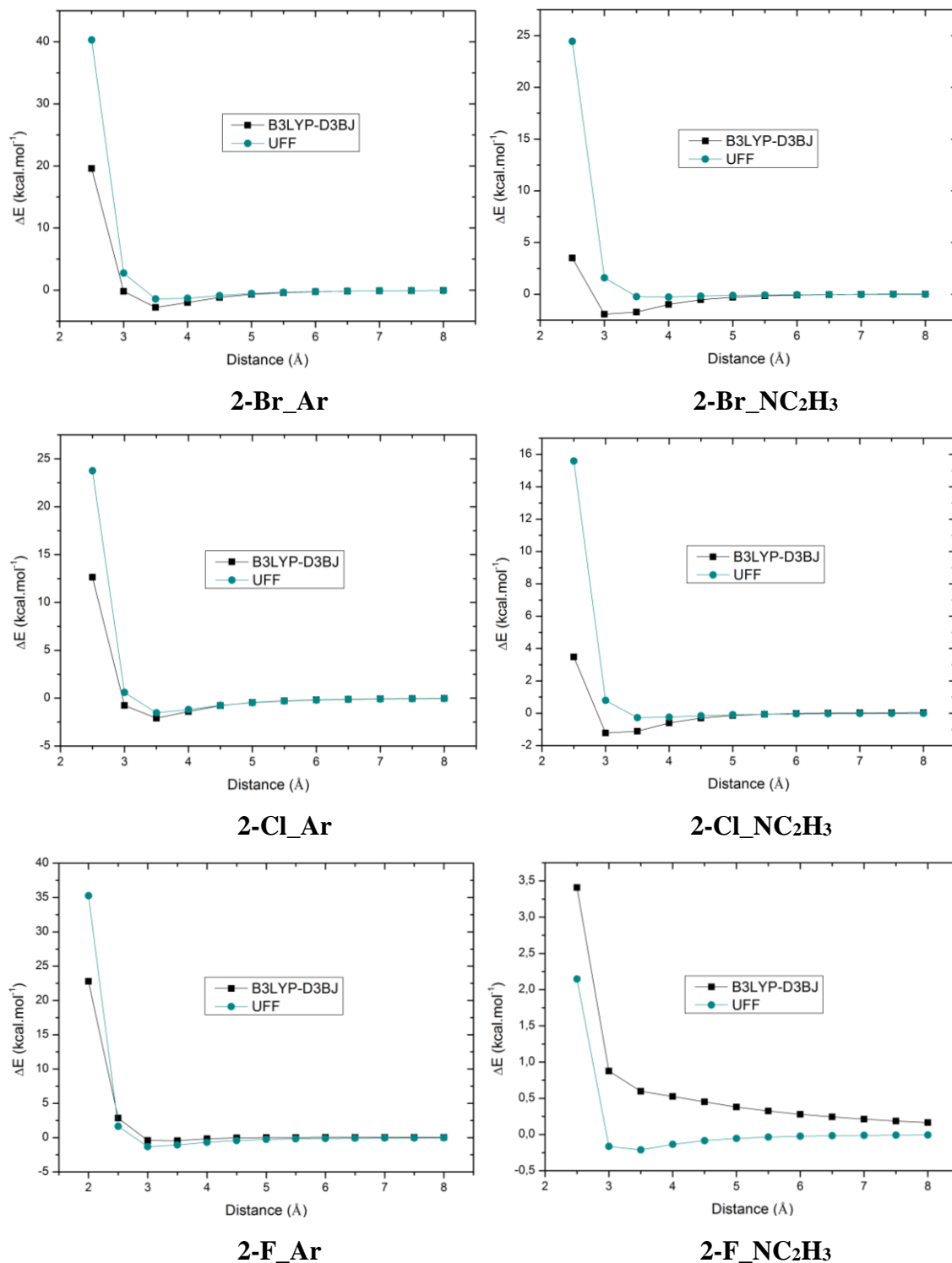
**Figure S10.** Energy decomposition analysis of substituted s-Triazine and substituted benzenes (2-XY\_Ar) interaction potential curve, when Y = H.



