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NMR, solvation and theoretical investigations of conformational isomerism in 2-X-cyclohexanones (X = NMe_2, OMe, SMe and SeMe)

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ABSTRACT: The conformational equilibria of 2-*N*,*N*-dimethylamino- (**1**), 2-methoxy- (**2**), 2-methylthio- (**3**) and 2-methylselenocyclohexanone (**4**) were determined in various solvents by measurement of the $^3J_{H\text{-}2,H\text{-}3}$ couplings. The observed couplings were analyzed using theoretical and solvation calculations to give both the conformer energies in the solvents studied plus the vapor-phase energies and the coupling constants for the distinct conformers. These gave the conformer energies and couplings of **2**–**4**. The intrinsic couplings for the 2-*N*,*N*-dimethylamino compound were determined by the molecular mechanics PCMODEL program. The axial conformation in **1** is the most polar and also more stable in DMSO solution ($E_{eq} - E_{ax} = 0.05\,kcal\,mol^{-1}$) and the pure liquid, while the equatorial conformer predominates in the remaining solvents studied (except in CCl_4, where self-association is observed). In the methoxy ketone (**2**) the equatorial conformation is more stable in the vapor ($E_{eq} - E_{ax} = -0.30\,kcal\,mol^{-1}$) and in all solvents. The opposite behavior is shown by **3** and **4**, where the axial conformation is the more stable one in the vapor phase ($E_{eq} - E_{ax} = 1.60$ and $2.95\,kcal\,mol^{-1}$ for **3** and **4**, respectively) and is still the prevailing conformer in solution. The axial predominance for **3** and **4** is attributed to hyperconjugation between the electron lone pair of the hetero-substituent and the π^*_{CO} orbital. This interaction is stronger for **3** and **4** than in the case of **1** and **2**, where the '*gauche* effect' in the equatorial conformation should be more effective in stabilizing this conformation. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: conformational analysis; 2-substituted cyclohexanones; NMR spectroscopy; theoretical calculations; solvation theory

INTRODUCTION

Cyclohexanones are useful models for the rationalization of several factors in the synthetic[1,2] and physical organic chemical[3–7] fields. In the latter, there is great interest in the determination of the conformational equilibrium of 2-substituted cyclohexanones and the study of the effects which govern their equilibrium. The main techniques which have been applied in conformational analysis of 2-substituted cyclohexanones and of several other molecules are NMR, through the measurement of chemical shifts or coupling constants, and through the measurement of the band intensities corresponding to each conformer in the infrared spectra. In the NMR method, rigid derivatives have been used for determination of individual chemical shifts or couplings, but this procedure has been criticized by Wolfe and Campbell[8] because of the presence of the bulky group, often a *tert*-butyl group, which can cause distortions in the ring's geometry. Moreover, the determination of conformer populations through the direct measurement of the band intensities in the infrared spectrum may not lead to reliable values, since the conformers can present different molar absorptivities.[9] With these considerations, we propose the application of a methodology for conformational analysis based on NMR, theoretical calculations and solvation theory, which avoids the approaches in the classical methods. This work complements a recent study carried out for 2-halocyclohexanones (halo = F, Cl, Br and I),[5,7] now applied to systems conformationaly more flexible than the halo ketones, owing to the possible rotation of the substituent group [NMe_2 (**1**), OMe (**2**), SMe (**3**) and SeMe (**4**)], in addition to ring interconversion (Fig. 1).

It has been shown for the 2-halocyclohexanones[7] that the halogen volume influences the $n_X \rightarrow \pi^*_{CO}$ hyperconjugation in the axial conformation, with the largest halogen (or the one with the n_X orbital of highest energy) being preferred for such interaction. Moreover, in the case of small and more electronegative substituents, such

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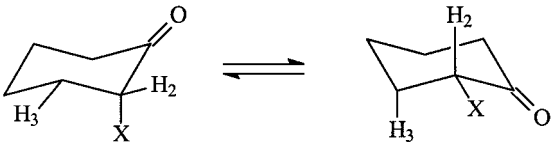

X = NMe_2 (**1**), OMe (**2**), SMe (**3**) and SeMe (**4**)

Figure 1. Conformational equilibrium for 2-X-cyclohexanones

as fluorine, there is an interaction which favors the equatorial form, namely the '*gauche* effect.' The origin of this effect has been much debated in the literature, and it is properly discussed in a review by Senderowitz and Fuchs.[10] The fact is that compounds **1–4** may present both intramolecular interactions, $n_X \rightarrow \pi^*_{CO}$ hyperconjugation and the '*gauche* effect,' in addition to the classical steric and electrostatic repulsions, hence their conformational isomerism is governed by a balance among them.

