

**AVALIAÇÃO TEÓRICA E EXPERIMENTAL  
DAS INTERAÇÕES INTRA E  
INTERMOLECULARES NO ISOMERISMO  
CONFORMACIONAL DE 2-  
HALOCICLOEXANONAS**

**JAKELYNE VIANA COELHO**

**2010**

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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 Agroquímica e Agrobioquímica, para a obtenção do título de Mestre.

Orientador  
Prof. Dr. Matheus Puggina de Freitas

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APROVADA em 25 de fevereiro de 2010

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## DEDICATÓRIA

*A Deus.*

*Aos meus amados pais e irmãos.*

*Ao meu querido Cris.*

*Ao meu orientador, Matheus Puggina de Freitas.*

*Aos grandes amigos de Lavras, ofereço.*

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## LISTA DE ABREVIATURAS E SÍMBOLOS

BC	2-bromocicloexanona/ 2-bromocyclohexanone
B3LYP	método DFT de Becke, usando correlação de Lee, Yan e Parr
CIC	chlorocyclohexanone
DFT	teoria funcional de densidade
DSO	diamagnetic spin orbit
FC	fluorocyclohexanone Fermi Contact
HF	Hartree-Fock
IC	iodocyclohexanone
LP	lone pair
MP2	correlação eletrônica de Möller-Plesset de segunda ordem
NBO	natural bond orbital
NBODEL	natural bond orbital deletion
NMR	nuclear magnetic resonance
PSO	paramagnetic spin orbit
RMN	ressonância magnética nuclear
SD	spin dipolar
XC	halocyclohexanones
$J$	constante de acoplamento/coupling constant
$\delta$	deslocamento químico

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## RESUMO GERAL

COELHO, Jakelyne Viana. **Avaliação experimental e teórica das interações intra e intermoleculares no isomerismo conformacional de 2-halocicloexanonas**. 2010. 57p. Dissertação (Mestrado em Agroquímica) - Universidade Federal de Lavras, Lavras, MG\*.

As preferências conformacionais de 2-halocicloexanonas foram investigadas com sucesso, no passado. No entanto, em virtude dos recursos e conhecimento disponíveis na época, os fatores que governam esses interessantes sistemas modelo não puderam ser precisamente determinados. Atualmente, dispõem-se de ferramentas computacionais e novas tendências fenomenológicas capazes de explicar o comportamento conformacional de uma série de compostos. As 2-halocicloexanonas são sistemas carbonílicos  $\alpha$ -substituídos úteis para racionalizar interações intra e intermoleculares, isto é, possuem características que permitem confrontar efeitos clássicos (interações estéricas e eletrostáticas) e orbitales (hiperconjugação), o que tem mostrado ser o estado da arte em físico-química orgânica. Portanto, entender os fatores que regem os equilíbrios conformacionais desses compostos foram o alvo do nosso estudo. No primeiro estudo, utilizando análises natural bond orbital (NBO), por meio de reações isodésmicas, comprovou-se que a introdução de um átomo de halogênio em posição *alfa* na cicloexanona favorece a forma *axial*, em relação à cicloexanona não substituída. Por outro lado, as interações no confôrmero *equatorial* são predominantemente repulsivas. Em outro estudo, uma evidência experimental da existência de interações orbitales foi observada. O grupo carbonila da 2-bromocicloexanona (BC) mostrou ter um importante papel na transmissão de informação de *spin* nuclear ao longo da rota de acoplamento. O último trabalho visou explicar o comportamento espectroscópico (infravermelho) da BC na fase vapor, que difere do esperado para o estado isolado. Cálculos de dímeros foram realizados, sugerindo a ocorrência de autoassociação. Observou-se que a autoassociação se deve às interações dipolo-dipolo, essencialmente devido à polaridade das ligações C-Br e, principalmente, C=O. Portanto, essas interações devem ser levadas em consideração, juntamente com efeitos estéricos e hiperconjugativos, quando se analisam os equilíbrios conformacionais da 2-bromocicloexanona e de sistemas semelhantes, mesmo na fase vapor.

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\* Comitê Orientador: Matheus Puggina de Freitas – UFLA (Orientador); Teodorico de Castro Ramalho – UFLA

## GENERAL ABSTRACT

COELHO, Jakelyne Viana. **Theoretical and experimental evaluation of intra and intermolecular interactions in the conformational isomerism of 2-halocyclohexanones**. 2010. 57p. Dissertation (Master in Agrochemistry) - Federal University of Lavras, Lavras, MG\*.

The conformational preferences of 2-halocyclohexanones (XC) were investigated successfully in the past. However, due to the resources and knowledge available at the time, the factors governing these interesting model systems could not be precisely determined. Currently, there are computational tools and new phenomenological trends capable of explaining the conformational behavior of a series of compounds. The XC are  $\alpha$ -substituted carbonyl compounds useful to rationalize intra and intermolecular interactions, *i.e.*, they have features that allow confronting classical (steric and electrostatic interactions) and orbital (hyperconjugation) effects, which have shown to be the state of the art in physical organic chemistry; therefore, the goal of this study was to understand the factors governing the conformational equilibria of these compounds. In the first study, using NBO (Natural Bond Orbital) analysis and isodesmic reactions, it was shown that the introduction of an *axial* 2-position halogen atom in cyclohexanone is more favored, in relation to the cyclohexanone itself, when compared to the *equatorial* entrance. Moreover, the interactions in the equatorial conformer are predominantly repulsive. In another study, an experimental evidence of the existence of orbital interactions was observed. The carbonyl group of 2-bromocyclohexanone (BC) was shown to play an important role in the transmission of spin information along the coupling pathway. The last work aimed at explaining the spectroscopic (infrared) behavior of the BC spectrum in the vapor phase, which differs from that expected for the isolated state. Calculations for dimeric structures were performed, suggesting the occurrence of self-association. It was observed that self-association is due to dipole-dipole interactions, mainly due to the polarity of bonds C-Br and, especially, C=O bond. Therefore, these interactions should be taken into account, together with steric and hyperconjugative effects, when analyzing the conformational equilibria of BC and similar systems, even in the vapor phase.

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\* Guidance Committee: Matheus Puggina de Freitas – UFLA (Adviser); Teodorico de Castro Ramalho – UFLA

## **CAPÍTULO 1**

### **INTRODUÇÃO GERAL E REFERENCIAL TEÓRICO**

## 1 INTRODUÇÃO GERAL

As preferências conformacionais das 2-halocicloexanonas (XC), cujas dinâmicas oscilam entre as formas *axial* e *equatorial* (Figura 1), foram investigadas com sucesso no passado, especialmente para o composto em solução (Freitas et al., 2001; Yoshinaga et al., 2002). No entanto, em virtude dos recursos e do conhecimento disponíveis na época, os fatores que governam esse interessante sistema modelo não puderam ser precisamente determinados.

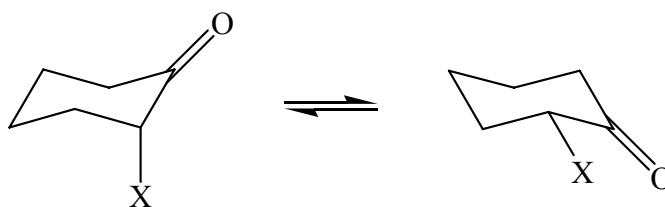


FIGURA 1 Equilíbrio conformacional das 2-halocicloexanonas.

Compostos carbonílicos  $\alpha$ -substituídos são interessantes sistemas para racionalizar os efeitos governantes em equilíbrios conformacionais de moléculas mais complexas, uma vez que o grupo C=O possui uma característica singular, já que pode atuar como doador ou receptor de elétrons, interagindo com eletrófilos e nucleófilos, respectivamente (Rauk, 2001).

As XC são modelos úteis para investigar os efeitos intra e intermoleculares operantes em sistemas carbonílicos. Primeiro, por conterem grupos eletronegativos e volumosos. Dessa forma, efeitos estéricos e interações coulômbicas podem ser avaliados. Essas características também determinam o comportamento conformacional das moléculas em solução quando se varia a polaridade do solvente. Segundo, por conterem grupos doadores (elétrons livres



e orbitais ligantes de alta energia) e aceptores (principalmente o sistema  $\pi$ ) de elétrons, o que tem demonstrado ser significativamente importante em equilíbrios conformacionais de cetonas  $\alpha$ -substituídas (Kallies et al., 1997; Coelho et al., 2008). Este é um efeito intrínseco de cada conformação e, portanto, aproximadamente independente do meio de solvatação. Dessa forma, as XC emergem como sistemas modelo úteis para se racionalizar os fatores operantes em equilíbrios conformacionais, uma vez que apresentam sítios importantes que conduzem a interações estéricas, eletrostáticas e orbitales, invariavelmente presentes e particularmente importantes em síntese orgânica e bioquímica (no estudo de interações enzima-substrato, por exemplo).

Os próximos três capítulos desta dissertação são referentes às três frentes de estudo que seguimos.

No primeiro capítulo, reações isodésmicas foram propostas para avaliar o papel das interações hiperconjugativas no equilíbrio conformacional das XC. Estas foram aplicadas para avaliar em qual confôrmero (*axial* ou *equatorial*) as interações hiperconjugativas predominavam. Para isso, análises NBO (Natural Bond Orbital) foram aplicadas, com ênfase nas interações de maior interesse  $LP_X \rightarrow \pi^*_{CO}$ ,  $\sigma_{CX} \rightarrow \pi^*_{CO}$ ,  $\sigma_{C-H} \rightarrow \pi^*_{CO}$ .

Nos dois capítulos seguintes, a 2-bromocicloexanona foi o composto escolhido para os estudos experimentais. Esta escolha se justifica pelo fato de a mesma ser de fácil manuseio e apresentar uma rota de síntese bastante conhecida e de simples execução (Yoshinaga et al., 2002).

No segundo capítulo, fez-se o uso de espectroscopia de ressonância magnética nuclear (RMN), juntamente com cálculos teóricos. Neste estudo, por meio das constantes de acoplamento, buscou-se uma evidência experimental da existência de interações hiperconjugativas existentes na BC. O grupo carbonila demonstrou grande influência na transmissão do acoplamento *spin-spin* a longa

distância  ${}^4J_{\text{HH}}$ , fornecendo informações conclusivas sobre interações intramoleculares operantes nas XC.

O último capítulo visou compreender o comportamento anômalo da BC na fase vapor. Cálculos de possíveis estruturas diméricas foram realizados, sugerindo a existência de autoassociação na fase vapor e, provavelmente, também em soluções apolares.