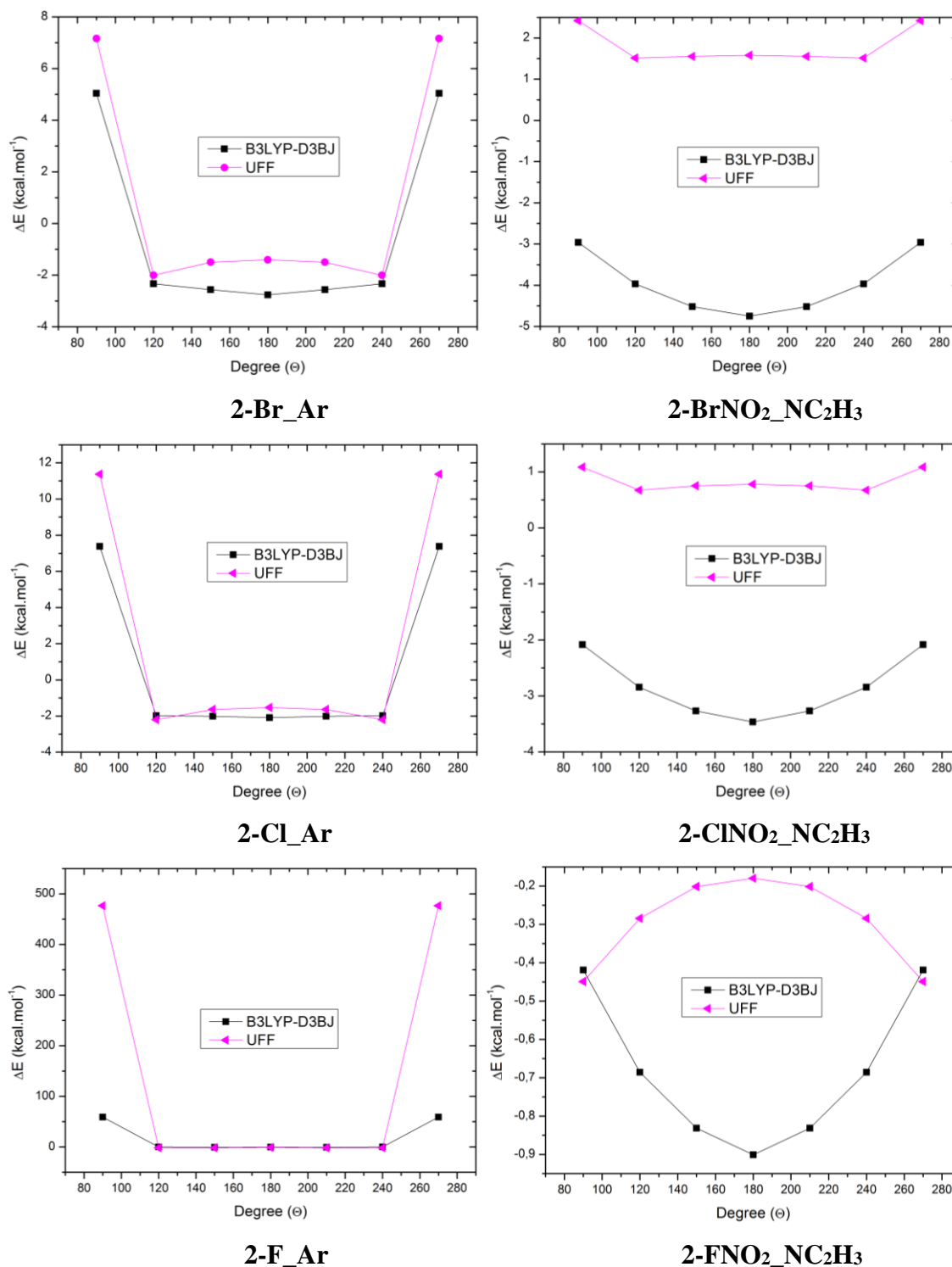


**Figure S11.** Energy decomposition analysis of substituted s-Triazine and substituted benzenes (2-XY\_Ar) interaction potential curve, when Y = H or NO<sub>2</sub>.