The methodology used in this work for conformational analysis has been fully described in detail by Abraham and Bretschneider,[11] but it can also be found in several other reports.[5,7,12–17]

EXPERIMENTAL

Compounds **1**, **3** and **4** were synthesized according to a literature procedure.[4] Compound **2** was purchased from Aldrich.

The ^{1}H NMR spectra were recorded on a Varian Gemini-300 spectrometer operating at 300.06 MHz. Spectra were taken with ca 20 mg cm^{-3} solutions with a probe temperature of 22 °C. [$^2H_{12}$]Cyclohexane was used as the deuterium lock for the CCl_4 solutions. All spectra were referenced to internal TMS. Typical conditions were a spectral width of 2500 Hz with 32 K data points, acquisition time 6.8 s, zero-filled to 128 K to give a digital resolution of 0.04 Hz per point.

RESULTS AND DISCUSSION

Calculations and NMR experiments

The stable conformers of **2–4** were found after scanning the dihedral angle H—C—X—Me (X = O, S and Se) or the H—C—N lone pair for **1**, of their axial and equatorial conformations through the AM1 semi-empirical method. Each minimum found in the potential energy surface was then optimized using the B3LYP method with the 6–311 + g(d,p) basis set, available in the Gaussian 98 program.[18] These minima are illustrated in Fig. 2, and the most stable form for both axial and equatorial conformations was used for the energy differences and coupling constant calculations, which are mentioned below. The axial g^- form is not a minimum for **3** and **4** at the level of theory carried out.

For **1**, the axial *anti* and equatorial g^- forms were the most stable conformations and should direct the conformational isomerism for the *N*,*N*-dimethylamino derivative [see Table 1 for the B3LYP/6–311 + g(d,p) conformational stabilities]. However, their calculated dipole moments do not differ much from one another, the axial form being slightly more polar (3.1 D) than the equatorial form (2.7 D), suggesting a small dependence of conformer populations on the solvent polarity. The axial percentage will increase with increase in the solvent relative permittivity, ε (dielectric constant). The situation for **2–4** is different, since the preferred conformations have dipole moments different enough to allow a significant dependence of the conformer molar fractions on the

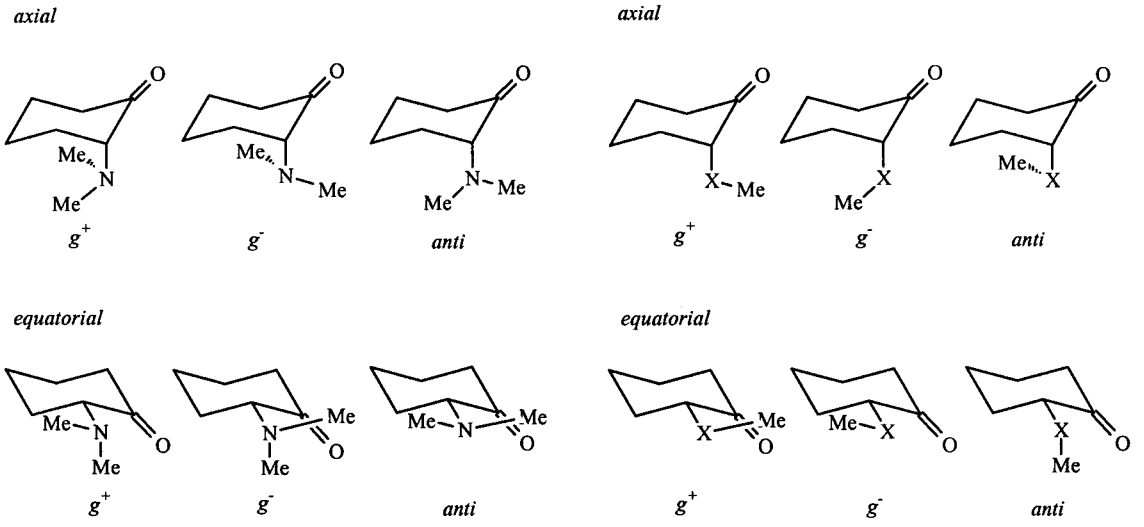

Figure 2. Stable conformations for **1–4**. Axial g^- form is not a minimum for **3** and **4**