Dessa forma, este trabalho visa contribuir para a compreensão dos efeitos que regem o equilíbrio conformacional das XC e ressaltar a importância das interações hiperconjugativas, juntamente com os efeitos clássicos, em estudos de equilíbrios conformacionais.

## 2 REFERENCIAL TEÓRICO

### 2.1 Análise conformacional e cálculos teóricos

As diferentes geometrias que as moléculas podem adotar no espaço, por meio da rotação de ligações simples, são chamadas de conformações. A maioria das conformações é instável, pois não está localizada nos mínimos de energia. Conformações estáveis são chamadas de confôrmeros ou rotâmeros que, geralmente, não podem ser isolados devido à pequena barreira de energia que os separa.

A existência de diferentes conformações foi inicialmente sugerida para a molécula de cicloexano, em 1890, por Sachse, que reconheceu a existência de dois tipos de ligações: *axiais e equatoriais* (Sachse, 1890). Desde então, ele é considerado o fundador da análise conformacional. Atualmente, sabe-se que as rotações nas ligações carbono-carbono do cicloexano podem formar dois confôrmeros distintos, sendo a forma cadeira  $5 \text{ kcal mol}^{-1}$  mais estável que a forma barco (Eliel et al., 1994). Alguns estudos se seguiram (Eliel & Martin, 1968; Eliel et al., 1994) até a publicação do trabalho clássico de Barton sobre as conseqüências físicas e químicas da conformação cadeira nas propriedades de esteróides (Barton, 1950).

Graças às ideias de Barton, há várias décadas o tema análise conformacional se tornou parte da química, sendo essencial para compreender estereoquímica, mecanismos e reatividade, entre outros tópicos. O grande interesse está fortemente ligado ao fato de diferentes conformações afetarem as propriedades moleculares, ou seja, diferentes conformações apresentam propriedades físico-químicas distintas e são essas propriedades que possibilitam os estudos nesta área da química.

Dentro do contexto conformacional, o estudo de diversos compostos tem levado à proposição de diversos fatores que determinam/afetam o equilíbrio conformacional. Repulsões eletrostáticas, estéricas e, recentemente, interações hiperconjugativas têm sido utilizadas para esclarecer a estabilidade de muitos sistemas orgânicos, até mesmo os mais simples.

Repulsões eletrostáticas ocorrem quando dois grupos polares estão próximos na mesma molécula. Com isso, o mínimo de energia global fica afetado por repulsões dipolares, sendo, portanto, um importante fator a ser considerado em estudos de equilíbrios conformacionais.

As repulsões estéricas manifestam-se quando dois grupos são colocados a uma distância mais próxima que a soma dos seus raios de van der Waals, ocorrendo, assim, a sobreposição de nuvens eletrônicas e fortes interações entre os elétrons. Dessa forma, um determinado átomo tende a ficar o mais distante possível do outro para conferir maior estabilidade à molécula (Solomons & Fryhle, 2004).

Interações hiperconjugativas ou interações de orbitais são fenômenos de deslocalização eletrônica. São duas as possibilidades de maior interesse que podem afetar o equilíbrio conformacional: 1) interação entre um orbital cheio e um orbital vazio e 2) interação entre dois orbitais cheios. Na possibilidade 1, normalmente, ocorre uma estabilização, uma vez que a interação entre o orbital vazio e o orbital cheio possibilita a diminuição de energia no confôrmero. Na possibilidade 2 ocorre o contrário, isto é, gera-se uma desestabilização do confôrmero, devido à máxima sobreposição dos orbitais, forçando a molécula a adotar uma conformação que minimize esta interação.

As interações eletrônicas, além de influenciarem na estabilidade relativa dos confôrmeros, modificam a estrutura eletrônica da molécula, causando deslocamentos espectrais (deslocamentos químicos, frequências vibracionais),

variações em ângulos e distância de ligação, nucleofilicidade, basicidade, acidez e reatividade (Rodrigues, 2003).

O estudo sobre as preferências conformacionais vem abrangendo interesses de químicos e bioquímicos, principalmente sobre a reatividade e a estereoquímica de muitas reações e interações com sítios ativos. Se a porcentagem de cada conformação puder ser calculada, predições mais detalhadas sobre a reatividade e a estereoquímica poderão ser feitas (Smith, 1994). Na bioquímica, sua potencialidade é bastante elevada, como, por exemplo, no planejamento racional de fármacos e no comportamento conformacional de aminoácidos naturais, pois sua estrutura e mobilidade conformacional determinam a variedade e a especificidade funcional nas proteínas e polipeptídeos (Lesarri et al., 2002).

Para o estudo em análise conformacional, várias técnicas são empregadas. Dentre elas, pode-se destacar a ressonância magnética nuclear (RMN), as espectroscopias no infravermelho, microondas e fotoeletrônica, cada uma com suas peculiaridades, vantagens e desvantagens.

A RMN é uma das técnicas de maior destaque, uma vez que possibilita o estudo de moléculas em solução. Dessa forma, podem ser obtidas informações a respeito do comportamento de uma droga em um meio fisiológico. Pode-se também estudar as diferenças conformacionais adquiridas por uma molécula em diferentes meios (solventes) e, em alguns casos, a “família” de conformações adotadas por um dado sistema (Yu et al., 2006).

Paralelamente aos métodos experimentais, os cálculos teóricos vêm sendo cada vez mais aplicados na determinação do equilíbrio conformacional de uma série de moléculas, trazendo importantes informações a respeito das interações que governam esses equilíbrios (Freitas et al., 2002; Freitas et al., 2003). Muitas vezes, estes têm se tornado imprescindíveis na

complementaridade de resultados espectroscópicos, podendo prever geometrias, interações e preferências conformacionais de maneira mais exata. Na utilização desses cálculos, é extremamente importante a escolha correta do conjunto de funções de base para o resultado final, seja em termos de precisão ou de tempo de cálculo.

Duas áreas da química computacional são voltadas para o estudo de moléculas: a mecânica molecular, que utiliza leis da mecânica clássica para prever estruturas e propriedades de moléculas, e a estrutura eletrônica, que se baseia nas leis da mecânica quântica. O presente trabalho foi realizado utilizando cálculos baseados na estrutura eletrônica.

Os métodos da estrutura eletrônica subdividem-se em três classes: *ab initio*, semiempíricos e teoria do funcional de densidade (DFT).

Os métodos semiempíricos utilizam parâmetros derivados de dados experimentais para simplificar os cálculos. Os *ab initio* não utilizam nenhum parâmetro experimental, apenas os valores da velocidade da luz, massa, carga do elétron e dos núcleos e a constante de Planck (Foresman, 1993).

No caso de moléculas pequenas, os cálculos *ab initio* são os que têm sido mais utilizados e fornecem informações a respeito das diferenças de energia entre os conformeros mais estáveis, os momentos de dipolo e as geometrias de cada possível conformero no vácuo ou num meio de solvatação (Foresman, 1996; Frisch, 1998).

O método Hartree-Fock (HF) é o mais comum dentre os *ab initio*. Com ele, cada elétron é representado por uma função de onda que possui dependência apenas nas coordenadas daquele elétron. A probabilidade de encontrar um elétron em um dado ponto nas vizinhanças de um núcleo é determinada apenas pela posição em relação ao núcleo, mas não em relação aos outros elétrons. Dessa forma, a teoria HF é deficiente por não levar em consideração correlação

eletrônica, o que significa que HF leva em consideração o efeito médio da repulsão eletrônica, mas não a interação explícita elétron-elétron.

Para suprir essa limitação, outros métodos foram desenvolvidos, os quais incluem alguns efeitos de correlação eletrônica, como o método MP2 (teoria de perturbação de segunda ordem Möller-Plesset) (Möller, 1994), o qual contabiliza as interações instantâneas dos pares de elétrons com *spins* opostos e leva em consideração as interações individuais entre os elétrons. Porém, necessita de recursos computacionais mais sofisticados, pois seu cálculo é mais complexo e requer um maior tempo de máquina (Foresman, 1993).

Uma terceira classe de métodos da estrutura eletrônica, os métodos da teoria do funcional de densidade (DFT), tem sido amplamente empregada. Os métodos DFT são similares aos outros métodos *ab initio* em vários aspectos. Porém, usualmente, alcança melhor precisão do que a teoria HF com somente um modesto aumento de custo (tempo computacional), porém, menor do que o MP2. Os métodos DFT também incluem alguns dos efeitos de correlação eletrônica muito menos dispendiosos do que os métodos de correlação tradicionais. A proposta do DFT consiste em obter informações sobre um dado sistema a partir de sua densidade eletrônica. A energia de troca e correlação, presente no DFT, é definida como um funcional de densidade eletrônica e inclui todos os termos não-clássicos. A correlação eletrônica introduz o termo de troca referente à correlação entre elétrons de mesmo *spin* e a diferença entre a energia cinética exata e a do sistema de elétrons que não interagem. Esse funcional é que torna o DFT diferencial frente aos métodos *ab initio* (Duarte & Rocha, 2007).

Dentre os métodos DFT, o método B3LYP (método de Beck no qual está incluído o funcional de correlação desenvolvido por Lee, Yang e Parr) pode fornecer geometrias iguais ou melhores do que o método MP2, pois essa teoria

necessita de menos recursos computacionais e, portanto, conjuntos de bases mais sofisticados podem ser empregados (Foresman, 1993).

A estrutura eletrônica molecular pode ser analisada pela teoria NBO (Natural Bond Orbitals), que localiza os orbitais moleculares e os transforma em orbitais canônicos, orbitais de ligação e de pares isolados, ficando de acordo com a visão química proposta por Lewis. Ainda são encontrados os orbitais de Rydberg. A teoria NBO fornece ferramentas para analisar a transferência de cargas de orbitais ligantes para orbitais antiligantes, bem como as implicações energéticas associadas (Weinhold & Landis, 2001).

## 2.2 Equilíbrio conformacional de halocicloexanonas

Um dos primeiros estudos sobre equilíbrios conformacionais em halocicloexanonas (XC) é de autoria de Allinger & Allinger (1958), ressaltando a dificuldade na identificação de qual banda de estiramento C=O correspondia a qual confômero no espectro infravermelho, o que foi resolvido com a introdução de derivados *t*-butílicos como compostos de referência.

As dificuldades na análise conformacional de XC, entretanto, não se restringem apenas à atribuição das bandas correspondentes aos confômeros. Bervelt et al. (1968) identificaram a presença de uma terceira banda na região de estiramento C=O para a 2-clorocicloexanona, que foi atribuída à ressonância de Fermi entre os níveis correspondentes à frequência fundamental  $\nu_{\text{C=O}}$  e o primeiro *overtone* da deformação metilênica ou metínica adjacente ( $\delta_{\text{CH}_2}$  ou  $\delta_{\text{CH}}$  entre 850 e 900  $\text{cm}^{-1}$ ). Isso foi parcialmente solucionado por meio da deuteração seletiva da cicloexanona em questão, mas que resultou em alteração dos valores de número de onda e intensidade das bandas.