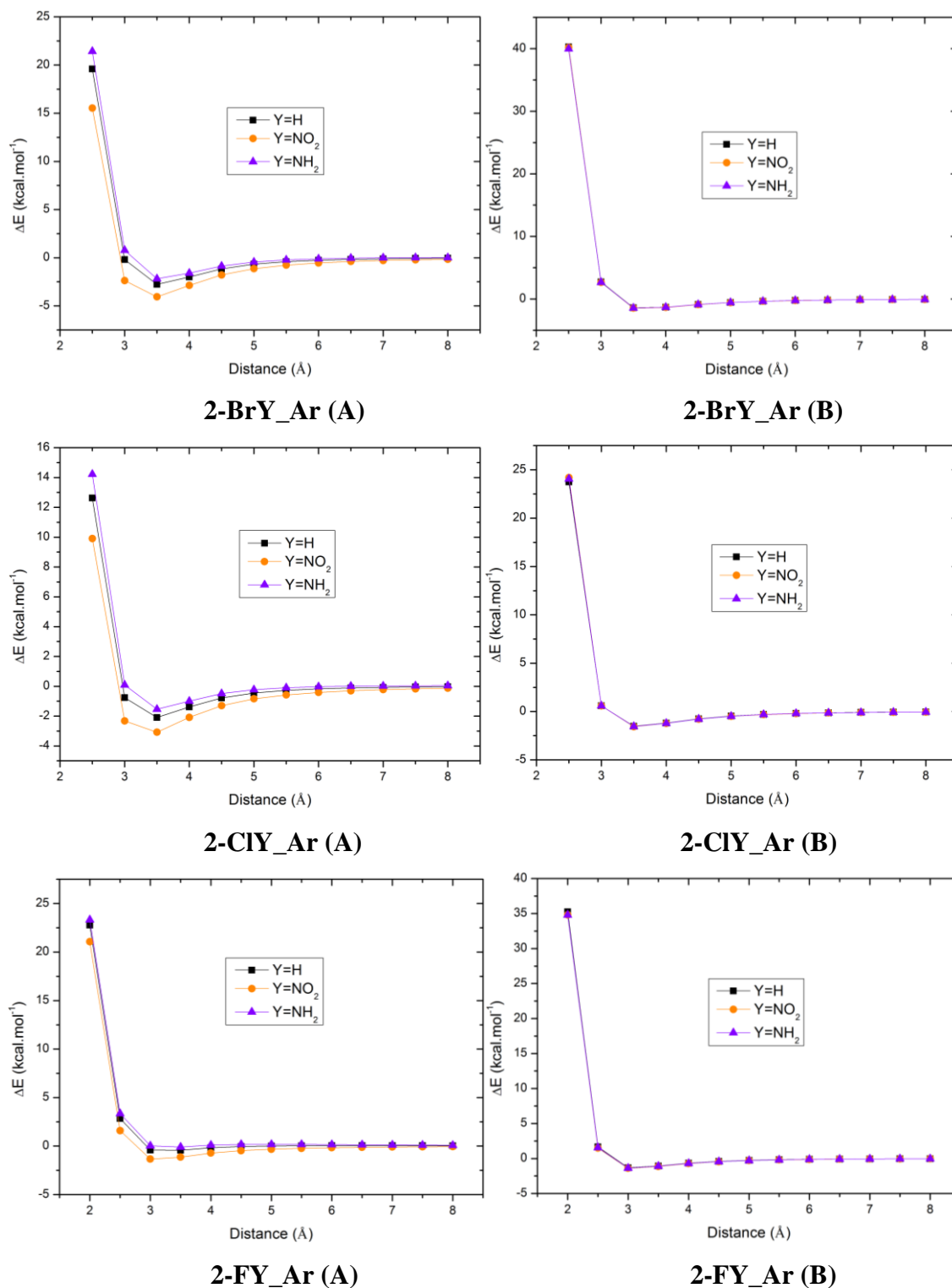
## 3. QM versus MM



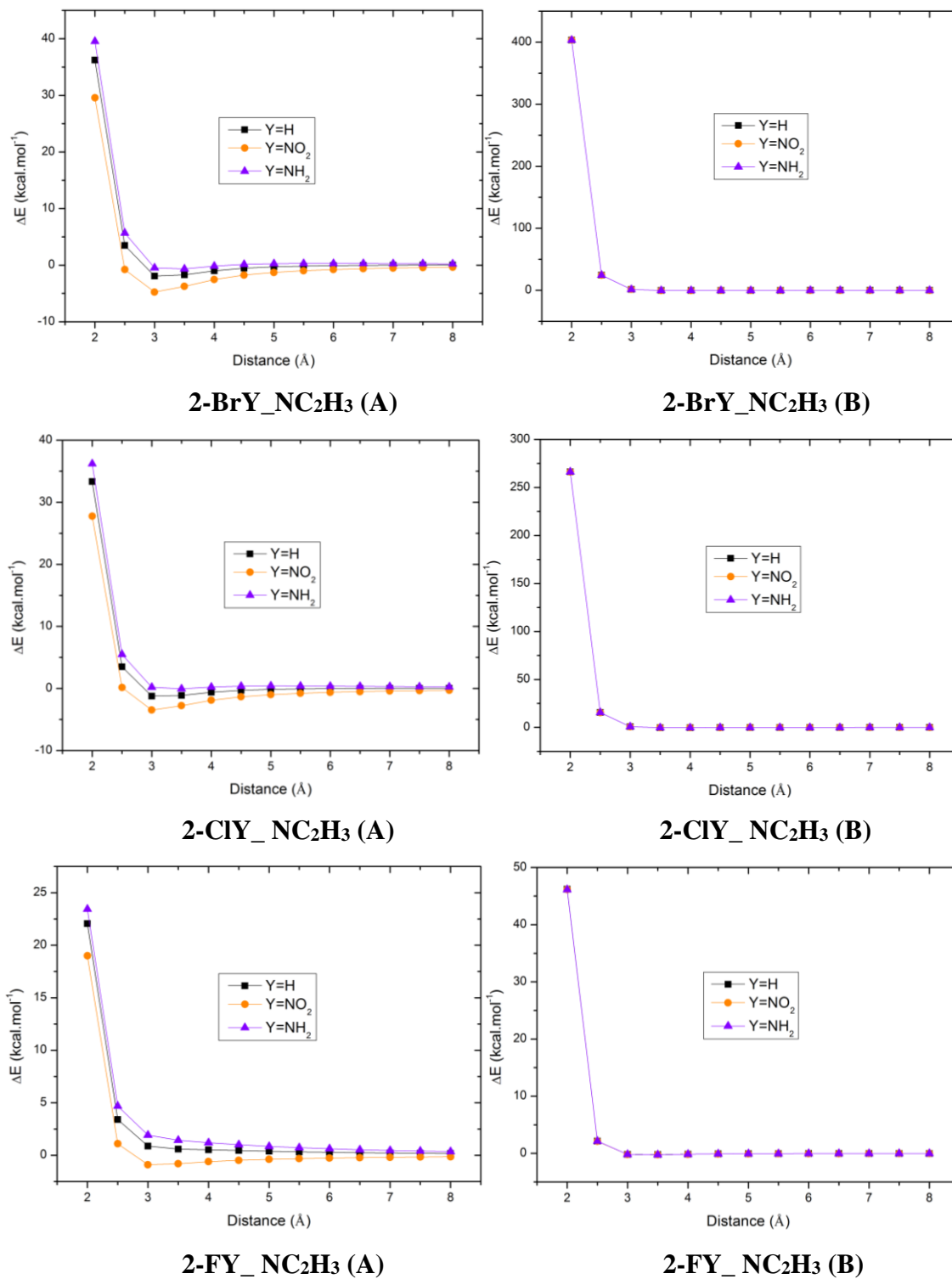
**Figure S12.** DFT-D3 versus UFF Potential Energy Curves of substituted s-Triazine...acceptor (2-XY\_Acceptor) interaction for  $\Theta = 180^\circ$ .



**Figure S13.** DFT-D3 versus UFF Potential Energy Curves of substituted s-Triazine...acceptor (2-XY\_Acceptor) interaction for  $r = r_e$  (see Table S7 and S8).



**Figure S14.** Potential Energy Curves of substituted *s*-Triazine...Benzene (2-XY\_Ar) interaction when Y = H, NO<sub>2</sub> or NH<sub>2</sub> and  $\Theta = 180^\circ$  at B3LYP-D3BJ/aug-cc-pVTZ (A) and UFF (B) levels.



**Figure S15.** Potential Energy Curves of substituted s-Triazine...NC<sub>2</sub>H<sub>3</sub> (2-XY\_NC<sub>2</sub>H<sub>3</sub>) interaction when Y = H, NO<sub>2</sub> or NH<sub>2</sub> and  $\Theta = 180^\circ$  at B3LYP-D3BJ/ug-cc-pVTZ (A) and UFF (B) levels.

#### 4. Towards a new empirical potential

**Table S9.** The new empirical potential parameters for Ar acceptor and  $\Theta = 180^\circ$ . Energies,  $\delta$  and  $\epsilon$  in kcal.mol<sup>-1</sup> and distances in Å.

| Dimer                   | $\delta$ | $\epsilon$ | $r_e$ UFF | $r_e$ DFT | $r_e$ Mod | $\Delta E_{UFF}$ | $\Delta E_{DFT}$ | $\Delta E_{LJ\ 12-6}$ | $\Delta E_{Mod}$ |
|-------------------------|----------|------------|-----------|-----------|-----------|------------------|------------------|-----------------------|------------------|
| 2-Br_Ar                 | 0.21394  | 1.96839    | 3.5       | 3.5       | 3.5       | -1.40            | -2.76            | -1.97                 | -1.96            |
| 2-BrNO <sub>2</sub> _Ar | 0.38405  | 2.42115    | 3.5       | 3.5       | 3.5       | -1.44            | -4.05            | -2.42                 | -2.65            |
| 2-BrNH <sub>2</sub> _Ar | 0.10385  | 1.76233    | 3.5       | 3.5       | 3.5       | -1.42            | -2.17            | -1.76                 | -1.63            |
| 2-Cl_Ar                 | 0.16932  | 1.78550    | 3.5       | 3.5       | 3.5       | -1.53            | -2.09            | -1.78                 | -1.72            |
| 2-ClNO <sub>2</sub> _Ar | 0.34688  | 2.19633    | 3.5       | 3.5       | 3.5       | -1.56            | -3.08            | -2.19                 | -2.36            |
| 2-ClNH <sub>2</sub> _Ar | 0.06345  | 1.54513    | 3.5       | 3.5       | 3.5       | -1.55            | -1.54            | -1.55                 | -1.38            |
| 2-F_Ar                  | -0.14098 | 0.57324    | 3.0       | 3.5       | 3.0       | -1.32            | -0.43            | -0.57                 | -0.38            |
| 2-FNO <sub>2</sub> _Ar  | 0.15242  | 1.37052    | 3.0       | 3.0       | 3.0       | -1.40            | -1.34            | -1.37                 | -1.27            |
| 2-FNH <sub>2</sub> _Ar  | -0.30420 | 0.35639    | 3.0       | 3.5       | 3.25      | -1.37            | -0.93            | -0.36                 | -0.19            |