Table 1. Relative energies (kcal mol^{-1}) (1 kcal = 4.184 kJ) and dipole moments (D) for compounds **1–4**[a]

			Axial			Equatorial		
Compound	X		g^+	g^-	*anti*	g^+	g^-	*anti*
1	NMe_2	E_{rel}	>5	>5	0.48	1.13	0	1.75
		μ	4.12	3.25	3.14	3.56	2.70	3.46
2	OMe	E_{rel}	0	1.48	>5	0.05	2.70	2.55
		μ	2.11	3.45		3.37	4.44	3.65
3	SMe	E_{rel}	0	—[b]	>5	2.04	2.93	2.63
		μ	1.98			3.45	4.70	3.60
4	SeMe	E_{rel}	0	—[b]	>5	2.80	2.66	3.27
		μ	2.10			3.35	4.57	3.50

[a] At the B3LYP/6–311 + g(d,p) level.
[b] Axial g^- is not a minimum.

solvent. In contrast to **1**, the main equatorial conformation for **2–4** (equatorial g^+ for **2** and **3** and g^- for **4**) is more polar than the most stable axial conformer (axial g^+), and so it is presumed that the equatorial percentage increases with increasing solvent dielectric constant. Because the axial form of **1** is more polar than the equatorial form, and in **2–4** the opposite is observed, it is suggested that $^3J_{H\text{-}2,H\text{-}3}$ (H-2 and H-3 *trans*) in **1** decreases with increasing solvent polarity, whereas in **2–4** it increases with increasing solvent polarity. This is due to the dihedral angle between H-2 and H-3$_{ax}$ in the axial conformer, which is close to 60° (smaller J), and in the equatorial conformer it is close to 180° (larger J) (see Fig. 1 for the hydrogen numbering). The other $^3J_{H\text{-}2,H\text{-}3}$ coupling (H-2 and H-3 *cis*) is an average between $^3J_{H\text{-}2ax,H\text{-}3eq}$ and $^3J_{H\text{-}2eq,H\text{-}3ax}$, which are similar in magnitude, and thus it does not vary so significantly with the solvent as the $^3J_{H\text{-}2,H\text{-}3}$ coupling (H-2 and H-3 *trans*), which varies between $^3J_{H\text{-}2eq,H\text{-}3eq}$ and $^3J_{H\text{-}2ax,H\text{-}3ax}$. For instance, whereas $^3J_{H\text{-}2,H\text{-}3\ (trans)}$ in **1** varies from 9.46 Hz in $CDCl_3$ to 7.39 Hz in DMSO-d_6, $^3J_{H\text{-}2,H\text{-}3\ (cis)}$ varies from 4.46 to 5.84 Hz in these solvents. Hence, the $^3J_{H\text{-}2,H\text{-}3\ (trans)}$ couplings are more appropriate for this study.

Before using the joint NMR and solvation methodology, reaction field parameters are required for the main conformations. These may be obtained through applying the calculated geometries to the MODELS program.[11] The structures used for **2** and **3** were the axial g^+ and equatorial g^+, and for **4** the axial g^+ and both the equatorial g^+ and g^- (owing to their similar energies). The parameters obtained are given in Table 2.

The experimental $^3J_{H\text{-}2,H\text{-}3\ (trans)}$ couplings obtained in different solvents (Table 3), together with the solvation theory, may then be used to search for the best solution for both the conformer energy difference and the values of J_{ax} and J_{eq}. The NMR data in Table 3 may be combined with the solvation calculations to provide a detailed account of the conformational equilibrium via Eqn (1).

$$\begin{aligned} J_{obs} &= n_{ax}J_{ax} + n_{eq}J_{eq} \\ n_{ax} + n_{eq} &= 1 \\ n_{eq}/n_{ax} &= e^{-\Delta E/RT} \\ \Delta E &= E_{eq} - E_{ax} \end{aligned} \quad (1)$$

where J_{obs} is the observed coupling, n_{ax} and n_{eq} are the mole fractions of the axial and equatorial conformers and J_{ax} and J_{eq} are the intrinsic coupling constants.

