Conformational Preferences of 2-Methoxy, 2-Methylthio, and 2-Methylselenocyclohexyl-*N*,*N*-dimethylcarbamate: A Theoretical and Experimental Investigation

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Studies on the conformational equilibria of 2-methoxy, 2-methylthio, and 2-methylselenocyclohexyl-*N*,*N*-dimethylcarbamate are reported. DNMR spectroscopy experiments at 203 K provided the percentages of each conformer in equilibrium. Theoretical calculations using the MP2, B3LYP, and B971 methods with cc-pVDZ basis set were applied to determine the differences in energy between the conformers. The analysis of the potential energy surface (PES) for each conformer showed the presence of two rotamers. NBO analysis provided an explanation of the factors (hyperconjugative and steric interactions) that drive rotamer and conformer preferences.

Introduction

The conformational analysis of six-membered rings has provided the foundation for modern stereochemistry, whose main objective is the determination of the molecular geometry, the relative energies of conformers included, and attempts to determine the major forces controlling the relative conformational stabilities.[1−4]

Investigation of the factors that determine the conformational preferences of substituents in these compounds have enriched our understanding of how organic fragments behave when joined together into a single compound.[1−9] Conformational preferences are usually explained by a balance between effects, namely, electron delocalization and steric repulsions.[10−13]

One of the most-reliable methods to measure conformational equilibrium constants is the determination of integral ratio intensities of NMR signals for individual conformers under "conformational inflexible" conditions. This occurs at low temperatures, when the inversion of the ring in substituted cyclohexanes becomes sufficiently slow in the NMR spectroscopy time scale. Zefirov et al.[6] calculated the conformational equilibrium constants for a series of 1,2-*trans*-disubstituted cyclohexanes by using this methodology through low-temperature ^{13}C NMR spectroscopy experiments.

The development in computational chemistry led to a large variety of studies using both theoretical and experimental methodologies.[7−13] Several computational studies describing the conformational behavior of monosubstituted cyclohexanes have been performed. These studies showed that the steric effects do not seem to exert a significant influence on the equatorial preference of the methyl group and substituents.[10,12]

Several *trans*-1,2-disubstituted cyclohexane derivatives have been studied[7,14−15] as models to evaluate the competition between important interactions such as hyperconjugative and either attractive or repulsive steric effects. Some researchers have investigated the conformational preferences of *trans*-2-halocyclohexanols and their methyl ethers.[14−15] It was verified that in halohydrins intra- and/or intermolecular hydrogen bonds lead the conformational equilibrium toward the *equatorial*−*equatorial* (*eq*−*eq*) conformer,[14−15] whereas, for their methyl ethers, the *eq*−*eq* population is not as large as that for the alcohols. Equilibrium is governed by steric and dipolar factors as well the "gauche effect".[14−15]

Recently, some cyclohexane derivatives with a carbamate as a substituent were investigated with respect to the rotational barrier of the carbamate portion[16−18] and the possible anticholinesterasic activity of one of the compounds.[17] Therefore, carbamate derivatives constitute an important class among biologically active compounds and attempts of correlating molecular structure to pharmacological activity is under way.[17−18]

This work reports on the conformational analysis of the cis and trans isomers of 2-methoxycyclohexyl-*N*,*N*-dimethylcarbamate (**1**), 2-methylthiocyclohexyl-*N*,*N*-dimethylcarbamate (**2**), and 2-methyselenocyclohexyl-*N*,*N*-dimethylcarbamate (**3**) (Figure 1), yet unknown in the literature, through NMR spectroscopy in association with theoretical calculations.

Experimental Section

Compounds. The compounds were synthesized starting from the parent ketones, which were either purchased (X = O) or obtained through procedures described in the literature.[19−22] These ketones were reduced with $LiAlH_4$ in THF at room temperature[19] to yield a mixture of cis and trans alcohols. After that, the corresponding alcohols were reacted with metallic sodium followed by *N*,*N*-dimethylcarbamyl chloride to yield the target compounds as a mixture of cis and trans isomers, which were separated through silica column elution. For compound **1**, we used hexane/ethyl acetate (8:2) and for compound **2**, benzene/ethyl acetate (8:2). It was not possible to isolate the compound **3** trans isomer because of its very low rate in the mixture.