**Table S10. The new empirical potential parameters for NC<sub>2</sub>H<sub>3</sub> acceptor and  $\Theta = 180^\circ$ . Energies,  $\delta$  and  $\varepsilon$  in kcal.mol<sup>-1</sup> and distances in Å.**

| Dimer   | $\delta$ | $\varepsilon$ | $r_{e\text{UFF}}$ | $r_{e\text{DFT}}$ | $r_{e\text{Mod}}$ | $\Delta E_{\text{UFF}}$ | $\Delta E_{\text{DFT}}$ | $\Delta E_{\text{LJ 12-6}}$ | $\Delta E_{\text{Mod}}$ |
|---|----------|---------------|-------------------|-------------------|-------------------|-------------------------|-------------------------|-----------------------------|-------------------------|
| 2-Br_NC <sub>2</sub> H <sub>3</sub>                 | 1.23742  | 0.74280       | 3.75              | 3.0               | 3.0               | -0.29                   | -1.92                   | -0.74                       | -1.80                   |
| 2-BrNO <sub>2</sub> _NC <sub>2</sub> H <sub>3</sub> | 2.15009  | 1.18254       | 3.75              | 3.0               | 2.75              | -0.29                   | -4.75                   | -1.18                       | -5.81                   |
| 2-BrNH <sub>2</sub> _NC <sub>2</sub> H <sub>3</sub> | 0.64871  | 0.43428       | 3.75              | 3.5               | 3.25              | -0.29                   | -0.65                   | -0.43                       | -0.65                   |
| 2-Cl_NC <sub>2</sub> H <sub>3</sub>                 | 1.05770  | 0.58386       | 3.75              | 3.0               | 3.25              | -0.28                   | -1.22                   | -0.64                       | -1.25                   |
| 2-ClNO <sub>2</sub> _NC <sub>2</sub> H <sub>3</sub> | 1.34688  | 0.99549       | 3.75              | 3.0               | 2.75              | -0.29                   | -3.47                   | -0.99                       | -5.19                   |
| 2-ClNH <sub>2</sub> _NC <sub>2</sub> H <sub>3</sub> | 0.06345  | 0.10182       | 3.75              | 3.5               | 3.5               | -0.28                   | -0.37                   | -0.10                       | -0.13                   |
| 2-F_NC <sub>2</sub> H <sub>3</sub>                  | -0.81542 | 0.37258       | 3.25              | -                 | 3.75              | -0.23                   | -                       | -0.37                       | -0.12                   |
| 2-FNO <sub>2</sub> _NC <sub>2</sub> H <sub>3</sub>  | 0.95215  | 0.46929       | 3.25              | 3.0               | 2.75              | -0.24                   | -0.90                   | -0.47                       | -1.04                   |
| 2-FNH <sub>2</sub> _NC <sub>2</sub> H <sub>3</sub>  | -1.90031 | 0.35639       | 3.25              | -                 | 4.5               | -0.24                   | -                       | -0.36                       | -0.04                   |

The new potential deduction has started from LJ 10-6 potential (S1) without  $\varepsilon$ , named  $E_{st}$ .

$$E_{LJ\ 10-6} = \varepsilon \left\{ \left( \frac{r_e}{r} \right)^{10} - 2 \left( \frac{r_e}{r} \right)^6 \right\} \quad (\text{S1})$$

$$E_{st} = \left\{ \left( \frac{r_e}{r} \right)^{10} - 2 \left( \frac{r_e}{r} \right)^6 \right\} \quad (\text{S2})$$

The  $E_{st}$  potential, as well as LJ 10-6, is divided in two parts: the repulsive (S3) and the attractive functions (S4).

$$E_{rep} = \left( \frac{r_e}{r} \right)^{10} \quad (\text{S3})$$

$$E_{att} = -2 \left( \frac{r_e}{r} \right)^6 \quad (\text{S4})$$

In accordance to our findings, the corrections should be applied in order to decrease the low range energies. In other words, reduce the repulsion. The modified repulsion function,  $E_{mod-rep}$ , modifies the repulsion energy in function of  $\delta$  and  $\Theta$ .

$$E_{mod-rep} = \left( \frac{r_e + \delta \cos \Theta / 6}{r} \right)^{10} \quad (S6)$$

$$\delta = \frac{\beta V_{max}}{4\pi\alpha^3} \quad (S7)$$

In (S6),  $\Theta$  is the interaction angle and  $\delta$  is a quantum parameter in function of  $V_{max}$  and the halogen van der Waals radii ( $\alpha$ ) (S7).  $\beta$  is an empirical constant depending on the halogen bond acceptor,  $\beta = 2.5$  for lone pair acceptors and  $\beta = 0.432$  for aromatic acceptors. It is worth noticing that (S6) becomes equivalent to (S3) when  $\Theta = 90^\circ$ . The units of  $V_{max}$  and  $\alpha$  are *hartree* ( $E_h$ ) and *nm*, respectively.