A quantificação dos confômeros utilizando espectroscopia no infravermelho é feita, geralmente, comparando-se as intensidades ou áreas das



bandas de cada um dos isômeros e o problema da sobreposição de bandas vem sendo resolvido computacionalmente, por meio da deconvolução analítica das mesmas (Freitas et al., 2001; Olivato et al., 1998). Contudo, além do problema da sobreposição de bandas, a principal aproximação que vem sendo efetuada em estudos por infravermelho é a consideração de que a banda de carbonila apresenta o mesmo valor de absorvidade molar para os dois confôrmeros e de que este valor não se altera com a mudança de solvente. Essa aproximação tem demonstrado ser equivocada (Freitas et al., 2003).

Na década de 1960, Garbisch (1964) utilizou, pela primeira vez, a espectroscopia de RMN no estudo de equilíbrios conformacionais de XC, abrindo as portas para outros estudos (Chen & Frève, 1965; Pan & Stothers, 1967). Na década seguinte, surgiram trabalhos mais elaborados, tanto em termos de metodologia quanto na interpretação dos resultados (Eisenstein et al., 1974; Metras et al., 1975; Metzger et al., 1980).

A metodologia utilizada em RMN baseia-se no estudo das constantes de acoplamento ( $J$ ) ou deslocamento químico ( $\delta$ ) do  $\alpha$ -hidrogênio, utilizando derivados rígidos como compostos de referência (Basso et al., 1993) ou a teoria de solvatação desenvolvida por Abraham e Bretschneider (1974), para avaliar o comportamento de  $J$  e, conseqüentemente, do equilíbrio conformacional, com a variação do solvente ou temperatura (Freitas et al., 2001; Yoshinaga et al., 2002). Na fase gasosa e em solução de solventes apolares/pouco polares, há maior preferência pela conformação *axial*. Esse comportamento tem sido atribuído à forte interação eletrostática  $\text{Br}^{\delta-} \cdots \delta\text{O}=\text{C}$  no confôrmero *equatorial* e a uma interação orbitalar atrativa do tipo  $n_{\text{Br}} \rightarrow \pi^*_{\text{CO}}$  no confôrmero *axial* (Eisenstein et al., 1974; Freitas et al., 2001; Yoshinaga et al., 2002). O mesmo foi observado para cicloexanonas com os  $\alpha$ -substituintes  $\text{NMe}_2$ ,  $\text{OMe}$ ,  $\text{SMe}$  e  $\text{SeMe}$  (Freitas et al., 2003). Porém, há relatos de que em solventes apolares, e mesmo na fase gasosa, o anidrido acético, a acetona e a própria 2-

bromocicloexanona podem se autoassociar (Allinger & Allinger, 1958; Pennington & Kobe, 1957; Jones, 1928). Isso conduz a uma maior população de um dos confôrmeros.

Atualmente, dispõem-se de modernos softwares e máquinas de rápido processamento capazes de fornecer resultados mais precisos do que aqueles obtidos no início da década. Além disso, novas tendências sobre os fatores que regem isomerismos conformacionais, especialmente baseadas em interações hiperconjugativas, têm sido mais bem detalhadas na literatura e suas metodologias de análise estão muito mais acessíveis (Goodman et al., 2005). Portanto, as XC emergem novamente como sistemas modelo úteis para se racionalizar os fatores operantes em equilíbrios conformacionais, uma vez que apresentam sítios importantes que conduzem a interações estéricas, eletrostáticas e orbitales.

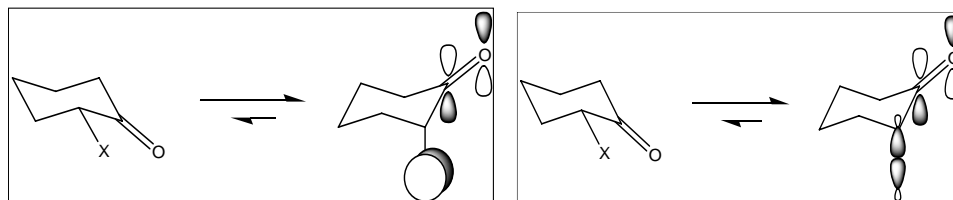


FIGURA 2 Principais interações de orbitais, envolvendo o orbital  $\pi^*_{C=O}$ , nas 2-halocicloexanonas.

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## **CAPÍTULO 2**

### **ORBITAL INTERACTIONS IN 2-HALOCYCLOHEXANONES AS ANALYZED BY MEANS OF THEORETICAL CALCULATIONS**

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**ORBITAL INTERACTIONS IN 2-HALOCYCLOHEXANONES AS  
ANALYZED BY MEANS OF THEORETICAL CALCULATIONS**

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**1 ABSTRACT**

The stereoelectronic interactions governing the conformational isomerism of 2-halocyclohexanones have been investigated by using an isodesmic reaction model. It has been found that 2-*axial* halogenation of cyclohexanone is thermodynamically favoured, whilst insertion of an *equatorial* bromine or iodine is not. Overall, inclusion of *axial* halogens in cyclohexanone is preferred to *equatorial* entrance and, according to NBO calculations, this behaviour is due to electron donation from nonbonding and C-X orbitals to  $\pi^*_{\text{CO}}$  antibonding orbital, in addition to steric and electrostatic effects.

**Keywords:** isodesmic reaction; conformational analysis; NBO; 2-halocyclohexanones

## 2 INTRODUCTION

2-Halocyclohexanones (**XC**) are interesting model compounds to study intramolecular interactions, because they contain polar moieties (useful to evaluate electrostatic interactions), they are substituted by a voluminous atom (appropriate to evaluate steric repulsion), and it possesses good electron donor ( $\sigma_{C-X}$  and  $n_X$ ) and acceptor ( $\pi^*_{C=O}$ ) orbitals (suitable to study hyperconjugative interactions). 2-Halocyclohexanones experience *axial-equatorial* conformational isomerisation (Figure 1), with the *axial* form dominant at the isolated state, decreasing in population on going from nonpolar to progressively more polar solutions (Freitas et al., 2001; Yoshinaga et al., 2002). Other 2-substituted cyclohexanones have also been studied and demonstrated similar behaviour (Yoshinaga et al., 2002; Freitas et al., 2003).

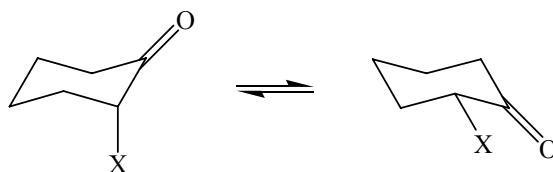


FIGURE 1 Conformational isomerism of 2-halocyclohexanones.

Based on interpretation somewhat intuitive (Eisenstein et al. 1974) or on indirect theoretical parameters (Yoshinaga et al., 2002), the conformer stabilization of **XC** has been assigned to be due to hyperconjugative  $n_X \rightarrow \pi^*_{C=O}$  interaction, in addition to steric and dipolar repulsion. Similar explanations have been given to other carbonyl and thiocarbonyl systems (Kallies et al., 1997; Ducati et al., 2008; Coelho et al., 2008). Recently, a through carbonyl  $^4J_{H,H}$  long-range coupling gave experimental insight about the hyperconjugative nature of the interactions governing the conformational isomerism of 2-

bromocyclohexanone (Coelho et al., 2009). According to this NMR study, the enhanced coupling pathway was due to the transmission of spin-spin information through electron delocalization from  $\sigma_{\text{C-H}}$  to  $\pi^*_{\text{C=O}}$  orbital.

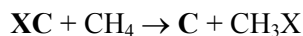
However, no direct, quantitative evidence, such as that provided by natural bond orbital (NBO) analysis, has been given to support the idea that orbital interactions play an important role in describing the conformational isomerism of **XC**. Thus, an isodesmic reaction model, which was similarly applied with success to account for the anomeric effect in fluorinated pnictogen compounds (Martins & Freitas, 2008), was used here to derive useful interpretation about intramolecular interactions operating in both *axial* and *equatorial* **XC**. Moreover, NBO analysis was carried out and energy of orbital levels obtained to account for the hyperconjugative interactions existing in both conformers and, therefore, contributing for the conformational isomerism of **XC**.

### 3 COMPUTATIONAL METHODS

Density Functional Theory (DFT) calculations were carried out using the *Gaussian 03* program (Frisch et al., 2004). Geometries were optimized using the hybrid functional B3LYP (Becke, 1988; Lee et al., 1988) and the aug-cc-pVTZ (Dunning et al., 1998) basis set; for 2-iodo-cyclohexanone, the corresponding pseudo-potential aug-cc-pVTZ-PP (Peterson et al., 2003) was used. Natural Bond Orbital (NBO) (Glendening et al., 2004) calculations were performed at the same level of theory. Orbital energies were obtained at the HF/6-31g(d,p) level (LANL2DZ pseudopotential for the iodine derivative).

## 4 RESULTS AND DISCUSSION

In order to obtain the thermodynamic data, the following isodesmic reaction was considered:



where  $\mathbf{XC}$  corresponds to the 2-halocyclohexanone ( $\mathbf{X} = \text{F, Cl, Br and I}$ ) and  $\mathbf{C}$  to cyclohexanone. Both *axial* and *equatorial* conformers of  $\mathbf{XC}$  were considered in this reaction.

Reaction enthalpies were obtained from the energy data of each compound of the above reaction. Table 1 shows that reactions involving *axial* conformers are all endothermic, decreasing from 2-fluorocyclohexanone to 2-iodocyclohexanone. Therefore, the inclusion of an halogen atom at the *axial* 2-position in cyclohexanone is favoured, suggesting that attractive interactions in *axial* 2-halocyclohexanones take place and overcome repulsive forces, like steric hindrance and electrostatic repulsion. Such attractive interactions are supposed to be due to electrostatic attraction between the negatively charged halogen and the positively charged *syn*-1,3-diaxial hydrogens (Freitas et al., 2002). However, NBO calculations reveal that hyperconjugation involving the  $\pi^*_{\text{CO}}$  orbital as an electron acceptor must play a decisive role in describing the conformational isomerism of 2-halocyclohexanones. The electron delocalization interactions described as  $\sigma_{\text{CX}} \rightarrow \pi^*_{\text{CO}}$  in the *axial* conformer decrease on going from the iodine (best *sigma* electron donor) to the fluorine derivative (Table 2). This behaviour is opposite to the  $\Delta H_{\text{ax}}$  trend of Table 1 due to the increasing halogen size from F to I.