For **1**, an anomalous behavior of J in CCl_4 solution and pure liquid is observed, since its value is smaller than that expected if a sequence of J with the solvent polarity were followed. The fact is that a self-association in the axial conformation is probably occurring in these media, which causes a decrease in the J_{obs} value. Self-association

Table 2. MODELS reaction field parameters for compounds **1–4**

Compound	X		k[a]	h[a]	l	V_M[b]	μ[c]
1	NMe_2	Axial	1.6107	2.6564	0.5518	147.298	2.56
		Equatorial	1.3011	1.9708	0.5518	147.298	2.30
2	OMe	Axial	0.7621	3.9903	0.5489	124.019	1.61
		Equatorial	2.7808	2.0078	0.5489	124.019	3.08
3	SMe	Axial	0.7058	4.4778	0.5508	117.709	1.51
		Equatorial	3.5046	2.4482	0.5508	117.709	3.37
4	SeMe	Axial	0.6936	3.3366	0.5475	128.909	1.57
		Equatorial[d]	3.5868	3.0536	0.5475	128.909	3.12

[a] In kcal mol^{-1}.
[b] In cm^3 mol^{-1}.
[c] In debye.
[d] Averaged values of g^+ and g^- forms.

Table 3. Observed and (calculated)[a] $^3J_{H\text{-}2,H\text{-}3}$ (Hz) for compounds **1**–**4** in various solvents

Solvent	ε	**1**	**2**	**3**	**4**
CCl_4	2.2	4.04, 7.33[c]	5.53, 9.30 (9.31)	4.01, 4.01 (3.97)	3.60, 3.60 (3.68)
$CDCl_3$	4.8	4.46, 9.46	5.62, 9.95 (9.87)	4.86, 4.86 (4.70)	4.02, 4.02 (3.95)
CD_2Cl_2	8.9	4.27, 8.79	6.18, 10.18 (10.17)	5.22, 5.22 (5.31)	4.35, 4.35 (4.25)
Acetone-d_6	20.7	4.27, 8.05	4.45, 7.50[c]	5.41, 5.41 (6.02)	4.71, 4.71 (4.73)
CD_3CN	37.5	5.13, 7.90	5.63, 10.50 (10.58)	5.31, 6.60 (6.55)	5.10, 5.10 (5.12)
DMSO-d_6	46.7	5.84, 7.39	5.71, 10.66 (10.63)	5.34, 6.90 (6.77)	5.29, 5.29 (5.32)
Pure liquid	—[b]	5.49, 7.45[c]	5.61, 9.60 (9.64)	5.04, 5.04 (4.72)	3.80, 3.80 (3.82)

[a] The r.m.s. errors were 0.06, 0.30 and 0.06 Hz for **2**, **3** and **4**, respectively.
[b] The solute relative permittivity was obtained through interpolating the J values in an ε versus $^3J_{H\text{-}2,H\text{-}3\ (trans)}$ plot. They were 3.4 for **2**, 4.9 for **3** and 3.5 for **4**.
[c] Abnormal values due to solute–solvent electrostatic interaction.

Table 4. Intrinsic coupling constants (Hz) calculated through BESTFIT and PCMODEL for compounds **1**–**4**

		BESTFIT		PCMODEL	
Compound	X	$^3J_{H\text{-}2eq,H\text{-}3eq}$	$^3J_{H\text{-}2ax,H\text{-}3ax}$	$^3J_{H\text{-}2eq,H\text{-}3eq}$	$^3J_{H\text{-}2ax,H\text{-}3ax}$
1	NMe_2			3.31	11.81
2	OMe	3.19	11.71	3.61	11.30
3	SMe	2.82	12.02	1.97	12.31
4	SeMe	3.49	12.21	1.95	12.38

phenomena are commonly observed in other carbonyl compounds[19–21] and should also be present in **1**. For **2**, the abnormal values of J in acetone-d_6, which are smaller than expected, may be attributed to an electrostatic interaction between solute and solvent, which is stronger in the equatorial than in the axial form.