The modifications on (S3) have turned  $E_{st}$  into a dysfunctional potential, thus it must be repaired modifying (S4) as well.

$$\gamma = \left[ \frac{2^{2-\delta}(1-\delta)}{25r} \right]$$

$$E_{mod-att} = -2 \left( \frac{r_e}{r + \gamma} \right)^6 \quad (S8)$$

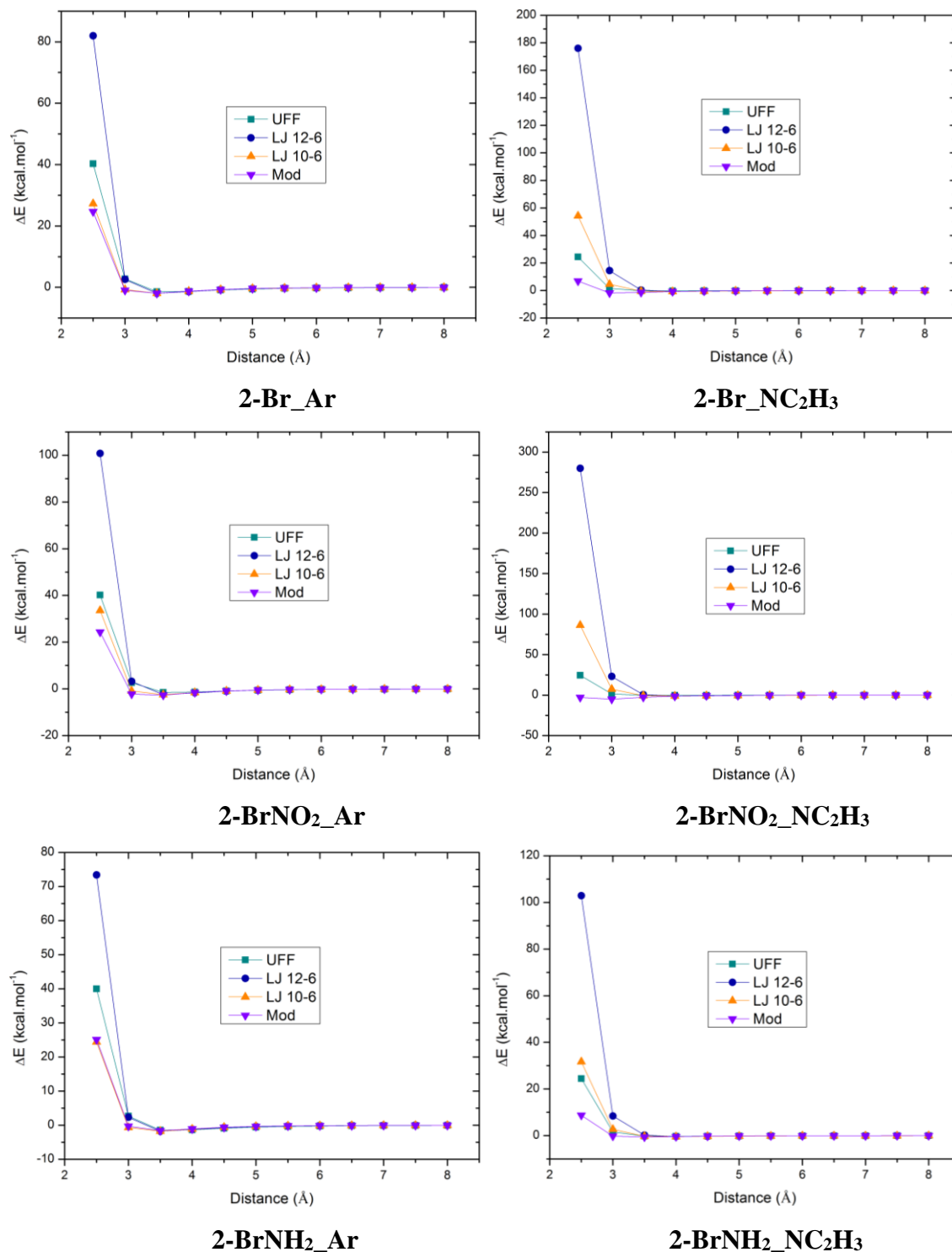
The adjustment on (S4) was carried out introducing another empirical parameter,  $\gamma$ .

The sum of modified functions (S6) and (S8) yields (S9).  $E_{mod}$  is a new potential designed to describe general halogen bonds with aromatic and lone pair acceptors. To plot  $E_{mod}$ , the energy parameter ( $\varepsilon$ ) was obtained by (S10), where  $\Delta E$  is the interaction energy at  $r_e$ . For the systems where DFT did not show a potential depth, was considered  $\Delta E_{UFF} = \Delta E_{DFT}$ .

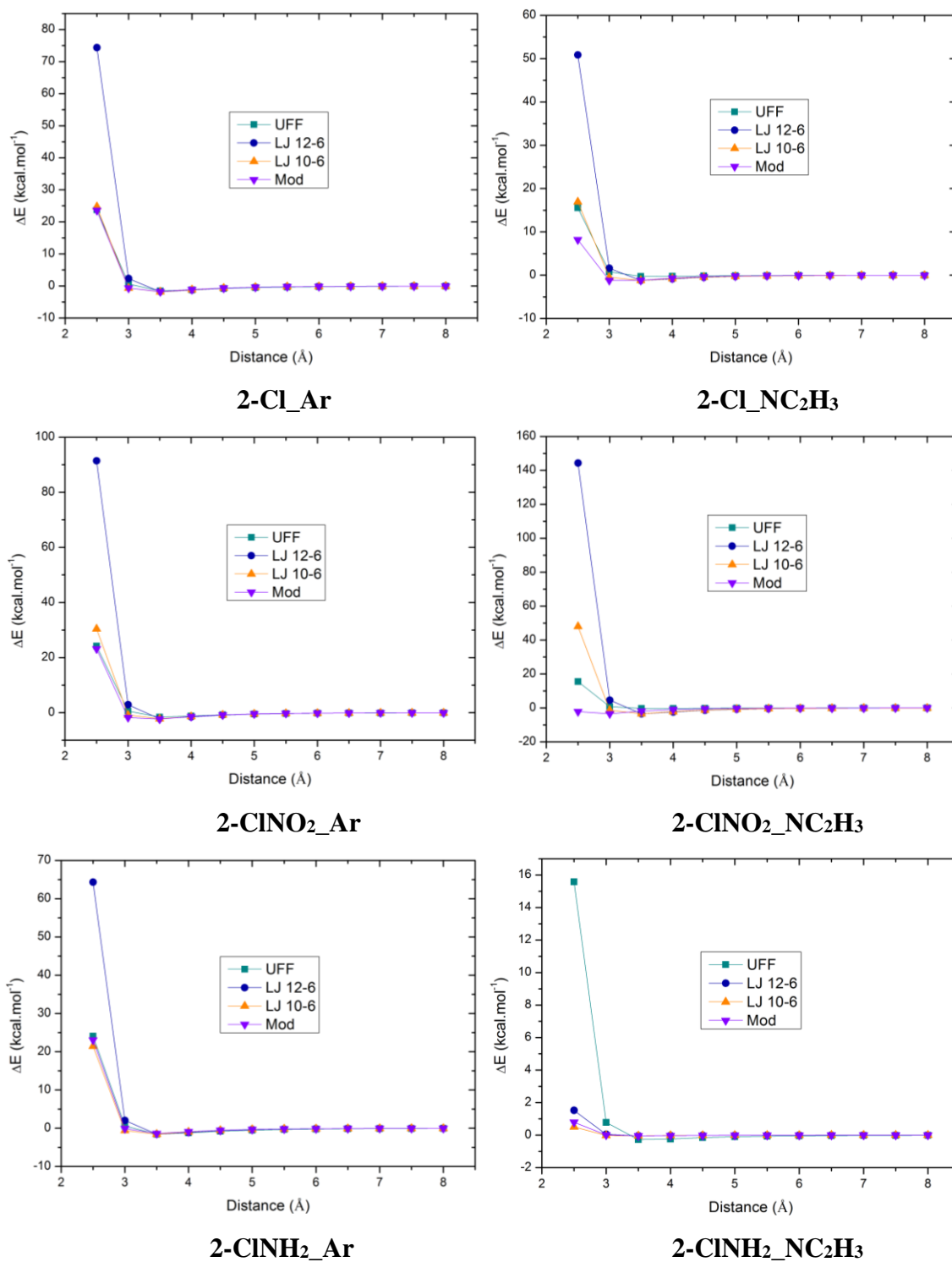
$$E_{mod} = \varepsilon \left\{ \left( \frac{r_e + \delta \cos \Theta / 6}{r} \right)^{10} - 2 \left( \frac{r_e}{r + \gamma} \right)^6 \right\} \quad (S9)$$