TABLE 1 Enthalpy differences (kcal mol<sup>-1</sup>) for the isodesmic reaction involving the *axial* and *equatorial* conformers of 2-halocyclohexanones.

	$\Delta H_{ax}$	$\Delta H_{eq}$	$\Delta\Delta H_{ax-eq}$
<b>FC</b>	4.65	4.37	0.28
<b>ClC</b>	1.88	0.77	1.11
<b>BrC</b>	1.41	-0.16	1.57
<b>IC</b>	0.95	-0.82	1.77

On the other hand, the model compounds experience interactions predominantly repulsive when bromine and iodine are inserted equatorially in the template cyclohexanone (exothermic reaction). For the *equatorial* 2-chlorocyclohexanone, the isodesmic reaction was found to be slightly endothermic (0.77 kcal mol<sup>-1</sup>), whilst the corresponding enthalpy for the fluorine derivative was strongly endothermic (4.37 kcal mol<sup>-1</sup>), but not like in the *axial* conformer (4.65 kcal mol<sup>-1</sup>). These indicate that interactions involving any halogen are more attractive in the *axial* conformer than in the *equatorial* one, as estimated by the  $\Delta\Delta H$  values of Table 1, in agreement with the trend observed for the orbital interactions mentioned above (Table 2).  $LP_X \rightarrow \pi^*_{CO}$ ,  $\pi_{CO} \rightarrow \sigma^*_{CX}$  and  $\sigma_{CX} \rightarrow \pi^*_{CO}$  interactions are operating in the *axial* conformer. Whilst  $\sigma_{CX} \rightarrow \pi^*_{CO}$  interactions are more stabilizing according to **FC**<**ClC**<**BrC**<**IC**, the corresponding interaction in the *equatorial* conformer ( $\sigma_{C-H2} \rightarrow \pi^*_{CO}$ ) practically does not vary. In order to found out the effect of all antibonding and Rydberg orbitals as electron acceptors in the conformational isomerism of 2-halocyclohexanones, as well as the effect of the  $\pi^*_{CO}$  orbital alone, these orbitals were removed from the calculations using the NBODEL keyword (Glendening et al., 2004). It was found that the *axial* conformer in all compounds is more

stabilized by hyperconjugation involving those orbitals, because deletion of antibonding and Rydberg orbitals becomes the *equatorial* conformer more stable than the *axial* in the isolated state ( $E_{eq-ax}$  of 16.07, 6.35, 3.87 and 7.31 kcal mol<sup>-1</sup> for **FC**, **CIC**, **BrC** and **IC**, respectively). The strong effect of removing the  $\pi^*_{CO}$  orbital gives the following energy differences ( $E_{ax-eq}$ ) in the isolated state: 0.62, 2.75, 3.13 and 5.35 kcal mol<sup>-1</sup> for **FC**, **CIC**, **BrC** and **IC**, respectively, indicating this orbital as the key electron acceptor ruling the conformational isomerism of 2-halocyclohexanones.

TABLE 2 Main orbital interactions (kcal mol<sup>-1</sup>) involving the  $\pi$  system for the *axial* and *equatorial* conformers of 2-halocyclohexanones.

Interaction	<b>FC</b> <sup>a</sup>	<b>CIC</b> <sup>a</sup>	<b>BrC</b> <sup>a</sup>	<b>IC</b> <sup>a</sup>
LP <sub>X</sub> → $\pi^*_{CO}$	-/1.53	-/2.21	-/2.12	-/1.87
$\sigma_{CX}$ → $\pi^*_{CO}$	-/1.34	-/4.21	-/5.88	-/8.51
$\sigma_{C-H2}$ → $\pi^*_{CO}$	5.5/-	5.21/-	5.29/-	5.46/-
$\pi_{CO}$ → $\sigma^*_{CX}$	-/2.92	-/3.53	-/3.79	-/3.73
$\pi_{CO}$ → $\sigma^*_{C-H2}$	1.63/-	1.70/-	1.74/-	1.78/-

<sup>a</sup> *equatorial/axial*.

The acceptor ability of the  $\pi^*_{CO}$  and  $\sigma^*_{CX}$  orbitals in each 2-halocyclohexanone, as well as the donor ability of  $\sigma_{CX}$  and nonbonding orbitals, were evaluated by estimating their energy levels to corroborate the orbital interaction trends (Table 3). According to the HF calculations, the HOMO and HOMO-1 in 2-halocyclohexanones have strong contribution of halogen lone pairs, especially those directed towards the  $\pi^*_{CO}$  orbital in the *axial* conformation. These electron donors, together with the third lone pair (the one

along with the C-X bond) and the  $\sigma_{\text{CX}}$  orbital, are nearly equivalent in energy when comparing the *axial* and *equatorial* conformers; however, the vacant  $\pi^*_{\text{CO}}$  orbital in the *axial* conformer seems to be better electron acceptor than in the *equatorial* one, due to its lower energy (excepting for **IC**). Importantly, the energy levels of  $\text{LP}_X$  and  $\sigma_{\text{CX}}$  increase according to **FC**<**ClC**<**BrC** (results for **IC** were obtained at a different level), leading to a decreasing energy gap with the  $\pi^*_{\text{CO}}$  orbital on going from 2-fluoro to 2-iodocyclohexanone, which is in agreement with the finding that  $\sigma_{\text{CX}} \rightarrow \pi^*_{\text{CO}}$  orbital interactions in the *axial* conformer are more effective according to **FC**<**ClC**<**BrC**<**IC**.

TABLE 3 Orbital energies (a.u.) for the *axial* and *equatorial* conformers of 2-halocyclohexanones.

Orbital <sup>a</sup>	<i>axial</i>				<i>equatorial</i>			
	F	Cl	Br	I	F	Cl	Br	I
LP1	-0.413	-0.342	-0.319	-0.391	-0.411	-0.345	-0.319	-0.391
LP2	-0.432	-0.347	-0.321	-0.395	-0.427	-0.349	-0.322	-0.393
LP3	-0.528	-0.434	-0.417	-0.449	-0.533	-0.441	-0.424	-0.442
$\sigma_{\text{C-X}}$	-1.179	-0.872	-0.761	-0.431	-1.189	-0.877	-0.766	-0.436
$\sigma^*_{\text{C-X}}$	-0.050	-0.099	-0.113	-0.213	-0.057	-0.110	-0.126	-0.170
$\pi_{\text{C=O}}$	-0.459	-0.460	-0.460	-0.458	-0.465	-0.471	-0.459	-0.456
$\pi^*_{\text{C=O}}$	-0.189	-0.190	-0.191	-0.138	-0.180	-0.180	-0.180	-0.178

<sup>a</sup> Orbitals contributing for the molecular orbitals identified as HOMO-n and LUMO+n (n = 0, 1, 2, ...).

## 5 CONCLUSIONS

It has been found that the introduction of a *2-axial* halogen in cyclohexanone is more stabilizing than inserting it at the *equatorial* position, and that *axial*  $\alpha$ -halogenation is an exothermic reaction. This is due to a balance between classical steric/electrostatic and non-classical (electron delocalization) effects. This latter type was found to be particularly due to  $\sigma_{\text{CX}} \rightarrow \pi^*_{\text{CO}}$  and  $\text{LP}_{\text{X}} \rightarrow \pi^*_{\text{CO}}$  interactions, playing a determinant role in the conformational isomerism of 2-halocyclohexanones.

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### **CAPÍTULO 3**

#### **ON THE $^4J_{\text{HH}}$ LONG-RANGE COUPLING IN 2-BROMOCYCLOHEXANONE: CONFORMATIONAL INSIGHTS**

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## ON THE ${}^4J_{\text{HH}}$ LONG-RANGE COUPLING IN 2-BROMOCYCLOHEXANONE: CONFORMATIONAL INSIGHTS

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### 1 ABSTRACT

2-Bromocyclohexanone is a model compound in which a  ${}^4J_{\text{H2,H6}}$  coupling constant is observed, whilst the corresponding  ${}^4J_{\text{H2,H4}}$  is absent. The observed long-range coupling is a result of the known *W*-type coupling, in the *axial* conformation, but also due to the less usual *diaxial* spin-spin coupling in the equatorial conformer. The carbonyl group plays a determining role in describing the coupling pathway, as concluded by natural bond orbital (NBO) analysis; whilst the  $\sigma_{\text{C2-H2}} \rightarrow \sigma^*_{\text{C1(O)-C6}}$  and  $\sigma_{\text{C6-H6}} \rightarrow \sigma^*_{\text{C1(O)-C2}}$  interactions in the *axial* conformer contribute for transmitting the spin information associated with the *W*-type coupling, the strong  $\sigma_{\text{C2-H2}} \rightarrow \pi^*_{\text{C=O}}$  and  $\sigma_{\text{C6-H6}} \rightarrow \pi^*_{\text{C=O}}$  hyperconjugations in the *equatorial* conformer define an enhanced coupling pathway for  ${}^4J_{\text{H2,H6}}$ , despite the inhibition of this coupling due to  $n_{\text{O}} \rightarrow \sigma^*_{\text{C(O)-C}}$  interaction and the large carbonyl angle. These findings provide experimental

evidence that orbital interactions contribute for the conformational isomerism of 2-bromocyclohexanone.

**Keywords:** NMR;  $^4J_{\text{HH}}$ ; 2-bromocyclohexanone; carbonyl group; NBO

## 2 INTRODUCTION

2-Bromocyclohexanone undergoes conformational isomerization between the *axial* and *equatorial* forms (Figure 1). (Freitas et al., 2001; Yoshinaga et al., 2002; Allinger & Allinger, 1958; Allinger et al., 1960; Chen & Fèvre, 1965; Allinger et al., 1966; Pan & Stothers, 1967; Garbisch, 1964). The 2-position hydrogen, free of interference in the  $^1\text{H}$  NMR spectrum, exhibits three coupling constants, owing to its spin-spin interaction with H-3, H-3' and H-6.<sup>[1]</sup> The long range  $^4J_{\text{H}_2,\text{H}_6}$  coupling is expected to operate in the *axial* conformer, according to the *W* coupling pathway (Contreras & Peralta, 2000), whilst the corresponding *diaxial* coupling in the *equatorial* conformer is usually smaller or even not observed (Gil & Geraldes, 1987).