The intrinsic coupling constants for **2**–**4** were obtained using the program BESTFIT.[11] This calculates the couplings in all the solvents for any given value of ΔE^V using the solvation energy calculated by MODELS[11] and then compares the observed and calculated couplings. The best agreement was obtained with the energy differences given in Table 5. In Table 4, the intrinsic couplings calculated through the molecular mechanics PCMODEL program[22] for the main conformers of **1**–**4** are also shown. The individual couplings calculated using both methods (BESTFIT[11] and PCMODEL[22]) were consistent, and the observed tendency, i.e. $^3J_{H\text{-}2ax,H\text{-}3ax}$ (equatorial conformer) increases as the heteroatom electronegativity decreases (O > N > S > Se), whereas $^3J_{H\text{-}2eq,H\text{-}3eq}$ (axial conformer) decreases with decreasing heteroatom electronegativity (except for the Se derivative). This tendency is in agreement with the substituent effect on the coupling constants $^3J_{HH}$, as predicted by Abraham *et al.*[23]

The conformational analysis may be performed through Eqn (1) and the BESTFIT[11] couplings. In the case of **1**, where the solvation theory[11] was not applicable, despite the large variation of J with change in solvent, the differences between the dipole moments of the two main conformations (one axial and the other equatorial) is too small, and does not justify such variations of J. MODELS[11] predicts smaller dependence of the conformer population of the NMe_2 derivative on the solvent than is observed. However, in the case of the OMe, SMe and SeMe derivatives, the calculations with MODELS[11] work well, and its results are in reasonable agreement with those from PCMODEL.[22] Hence, the individual coupling constants for **1** obtained through PCMODEL[22] and the BESTFIT[11] couplings for **2**–**4** may be used with confidence for their conformational analyses, the results of which are presented in Table 5.

Table 5. Energy differences ($E_{eq}-E_{ax}$, kcal mol^{-1}) and axial mole fractions for **1**–**4**

	$E_{eq}-E_{ax}$				n_{ax}			
Solvent	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Vapor		−0.30	1.60	2.95		0.38	0.94	0.99
CCl_4	0.07	−0.55	1.14	2.23	0.53	0.28	0.88	0.98
$CDCl_3$	−0.56	−0.75	0.80	1.70	0.28	0.22	0.80	0.95
CD_2Cl_2	−0.34	−0.88	0.58	1.38	0.36	0.18	0.73	0.91
Acetone-d_6	−0.14	−0.02	0.37	1.06	0.44	0.49	0.65	0.86
CD_3CN	−0.10	−1.10	0.23	0.86	0.46	0.13	0.60	0.81
DMSO-d_6	0.05	−1.13	0.17	0.78	0.52	0.13	0.57	0.79
Pure liquid	0.02	−0.67	0.79	1.90	0.51	0.24	0.79	0.96

Table 6. Axial conformer molar fractions of 2-substituted cyclohexanones in vapor and in $CDCl_3$

X	Vapor	$CDCl_3$	$CDCl_3$ (lit.[4])
F	0.64[a]	0.13[a]	0.17
Cl	0.86[a]	0.42[a]	0.45
Br	0.92[a]	0.66[a]	0.71
I	0.96[a]	0.85[a]	0.88
OMe	0.38	0.22	0.28
SMe	0.94	0.80	0.85
$SeMe_2$	0.99	0.95	0.92
NMe_2	—	0.28	0.44

[a] Ref. 7.

Table 6 presents the axial conformer molar fractions of 2-substituted cyclohexanones in the vapor and in $CDCl_3$, which includes data for the compounds described in this work (**1**–**4**) and for the halogen derivatives obtained previously[7] with the same method, and also data for the whole series obtained through Eliel's classical method through J, $\delta_{C\text{-}1}$ and $\delta_{C\text{-}2}$ values, using the *tert*-butyl derivatives as model compounds. The agreement between these series of results is remarkable.