$$\varepsilon = \sqrt{\Delta E_{DFT} \cdot \Delta E_{UFF}} \quad (S10)$$

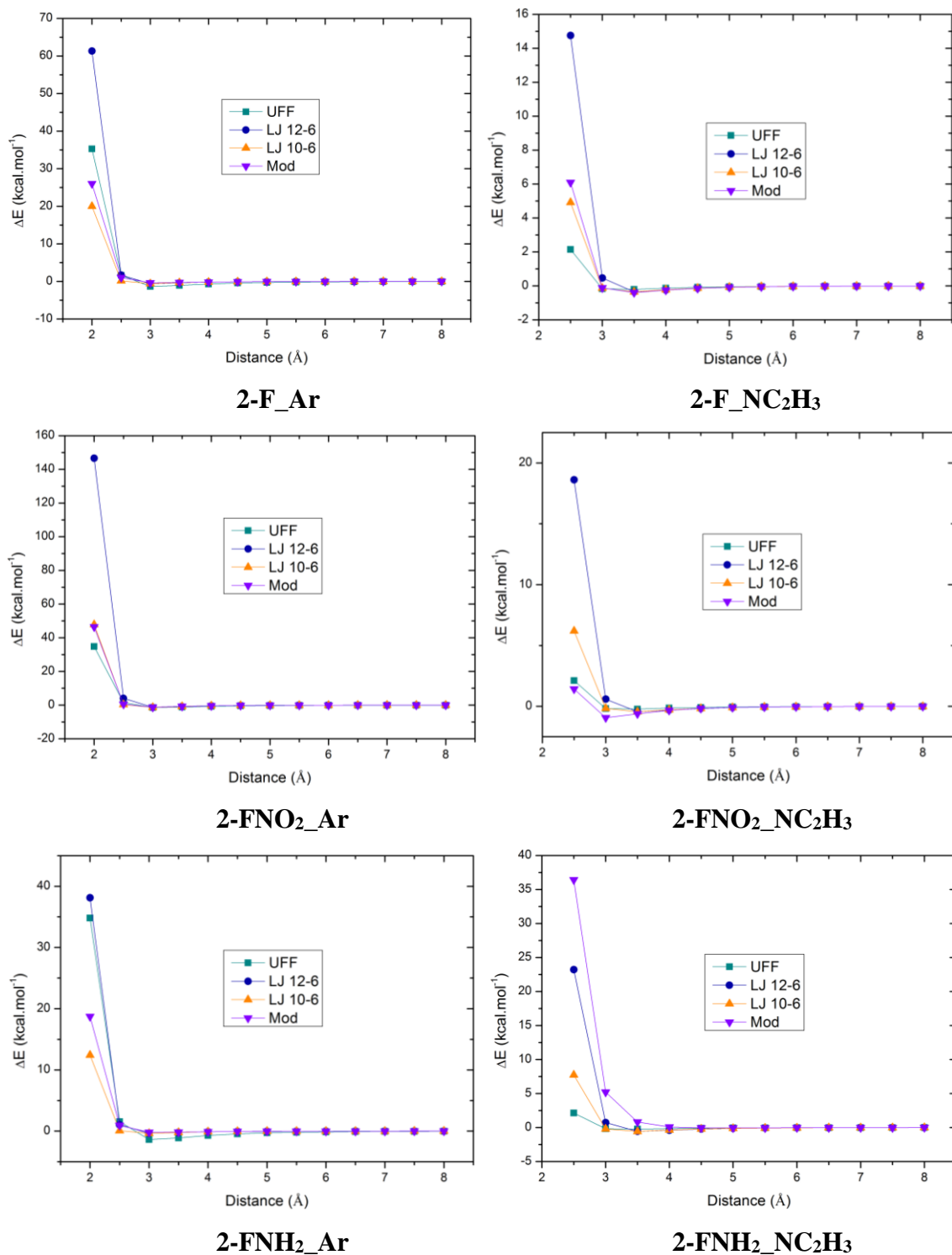




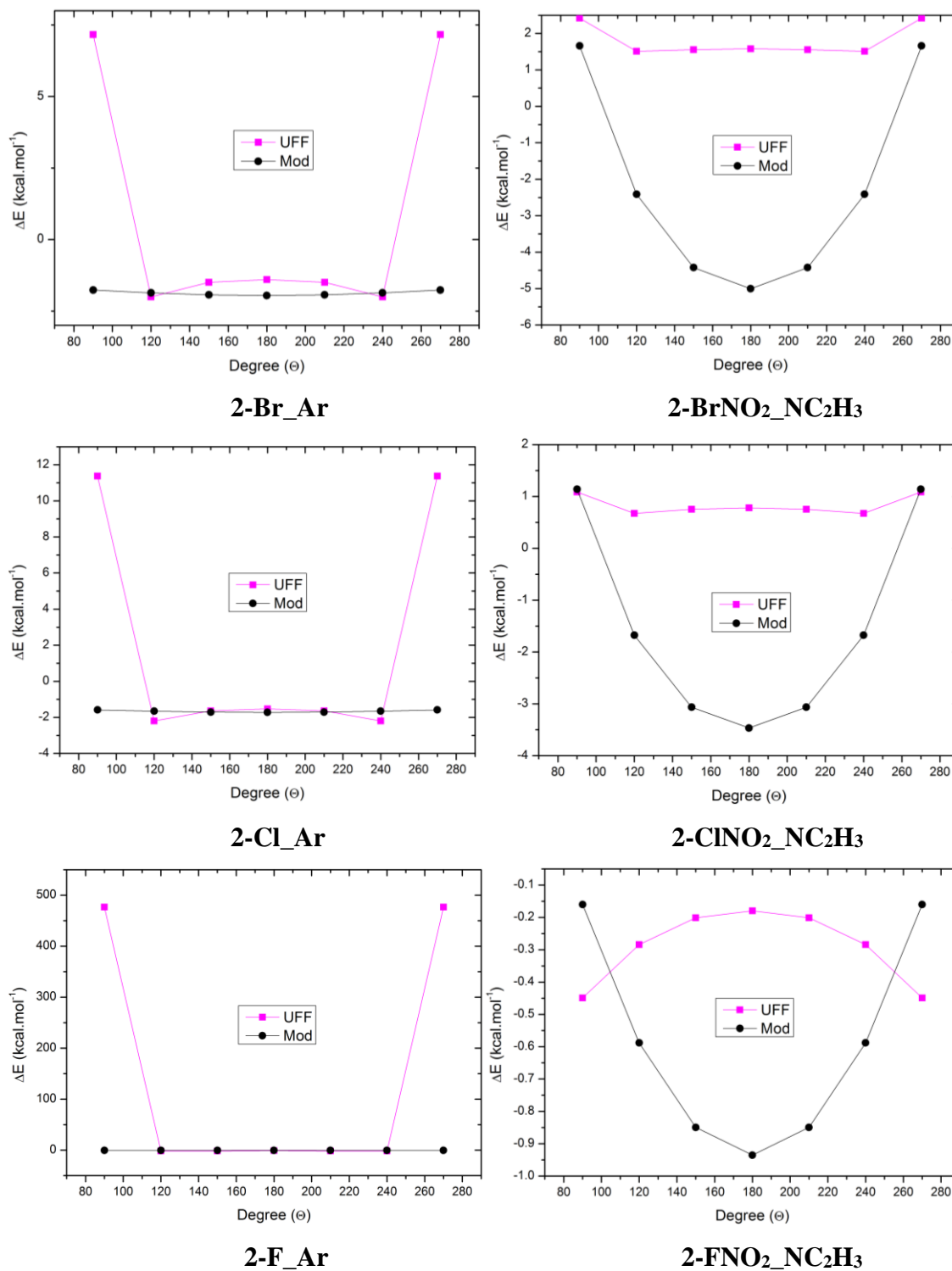
**Figure S16.** Potential Energy Curves of 2-BrY dimers when Y = H, NO<sub>2</sub> or NH<sub>2</sub> and  $\Theta = 180^\circ$  