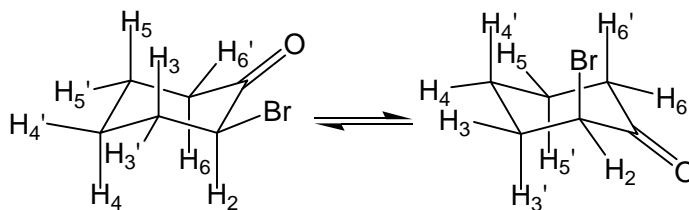


FIGURE 1 Conformers of 2-bromocyclohexanone.

Long-range  $^4J_{\text{H,H}}$  coupling constants were measured in rigid *tert*-butylcyclohexanes (Haddon & Jackman, 1973), with *W*-type coupling constants being significantly larger than *diaxial* and *equatorial-axial* couplings. However,  $^4J_{\text{H}_2,\text{H}_4}$  is not observed in 2-bromocyclohexanone, *i.e.* only a through-carbonyl long-range coupling has been observed in this compound for H2. The carbonyl group has shown to play a driving role in the through-the-bridge  $^3J_{\text{C,H}}$  couplings (actually  $^{3,4}J_{\text{C,H}}$  couplings) in norbornanone, in which a  $\sigma_{\text{C}_3-\text{C}_4} \rightarrow \sigma^*_{\text{C}_2=\text{O}}$  interaction defines an additional coupling pathway for  $^{3,4}J_{\text{C}_4,\text{H}_1}$ , but not for

${}^{3,4}J_{\text{C1,H4}}$ ; consequently, the former coupling constant was found to be significantly larger than  ${}^{3,4}J_{\text{C1,H4}}$  (Santos et al., 2008).

Since the conformational isomerism of 2-bromocyclohexanone is expected to be governed by orbital interactions, especially those involving the  $\pi^*_{\text{C=O}}$  orbital, in addition to steric and electrostatic interactions, the investigation of the origins of the through-carbonyl long-range  ${}^4J_{\text{H2,H6}}$  coupling must provide an experimental insight about the hyperconjugation role in this model system. In order to corroborate the  ${}^1\text{H}$  NMR findings, theoretical approaches were applied to rationalize the results.

### 3 EXPERIMENTAL AND COMPUTATION

2-Bromocyclohexanone was prepared by brominating cyclohexanone with  $\text{Br}_2$  in ether.  ${}^1\text{H}$  NMR spectra were acquired on a Varian GEMINI 300 spectrometer, operating at 300.07 MHz. Samples were prepared as solutions of 20 mg of solute in 0.6 ml of solvent ( $\text{CDCl}_3$ ,  $\text{CD}_2\text{Cl}_2$ , pyridine- $d_6$ ,  $\text{CD}_3\text{CN}$  and  $\text{DMSO}-d_6$ ), and the spectra were recorded at 300 K. The variable temperature experiments were carried out at 293, 273, 253, 233 and 213 K, from  $\text{CD}_2\text{Cl}_2$  solutions.  ${}^1\text{H}$  NMR (300.07 MHz,  $\text{CDCl}_3$ , 25°C, TMS):  $\delta$  (ppm) = 1.75 (m, 1H, H4), 1.84 (m, 1H, H5'), 1.96 (m, 1H, H5), 2.03 (m, 1H, H4'), 2.25 (m, 1H, H3), 2.35 (m, 2H, H3' and H6), 2.98 (dddd, 1H,  ${}^4J(\text{H,H}) = 0.7$  Hz,  ${}^3J(\text{H,H}) = 5.6$  and 9.7 Hz,  ${}^2J(\text{H,H}) = 14.4$  Hz; H6'), 4.45 (ddd, 1H,  ${}^4J(\text{H,H}) = 1.5$  Hz,  ${}^3J(\text{H,H}) = 4.6$  and 6.2 Hz, H2).

Geometry optimizations were carried out at the MP2/aug-cc-pVDZ level. Given the important role played by hyperconjugative interactions in the Fermi contact transmission in long-range couplings, hyperconjugative interactions were evaluated using the natural bond orbital (NBO) (Glendening et al., 2001) analyses as implemented in the Gaussian03 program (Frisch et al.,

2004), at the B3LYP/aug-cc-pVTZ level. DFT calculations of all four terms of  ${}^4J_{\text{H}_2,\text{H}_6}$  [Fermi contact (FC); spin dipolar (SD); paramagnetic spin orbit (PSO); and diamagnetic spin orbit (DSO)] were carried out using the EPR-III basis set for C and H (Barone, 1994), which is of a triple-zeta quality and includes diffuse and polarization functions. The *s* part of this basis set is enhanced to better reproduce the electronic density in the nuclear regions, since this point is particularly important when calculating the FC term. For O and Br, an aug-cc-pVDZ basis set was applied.

#### 4 RESULTS AND DISCUSSION

2-Bromocyclohexanone experiences *axial-equatorial* isomerization, and this can be demonstrated by changes in suitable coupling constants, *e.g.*  ${}^3J_{\text{H}_2,\text{H}_3}$ , when varying solvents and temperature. The calculated MP2/aug-cc-pVDZ energy difference ( $E_{\text{eq}}-E_{\text{ax}}$ ) between the two conformers in the isolated state is 2.1 kcal mol<sup>-1</sup>, which is in agreement with the experimental value; this energy difference decreases with increasing the medium polarity (Yoshinaga et al., 2002). The H<sub>2</sub>-C-C-H<sub>3</sub> dihedral angle in the *equatorial* conformer is close to 180° and, according to the early work by Karplus (Karplus, 1959; Karplus, 1960; Karplus, 1963), the corresponding  ${}^3J_{\text{H}_2,\text{H}_3}$  coupling constant is expected to be larger than in the *axial* conformer (the calculated  ${}^3J_{\text{H}_2,\text{H}_3}$  coupling constant corresponds to 3.6 and 14.4 Hz for the *axial* and *equatorial* conformers, respectively); thus, the average of this value is dependent on conformational changes. The  ${}^3J_{\text{H}_2,\text{H}_3}$  coupling constants of Table 1 indicate that the conformational equilibrium is shifted toward the *equatorial* conformer on going from less to more polar solvents, and from higher to lower temperatures in CD<sub>2</sub>Cl<sub>2</sub> solution. However, the long-range  ${}^4J_{\text{H}_2,\text{H}_6}$  coupling constant varies negligibly when changing medium and temperature conditions, indicating that



the *diaxial* coupling and the well known *W*-type coupling are of similar magnitude. Moreover, none  ${}^4J_{\text{H2,H4}}$  coupling is observed in 2-bromocyclohexanone, as confirmed by COSY experiments (Figure 2), suggesting that the carbonyl group plays an important role in transmitting the spin information along the coupling pathway. The  ${}^4J_{\text{H2,H6}}$  couplings in *cis*-4-*t*-butyl-2-bromocyclohexanone ( ${}^4J_{\text{H2,H6}}=1.2$  Hz) and in *trans*-4-*t*-butyl-2-bromocyclohexanone ( ${}^4J_{\text{H2,H6}}=1.7$  Hz) corroborate with results for 2-bromocyclohexanone. The advantage of 4-*t*-butyl derivatives is related to their rigid structure; in this case, the coupled hydrogen is fixed, which is favorable for the transmission of the spin-spin coupling.

TABLE 1 Dependencies of coupling constants (Hz) with solvents and temperature ( $^{\circ}\text{C}$ ) for 2-bromocyclohexanone.<sup>a</sup>

Solvent	${}^3J_{\text{H2,H3}}$	${}^3J_{\text{H2,H3}'}$	${}^4J_{\text{H2,H6}}$	Temp. <sup>b</sup>	${}^3J_{\text{H2,H3}}$	${}^3J_{\text{H2,H3}'}$	${}^4J_{\text{H2,H6}}$
$\text{CDCl}_3$	6.2	4.6	1.5	20	7.0	4.6	1.4
$\text{CD}_2\text{Cl}_2$	7.0	4.8	1.5	0	7.3	4.7	1.4
Pyridine- $d_6$	7.6	4.8	1.4	-20	7.6	4.8	1.4
$\text{CD}_3\text{CN}$	8.5	5.1	1.4	-40	8.0	4.8	1.5
$\text{DMSO-}d_6$	9.2	5.2	1.3	-60	8.5	5.0	1.5

<sup>a</sup> Solvent dielectric constants: 4.8 ( $\text{CDCl}_3$ ), 9.0 ( $\text{CD}_2\text{Cl}_2$ ), 12.4 (pyridine- $d_6$ ), 37.5 ( $\text{CD}_3\text{CN}$ ), and 46.7 ( $\text{DMSO-}d_6$ ).

<sup>b</sup> Experiments with variable temperature were performed in  $\text{CD}_2\text{Cl}_2$  solution.

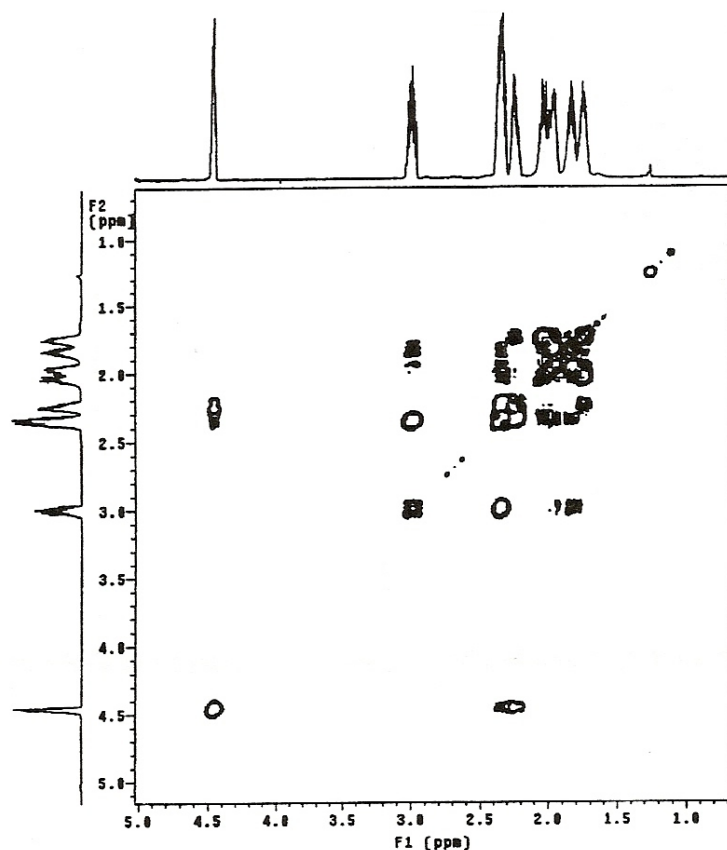


FIGURE 2 COSY spectrum of 2-bromocyclohexanone. There is no correlation between H-2 and H-4.