Conformational preferences

The conformational behavior of **1**–**4** (data in Table 5) can be interpreted as follows. An increase was observed, for instance in $CDCl_3$, of the axial population with increase in the heteroatom size and with decrease in the heteroatom electronegativity, on going from **1** to **4**. These indicate the steric and electrostatic nature of the interactions governing the conformational equilibrium of the compounds studied here. However, the non-classical origin of some other interactions existing in these molecules is known, namely σ_{CX}–π^*_{CO} and n_X–π^*_{CO} hyperconjugation and the '*gauche* effect.' The importance of all these effects in the conformational analysis of 2-substituted cyclohexanones has been shown in the literature.[3,5,7,10,24,25]

Dipolar repulsion between the heteroatom and the carbonyl oxygen has been invoked to explain the progressive larger stability of the most polar conformer with the increase in the solvent dielectric constant. *syn*-1,3-Diaxial steric repulsion also has a role in driving the equilibrium towards the equatorial conformation. These two terms, steric and electrostatic energies, may be obtained from the MODELS[11] calculations and their values are given in Table 7 for the calculated main conformers of **1**–**4**. The highest values for both the steric and electrostatic terms in the equatorial form of **2**–**4** is observed, which favors the axial conformation. However, the equatorial form in **2** is predominant in all states, indicating the strong importance of non-classical effects on this conformation, namely the '*gauche* effect.' For **1**, the steric effects on the axial conformation are larger than in the equatorial conformation, owing to *syn*-1,3-diaxial repulsion, whereas the dipole–dipole interaction is greater in the equatorial form than in the axial one, which suggests that, as for **2**, the preference for the equatorial form in **1** is also governed by the cited non-classical effect.

It is clear, then, that factors other than classical interactions lead the conformational isomerism of **1**–**4**. In the case of **1** and **2**, which bear highly electronegative substituents, there is a significant equatorial prevalence even in moderate or non-polar solvents. This can be explained by the '*gauche* effect,' whose origin has several explanations,[26–30] but it is usually formulated as follows: 'when electron pairs or polar bonds are placed or generated on adjacent pyramidal atoms, *syn*- or *anti*-periplanar orientations are disfavored energetically with respect to that structure which contains the maximum number of *gauche* interactions.'[26] In the case of **3** and **4**, which bear *n* orbitals higher in energy than **1** and **2**, and thus are more accessible to an n_X–π^*_{CO} donation, there is a markedly greater axial preference in comparison with the equatorial form, showing the importance of such interactions for substituents of the third or higher periods bearing lone pairs.

Additional and strong evidence that orbital interactions play an important role in the determination of the conformer populations comes from the high molar fractions for the axial conformer (n_{ax}) for most of the 2-substituted cyclohexanones (0.42–0.95) in contrast to the F, O and N derivatives (0.13, 0.22 and 0.28, respectively) (Table 6). The higher n_{ax} values are parallel to the large shielding effect (in ppm) of Cl (−8.7), Br (−8.7) and I (−7.5) in comparison with F (−6.3), and of S (−4.5) and Se (−4.6) in comparison with O (−2.1), and the low value for N (−0.4) on the carbonyl carbon chemical shifts,[25] in contrast to what might be expected from the inductive effect of the high electronegativities of F, O and N.[31] This means that the same orbital interactions that lead to a

Table 7. Steric (ΔE^{steric})[a] and electrostatic (ΔE^{elec})[b] energies (kcal mol^{-1}) for compounds **1**–**4**

Compound	X	E^{steric}_{eq}	E^{steric}_{ax}	ΔE^{steric}	E^{elec}_{eq}	E^{elec}_{ax}	ΔE^{elec}
1	NMe_2	1.83	2.25	−0.42	5.34	4.72	0.62
2	OMe	0.96	0.46	0.50	6.54	5.11	1.43
3	SMe	0.17	−0.28	0.45	5.73	3.94	1.79
4	SeMe	0.50	0.46	0.04	3.12	1.56	1.56

[a] $\Delta E^{steric} = E^{steric}_{eq} - E^{steric}_{ax}$.
[b] $\Delta E^{elec} = E^{elec}_{eq} - E^{elec}_{ax}$.

large shielding effect of the carbonyl carbon are responsible for the large population of the axial conformer.

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