plotted by Lennard Jones potentials,  $E_{mod}$  and UFF.



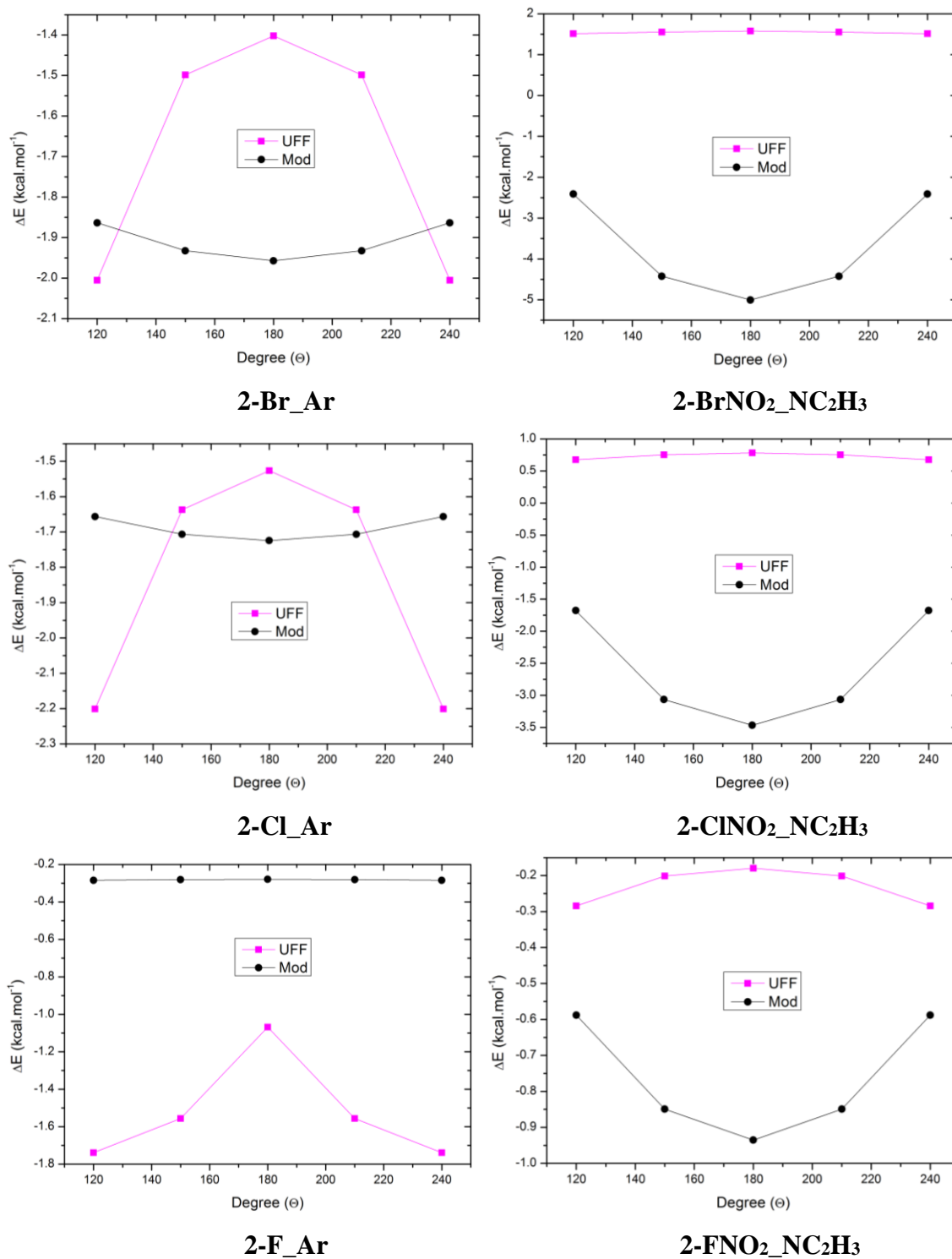
**Figure S17.** Potential Energy Curves of 2-CIY dimers when Y = H, NO<sub>2</sub> or NH<sub>2</sub> and  $\Theta = 180^\circ$  plotted by Lennard Jones potentials,  $E_{mod}$  and UFF.