The calculated  ${}^4J_{\text{H}_2,\text{H}_6}$  coupling constants for the *axial* and *equatorial* conformers (Figure 3) are in excellent agreement with the experimental values. Also, the calculated coupling constants were found to be very similar in the two conformers, as previously supposed. These calculated long-range coupling constants were found to be quite superior than  ${}^4J_{\text{H}_2,\text{H}_4}$ , which are in fact not observed in the experimental spectrum (calculated  ${}^4J_{\text{H}_{2\text{eq}},\text{H}_{4\text{eq}}} = 1.1$  Hz and  ${}^4J_{\text{H}_{2\text{eq}},\text{H}_{4\text{ax}}} = -0.8$  Hz for the *axial* conformer, and  ${}^4J_{\text{H}_{2\text{ax}},\text{H}_{4\text{ax}}} = 0.4$  Hz and  ${}^4J_{\text{H}_{2\text{ax}},\text{H}_{4\text{eq}}} = -0.1$  Hz for the *equatorial* conformer).  ${}^4J_{\text{H}_2,\text{H}_6}$  couplings can be

described using the two dihedral angles  $\text{H}_2\text{-C}_2\text{-C}_1\text{-C}_6$  ( $\Psi_1$ ) and  $\text{C}_2\text{-C}_1\text{-C}_6\text{-H}_6$  ( $\Psi_2$ ), but angles defined by bonds along to the coupling pathway can also dictate the actual coupling. When both dihedral angles are *antiperiplanar*, such as in the *W*-type coupling pathway, electron delocalization interactions from  $\text{C}_2\text{-H}_2$  and  $\text{C}_6\text{-H}_6$  increase the FC term of  ${}^4J_{\text{H}_2,\text{H}_6}$  (Contreras & Peralta, 2000) (according to the calculations, PSO and DSO terms for this long-range coupling are comparable to FC, but they cancel each other). However, this is not the case for the *equatorial* conformer, because both calculated  $\Psi_1$  and  $\Psi_2$  dihedral angles correspond to  $62^\circ$ . In addition, the carbonyl angle ( $\text{C}_2\text{-C}(\text{O})\text{-C}_6$ ) in 2-bromocyclohexanone (calculated  $115.8^\circ$  and  $112.5^\circ$  for the *axial* and *equatorial* conformers, respectively) is larger than the tetrahedral angle, which reduces  ${}^4J_{\text{H}_2,\text{H}_6}$  in comparison to  ${}^4J_{\text{H}_2,\text{H}_4}$  (Barfield & Smith, 1992; Smith & Barfield, 1993). Thus, why is the  ${}^4J_{\text{H}_2,\text{H}_6}$  coupling observed for the *equatorial* conformer (actually, the calculated value is slightly superior to the corresponding *W* coupling), while the  ${}^4J_{\text{H}_2,\text{H}_4}$  *W*-coupling does not appear in the spectrum? Both  $\sigma_{\text{C}_2\text{-H}_2}$  and  $\sigma_{\text{C}_6\text{-H}_6}$  bonding orbitals (which contain the  $\text{H}_2$  and  $\text{H}_6$  nuclei) strongly interact with the  $\pi^*_{\text{C}=\text{O}}$  orbital in the *equatorial* conformer, and this hyperconjugation defines the  ${}^4J_{\text{H}_2,\text{H}_6}$  coupling pathway (Table 2). The weaker  $\sigma_{\text{C}_2\text{-H}_2} \rightarrow \sigma^*_{\text{C}_1(\text{O})\text{-C}_6}$  and  $\sigma_{\text{C}_6\text{-H}_6} \rightarrow \sigma^*_{\text{C}_1(\text{O})\text{-C}_2}$  hyperconjugative interactions contribute for the *W* coupling in the *axial* conformer (these interactions are of secondary importance in the *equatorial* conformer). The  $\sigma_{\text{C}_2\text{-H}_2} \rightarrow \sigma^*_{\text{C}_3\text{-C}_4}$  and  $\sigma_{\text{C}_6\text{-H}_6} \rightarrow \sigma^*_{\text{C}_4\text{-C}_5}$  interactions, and corresponding reciprocal hyperconjugations, are substantially smaller in both conformers.

Therefore, the  $\pi^*_{\text{C}=\text{O}}$  orbital increases the efficiency of the  $\text{H}_2\text{-C}_2\text{-C}_1\text{-C}_6\text{-H}_6$  coupling pathway to transmit the spin information associated with the FC term in the *equatorial* conformer and, consequently, the  $\sigma_{\text{C}_2\text{-H}_2} \rightarrow \pi^*_{\text{C}=\text{O}}$  and  $\sigma_{\text{C}_6\text{-H}_6} \rightarrow \pi^*_{\text{C}=\text{O}}$  interactions contribute to the observation of the averaged  ${}^4J_{\text{H}_2,\text{H}_6}$

coupling constant for 2-bromocyclohexanone. On the other hand, electron delocalization interactions into the  $\sigma^*_{C2-H2}$  and  $\sigma^*_{C6-H6}$  antibonding orbitals cause a decrease in the FC term of  ${}^4J_{H2,H6}$  (Contreras & Peralta, 2000). In order to confirm that the  $\pi^*_{C=O}$  orbital plays an important role for the observation of  ${}^3J_{H2,H6}$ , the electron acceptor ability of the  $\pi^*_{C=O}$  orbital was enhanced by protonating the carbonyl oxygen; the expected consequence is an increase of this coupling constant. Moreover, in 2-bromocyclohexanone, the  $n_O \rightarrow \sigma^*_{C1-C2}$  and  $n_O \rightarrow \sigma^*_{C1-C6}$  hyperconjugative interactions are operative (Table 2), and upon protonation of the carbonyl oxygen atom an inhibition of these interactions takes place, yielding an increase in the  ${}^4J_{H2,H6}$  coupling (Figure 3). For the protonated systems, the  ${}^4J_{H2,H6}$  coupling constant in the *equatorial* conformer is significantly larger than in the *axial* conformer, indicating that electron delocalizations involving the  $\pi^*_{C=O}$  orbital are more affected after protonation.

TABLE 2 Important hyperconjugative interactions (kcal mol<sup>-1</sup>) obtained at the B3LYP/aug-cc-pVTZ level for 2-bromocyclohexanone

Interaction	axial	equatorial	axial-	equatorial-	axial	equatorial
			H <sup>+</sup>	H <sup>+</sup>	H <sup>+</sup>	H <sup>+</sup>
$\sigma_{C2-H2} \rightarrow \pi^*_{C1=O}$	-	4.8	0.7	8.0	0.5	8.5
$\sigma_{C6-H6} \rightarrow \pi^*_{C1=O}$	-	5.2	1.0	9.0	0.9	8.9
$\sigma_{C2-H2} \rightarrow \sigma^*_{C1(O)-C6}$	4.1	2.3	5.3	-	5.5	-
$\sigma_{C6-H6} \rightarrow \sigma^*_{C1(O)-C2}$	4.3	2.2	5.5	-	5.4	-
$\sigma_{C2-H2} \rightarrow \sigma^*_{C3-C4}$	3.0	-	2.4	-	2.5	-
$\sigma_{C6-H6} \rightarrow \sigma^*_{C4-C5}$	2.8	-	2.2	-	2.1	-
$n_O \rightarrow \sigma^*_{C1-C2}$	20.2	22.0	8.8	8.9	0.7	0.8
$n_O \rightarrow \sigma^*_{C1-C6}$	19.1	19.9	0.8	0.7	8.8	8.4

Overall, a rationalization on the long-range coupling in 2-bromocyclohexanone provides useful insights about governing effects in the conformational isomerism of such a model compound, namely the stabilizing vicinal  $\sigma_{\text{C-H}} \rightarrow \pi^*_{\text{C=O}}$  hyperconjugative interaction in the *equatorial* conformer, and a secondary  $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C=O}}$  interaction in the *axial* conformer. Since  $\sigma_{\text{C-Br}}$  is a better electron donor than  $\sigma_{\text{C-H}}$ , the  $\sigma_{\text{C-Br}} \rightarrow \pi^*_{\text{C=O}}$  interaction is probably operating strongly in the *axial* conformation, as confirmed by the NBO calculations (interaction energy = 5.5 kcal mol<sup>-1</sup>).

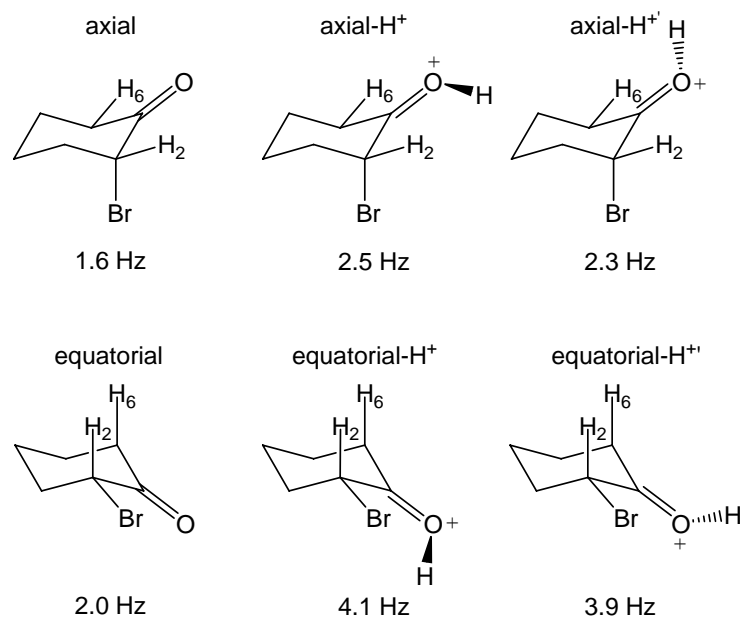


FIGURE 3 Calculated long-range  $^4J_{\text{H}_2, \text{H}_6}$  coupling constants for 2-bromocyclohexanone and for the protonated derivatives.

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## **CAPÍTULO 4**

### **THE CASE OF INFRARED CARBONYL STRETCHING INTENSITIES OF 2-BROMOCYCLOHEXANONE: CONFORMATIONAL AND INTERMOLECULAR INTERACTION INSIGHTS**

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*Letters*

**THE CASE OF INFRARED CARBONYL STRETCHING INTENSITIES  
OF 2-BROMOCYCLOHEXANONE: CONFORMATIONAL AND  
INTERMOLECULAR INTERACTION INSIGHTS**

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**1 ABSTRACT**

The infrared spectrum of 2-bromocyclohexanone in the vapor phase was obtained for the first time, and the conformational preference for this compound was surprisingly found to be similar to that expected from polar solutions, *i.e.* the most polar, *equatorial* conformer was the prevalent form. Theoretical calculations using a dimer model show that attractive intermolecular interactions in the *equatorial-equatorial* dimer are dominant, and it experiences a self-association stronger than in the *axial-axial* system even in vapor phase. This could explain the higher intensity of the *equatorial* C=O stretching band in the infrared spectrum of 2-bromocyclohexanone both in vapor and non-polar solvents.

**Keywords:** 2-bromocyclohexanone; carbonyl stretching vibration; conformational isomerism; self-association

## 2 INTRODUCTION

2-Bromocyclohexanone is a useful model system to analyze conformational isomerism and interactions governing conformer stability. This compound undergoes *equatorial-axial* interconversion (Figure 1), and several studies have used theoretical and experimental techniques to define the conformer populations and intramolecular interactions for each conformer both in the isolated and condensed phases (Allinger & Allinger, 1958a; Allinger & Allinger, 1958b; Freitas et al., 2001; Yoshinaga et al., 2002; Coelho & Freitas, 2009; Coelho et al., 2009; Freitas et al., 2003). The *equatorial* conformer of 2-bromocyclohexanone is more polar ( $\mu = 4.7$  D) than the *axial* one ( $\mu = 3.4$  D); therefore, it is expected that the *equatorial* preference in the conformational equilibrium increases on going from gas or non-polar solvents to increasingly more polar solvents. However, a different behavior has been observed from the expected trend when analyzing the carbonyl stretching intensities ( $I$ ): the higher wavenumber band, assigned to the *equatorial* conformer, is more intense in *n*-hexane ( $I_{ax}/I_{eq} \approx 1.1$ ) and cyclohexane ( $I_{ax}/I_{eq} \approx 1.2$ ) solution than in significantly more polar solvents, such as acetonitrile ( $I_{ax}/I_{eq} \approx 1.4$ ) and dimethyl sulfoxide ( $I_{ax}/I_{eq} \approx 1.5$ ) solutions (Freitas et al., 2003). This has been supposed to be attributed to different molar absorptivities between the conformers (Freitas et al., 2003) or to band couplings, *e.g.* for 2-chlorocyclohexanone, which exhibits a Fermi resonance between the carbonyl stretching mode and the first overtone of an adjacent C-H bond (Bervelt et al., 1968).

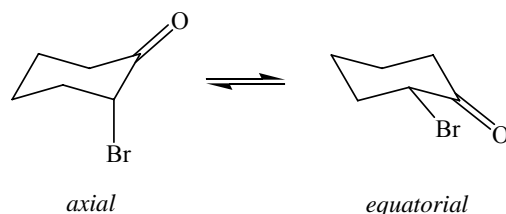


FIGURE 1 Conformational isomerism of 2-bromocyclohexanone.

However, it is well known that acetic anhydride self-associates in cyclohexane (Jones, 1928) and acetone dimerizes in the vapor phase (Pennington & Kobe, 1957), but there are no experimental results for 2-bromocyclohexanone in the vapor state, and the available data for the isolated molecule refer to those obtained by means of theoretical calculations (Freitas et al., 2001; Yoshinaga et al., 2002; Coelho & Freitas, 2009; Freitas et al., 2009). *Ab initio* (MP2/aug-cc-pVDZ) calculations have shown that the *axial* conformer of 2-bromocyclohexanone is *ca.* 2.1 kcal mol<sup>-1</sup> more stable than the *equatorial* one in the isolated state (Coelho et al., 2009), and a similar amount must be expected in non-polar solution, such as 2-bromocyclohexanone in *n*-hexane, opposite to observed through an infrared study (Freitas et al., 2003). Thus, this work aims at elucidating the origin of the spectroscopic behavior of 2-bromocyclohexanone, in order to rationalize its conformational preferences in the vapor phase using infrared spectroscopy and quantum chemical calculations as tools.

### 3 EXPERIMENTAL AND CALCULATIONS

#### 3.1 Synthesis and infrared measurement

Equimolar amounts of cyclohexanone and bromine (Br<sub>2</sub>) in diethyl ether were stirred at 0°C until discoloration (*ca.* 40 min.). The solution was washed with water (2×20mL) and NaHCO<sub>3</sub> 10% solution (2×20mL), and the ether was then evaporated. 2-Bromocyclohexanone was distilled at 65°C/2 mmHg, giving an 11% yield. The infrared spectrum of 2-bromocyclohexanone in the vapor phase was obtained by confining a tip of solute inside a 10 cm quartz cell with KBr windows. The spectrum was acquired with 32 scans, resolution of 1 cm<sup>-1</sup>, using a BOMEM MB100 spectrometer.

### 3.2 Theoretical calculations

The geometries of each conformer of 2-bromocyclohexanone were optimized at the HF/6-31g(d,p) level and energies were then computed. In order to obtain the intermolecular interaction energies and, consequently, insight about self-association, dimeric systems were built by accounting for the *equatorial-equatorial* and *axial-axial* aggregates (both *S* and *R* enantiomers were considered). Dimeric structures and energies were also computed at the HF/6-31g(d,p) level, using the Gaussian 03 program (Frisch et al., 2004). Furthermore, after each optimization the nature of each stationary point was established by calculating and diagonalizing the Hessian matrix (force constant matrix). The unique imaginary frequency associated with the transition vector (TV), *i.e.* the eigenvector associated with the unique negative eigenvalue of the force constant matrix, was characterized. Geometry optimizations for monomers and for the most important dimeric structures were also performed at the MP2/aug-cc-pVDZ level, and frequency calculations were carried out at the B3LYP/aug-cc-pVDZ level.

## 4 RESULTS AND DISCUSSION

The elected theoretical methodology, which was used as the standard methodology in our study, was HF/6-31g(d,p). Among other basis sets, the choice of the basis set 6-31g(d,p) improved the results, so that they are completely satisfactory. The 6-31g(d,p) basis set has also been shown to be satisfactory on similar structures (Freitas et al., 2001; Eisenstein et al., 1974).

The *ab initio* HF/6-31g(d,p) calculations indicates the *axial* conformer of 2-bromocyclohexanone as the most stable one in the isolated state by 2.5 kcal mol<sup>-1</sup>, which is in reasonable agreement with the MP2/aug-cc-pVDZ result obtained elsewhere (2.1 kcal mol<sup>-1</sup>) (Coelho et al., 2009). It is expected that the

*equatorial* conformation increases in population on going from the vapor and non-polar solvents to increasingly more polar solvents, since the *equatorial* conformer is significantly more polar than the *axial* form (calculated dipole moments of 4.7 D against 3.4 D, for the *equatorial* and *axial* conformers, respectively). In the isolated state, the calculated conformational energy is due to intramolecular interactions operating in 2-bromocyclohexanone, namely steric, electrostatic and hyperconjugative effects (Yoshinaga et al., 2002; Coelho & Freitas, 2009; Coelho et al., 2009; Freitas et al., 2001).

The conformers population may be experimentally estimated by measuring the relative infrared intensities of suitable, free from interference bands, e.g. the carbonyl stretching of *axial* and *equatorial* 2-bromocyclohexanone. This compound exhibits two superimposed bands in the carbonyl stretching region in the vapor state (Figure 2), with the stronger band centered at 1741  $\text{cm}^{-1}$  and the weaker one at 1726  $\text{cm}^{-1}$ . However, the infrared results obtained for 2-bromocyclohexanone in the vapor state (Figure 2) exhibit a C=O stretching band stronger for the *equatorial* conformer (1741  $\text{cm}^{-1}$ ) than for the *axial* form (1726  $\text{cm}^{-1}$ ), indicating the larger population of the *equatorial* conformer in the vapor phase (68%,  $E_{ax}-E_{eq} = 0.45 \text{ kcal mol}^{-1}$ ), determined according to the relative intensities of the *equatorial* and *axial*  $\nu_{\text{C=O}}$  bands. The assignment of the bands agrees with the calculated DFT frequency trends (1793  $\text{cm}^{-1}$  and 1774  $\text{cm}^{-1}$  for the *equatorial* and *axial* conformers, respectively). This behavior, opposite to the calculated energy in the isolated state, suggests a non-ideal gas system for 2-bromocyclohexanone, i.e. this compound seems to self-associate even in the vapor phase.

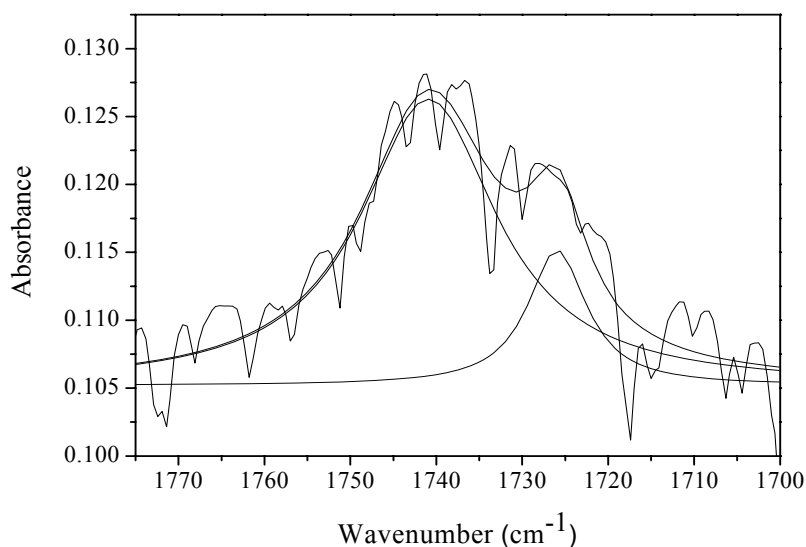


FIGURE 2 Infrared spectrum of 2-bromocyclohexanone (C=O stretching range), in the vapor phase. Band deconvolution was performed using Lorentzian function, with a curve fitting of  $R^2 = 0.872$ .

Self-association is mainly due to dipole-dipole interaction, essentially because of the interaction involving the polar C—Br and C=O bonds. Thus, these interactions must be taken into account, together with steric and hyperconjugative effects (especially for the isolated molecule), when the conformational equilibrium of 2-bromocyclohexanone and similar systems are analyzed. Furthermore, the absence of a third C=O stretching band and the apparent symmetry of the infrared peaks, both in vapor and solution (Freitas et al., 2003), reveal that 2-bromocyclohexanone does not experience the Fermi resonance phenomenon.