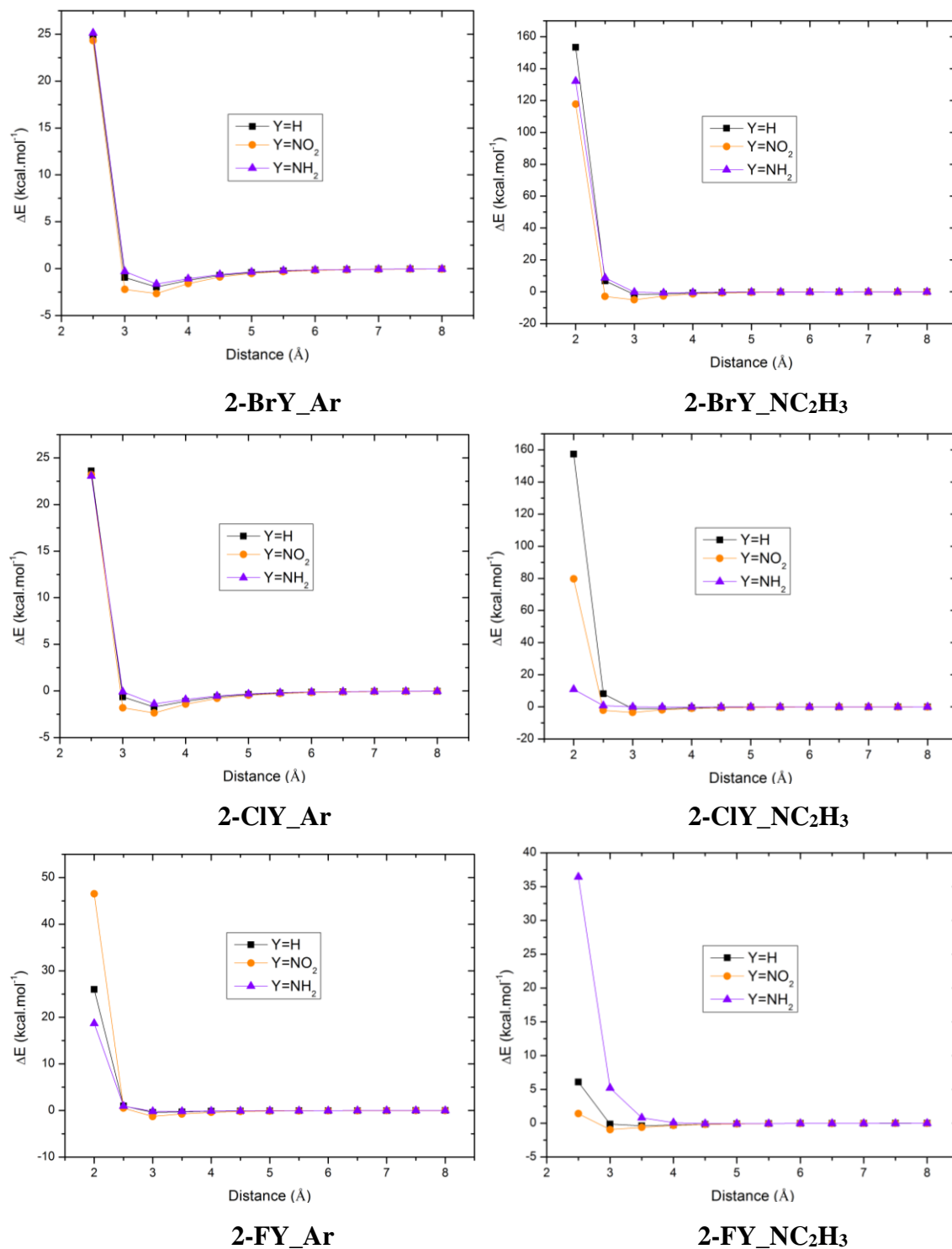
**Figure S18.** Potential Energy Curves of 2-FY dimers when Y = H, NO<sub>2</sub> or NH<sub>2</sub> and  $\Theta = 180^\circ$  plotted by Lennard Jones potentials,  $E_{mod}$  and UFF.



**Figure S19.** Potential Energy Curves of 2-XY dimers through  $\Theta$  when  $Y = \text{H}$  or  $\text{NO}_2$  and  $r = r_e$  (see Table S10 and S11) plotted by  $E_{mod}$  and UFF.



**Figure S20.** Potential Energy Curves of 2-XY dimers through  $\Theta$  inside the range of  $120^\circ$  to  $240^\circ$  when  $Y = \text{H}$  or  $\text{NO}_2$  and  $r = r_e$  (see Table S10 and S11) plotted by  $E_{mod}$  and UFF.



**Figure S21.** Potential Energy Curves of substituted s-Triazine...acceptor (2-XY\_Acceptor) interaction when Y = H, NO<sub>2</sub> or NH<sub>2</sub> and  $\Theta = 180^\circ$  plotted by  $E_{mod}$ .