In order to investigate the experimental data and corroborate the hypothesis above, HF/6-31g(d,p) calculations were performed to estimate the self-association of 2-bromocyclohexanone by using a dimer model. The dimer model has been successfully applied to understand intermolecular interactions in other six-membered rings (Duarte & Freitas, 2009). Small molecular interactions

in dimers may result in basis set superposition error (BSSE), thus requiring counterpoise correction (Boys & Bernardi, 1970; Simon et. al., 1996); however, BSSE is canceled or at least minimized in this work because relative, not absolute, energies between dimers, and also energy differences between dimers and monomers, are to be considered. The *axial-equatorial* dimer was not considered because the *equatorial/axial* proportion is the same (50% for each conformer) and therefore the intensity increment due to individual conformers in this dimer must be nearly equivalent; thus, we are approaching that only the *equatorial-equatorial* and *axial-axial* dimers are responsible for the relative intensities of the C=O bands. In this scenario, several possible approaches were optimized to represent the dimeric system (Figure 3). The DFT frequency calculations for the most important dimers indicate the same tendency as for monomers, *i.e.* the  $\nu_{\text{C=O}}$  for the main *equatorial-equatorial* dimer (structure **23**, Figure 4) is higher than for the main *axial-axial* dimer (structure **8**), that is  $1700.8 \pm 2.6 \text{ cm}^{-1}$  against  $1689.8 \pm 1.9 \text{ cm}^{-1}$ .



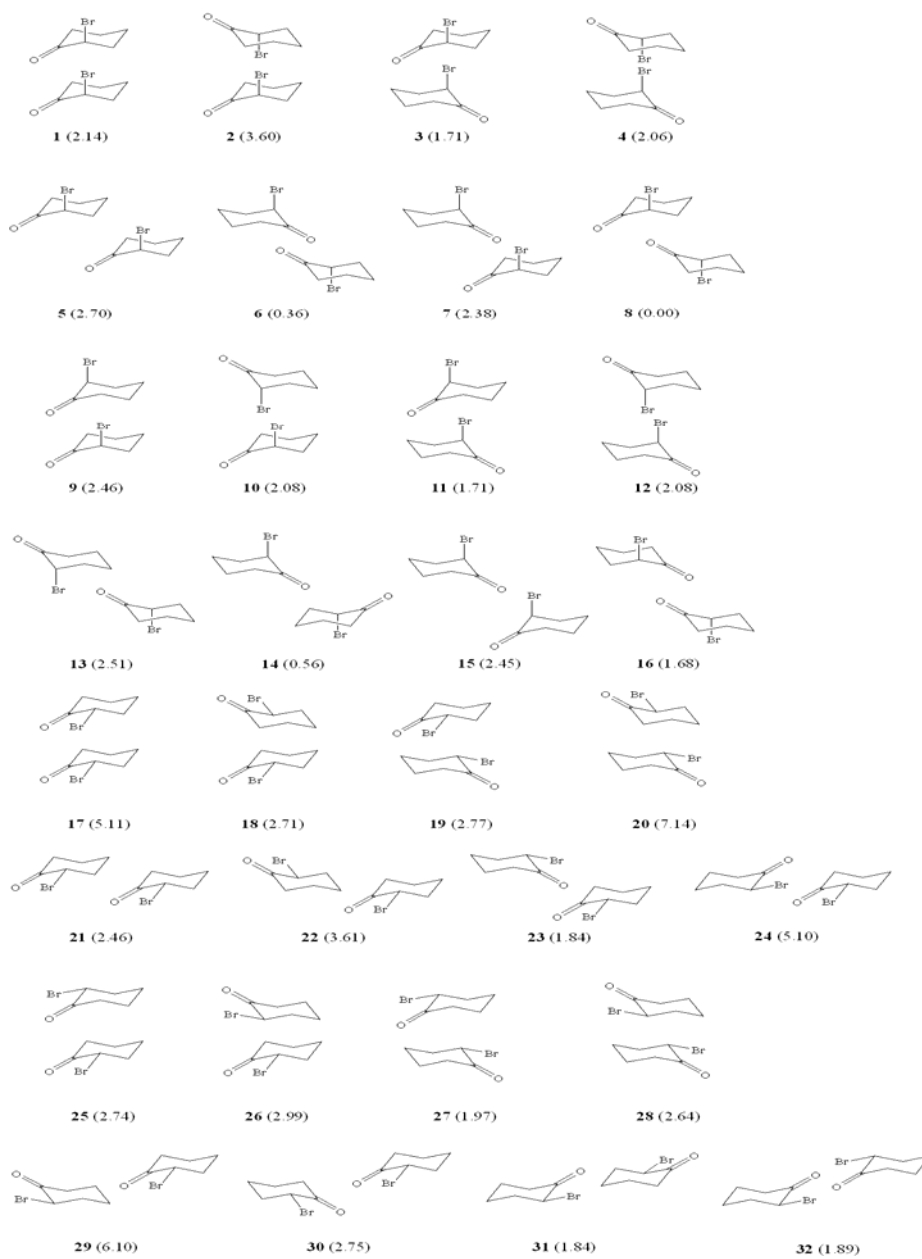


FIGURE 3 Input approaches to account for the dimeric structures *axial-axial* (**1-16**) and *equatorial-equatorial* (**17-32**). The relative HF/6-31g(d,p) energies for the optimized structures are given in parenthesis (in kcal mol<sup>-1</sup>).

According to the HF/6-31g(d,p) calculations, an *axial-axial* dimeric structure corresponds to the energy minimum (structure **8**, Figure 4), which is *ca.* 1.8 kcal mol<sup>-1</sup> more stable than the preferred *equatorial-equatorial* dimer (structure **23**). However, this figure changes when these elected dimeric structures are optimized at the more refined MP2/aug-cc-pVDZ level, *i.e.* the *equatorial-equatorial* dimer becomes the favored form by 0.6 kcal mol<sup>-1</sup>, in excellent agreement with the experimental infrared result obtained in this study ( $E_{ax}-E_{eq} = 0.45$  kcal mol<sup>-1</sup>). Despite the congruent energy values of HF/6-31g(d,p) for monomers ( $E_{eq}-E_{ax} = 2.5$  kcal mol<sup>-1</sup>) when compared to sophisticated methods, like MP2/aug-cc-pVDZ ( $E_{eq}-E_{ax} = 2.1$  kcal mol<sup>-1</sup>) (Coelho et.al., 2009), B3LYP/aug-cc-pVTZ ( $E_{eq}-E_{ax} = 1.6$  kcal mol<sup>-1</sup>) (Coelho & Freitas, 2009) and a NMR-based method ( $E_{eq}-E_{ax} = 1.5$  kcal mol<sup>-1</sup>) (Yoshinaga et al., 2002), the same parallelism may not be applied for the dimers of 2-bromocyclohexanone, probably because of the electron correlation problem using HF and, therefore, the difficulty in estimating steric hindrance.

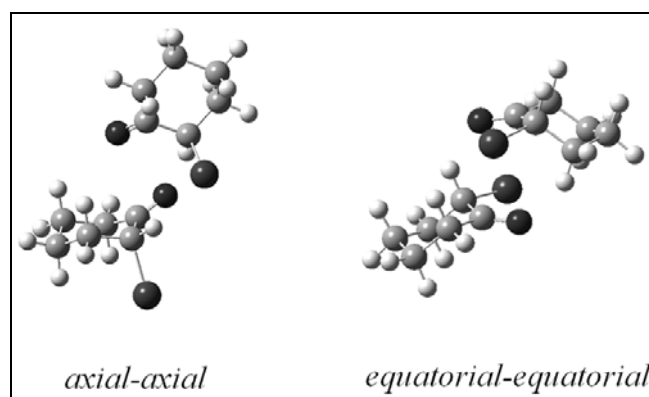


FIGURE 4 Optimized structures for the most stable *axial-axial* (**8**) and *equatorial-equatorial* (**23**) dimers ( $E_{eq-eg} - E_{ax-ax} = 1.84 \text{ kcal mol}^{-1}$ ). The corresponding energy difference obtained after optimization at the MP2/aug-cc-pVDZ level is  $-0.63 \text{ kcal mol}^{-1}$ .

The preference for the *equatorial* form in the vapor phase may be understood in terms of self-association, as hypothesized above, and this can be quantified by modeling the intermolecular interactions ( $E_{inter}$ ) in the dimer model, as computed by  $E_{inter} = E_{dimer} - 2 \times E_{monomer}$ . Using this approach and the MP2-based results, the intermolecular interaction for the *equatorial-equatorial* dimer is  $4.8 \text{ kcal mol}^{-1}$  more attractive than for the most stable *axial-axial* dimer. Overall, in addition to the dependency of molar absorptivities with conformation and medium, as stated elsewhere (Freitas et al., 2003; Bodot et al., 1967), 2-bromocyclohexanone experiences self-association even in the vapor phase, mainly due to dipole-dipole interactions, and this helps justifying the spectroscopic behavior and larger population of the *equatorial* conformer in solvents that favor intermolecular interactions, such as non-polar ones; in non-polar solution (cyclohexane). Moreover, Allinger & Allinger (1958b), determined that the molecular weight of 2-bromocyclohexanone in cyclohexane is 2.7 times larger than the corresponding value for the monomer ( $176 \text{ g mol}^{-1}$ ), suggesting self-association.

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## CONSIDERAÇÕES FINAIS

Os resultados deste estudo permitiram uma melhor compreensão das interações que governam o isomerismo conformacional dos compostos modelos (2-halocicloexanonas). Enquanto a espectroscopia de Ressonância Magnética Nuclear forneceu evidência experimental de que interações hiperconjugativas operam nesses sistemas modelo, particularmente na 2-bromocicloexanona, cálculos teóricos corroboraram os resultados. Por outro lado, espectroscopia no infravermelho, juntamente com os cálculos teóricos, comprovaram que a 2-bromocicloexanona não se comporta como gás ideal e tende a se autoassociar na fase vapor e, provavelmente, também em solução apolar. Dessa forma, comprova-se a extrema relevância da química computacional para desvendar fenômenos químicos.

A existência dos dois confôrmeros mais estáveis das XC se deve a um balanço de interações hiperconjugativas, em que se destaca o importante papel do orbital  $\pi^*_{C=O}$  como acceptor de elétrons em sistemas que envolvem deslocalização eletrônica. Somando-se a isso, interações clássicas, isto é, repulsões estéricas e eletrostáticas, contribuem para o balanço de forças que regem o equilíbrio conformacional de 2-halocicloexanonas.

Por fim, este trabalho faz menção à importância das energias de interações entre os orbitais ligantes e antiligantes na estabilização dos equilíbrios conformacionais, já que os efeitos clássicos (estéricos e eletrostáticos), na maioria das vezes, não são suficientes para explicar a estabilidade conformacional de um numeroso conjunto de moléculas.