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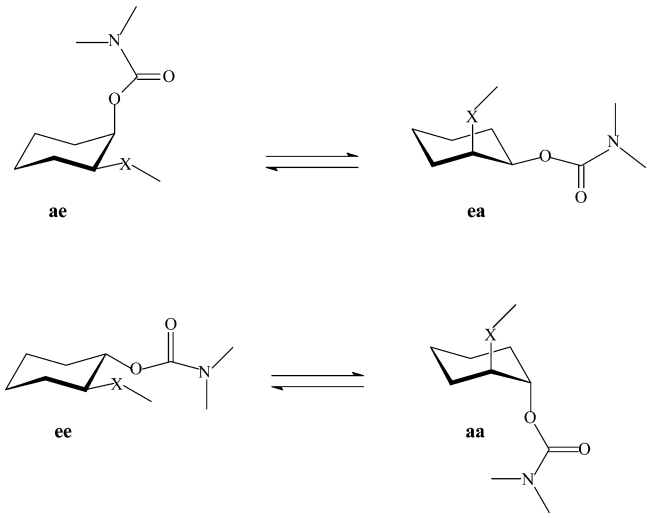

Figure 1. Conformational equilibrium of cis and trans isomers of *N*,*N*-dimethycarbamate 2-monossubstituted (X = O, S, and Se).

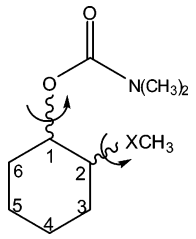

Figure 2. Pictorial presentation of the dihedral angle analyzed and key numbering of studied compounds.

NMR Spectroscopy Experiments. The compounds were characterized through ^{1}H and ^{13}C spectra and 2D NMR contour plots. The isomer assignments were done taking into account the chemical shifts and coupling constants of hydrogens H_1 and H_2. The spectra were obtained on a Varian Mercury Plus 300 operating at 300.06 MHz for ^{1}H and 75.46 MHz for ^{13}C. Spectra were obtained with ca. 20 mg cm^{-3} of acetone-d_6 as a solvent and probe temperature of 298 K referenced to Me_4Si under typical conditions for ^{1}H (spectral width 4000 Hz with 32 K data points and zero filled to 128 K to give a digital resolution of 0.03 Hz). The chemical shifts of the compounds studied are presented below, and the atom key numbering is shown in Figure 2.

The low-temperature ^{1}H and ^{13}C NMR spectra of ca. 10 mg of solutions of compounds **1**−**3** in 0.7 mL of acetone-d_6 at 203 K were recorded on Bruker AVANCE II$^+$-300 equipment operating at 300.13 MHz for ^{1}H and 75 MHz for ^{13}C.

Cis-2-methoxycyclohexyl-*N*,*N*-dimethylcarbamate. NMR- ^{1}H (C_3D_6O, 300.06 MHz; δ in ppm): δ 5.04 (1H, m, H_1); 3.37 (3H, m, CH_3) 3.31 (1H, m, H_2); 2.93 (6H, s, $2CH_3$); 1.90 (1H, m, H_{6eq}); 1.76 (1H, H_{3eq}); 1.72 (1H, m, H_{5eq}); 1.66 (1H, m, H_{3ax}); 1.57 (1H, m, H_{4eq}); 1.52 (1H, m, H_{6ax}); 1.39 (1H, m, H_{4ax}); 1.33 (1H, m, H_{5ax}). NMR- ^{13}C (C_3D_6O, 75.46 MHz, δ in ppm): δ 156.5 (C═O); 79.2 (C_2); 71.5 (C_1) 56.8 (CH_3); 36.5 (N−CH_3); 36.1 (N−CH_3); 28.5 (C_6); 27.8 (C_3); 22.6 (C_5); and 21.6 (C_4).

Cis-2-methylthiocyclohexyl-*N*,*N*-dimethylcarbamate. NMR- ^{1}H (C_3D_6O, 300.06 MHz; δ in ppm): δ 5.03 (1H, m, H_1); 2.94 (6H, s, $2CH_3$); 2.83 (1H, m, H_2); 2.11 (3H, m, CH_3) 1.99 (1H, m, H_{6eq}); 1.82 (1H, H_{3eq}); 1.73 (1H, m, H_{5eq}); 1.70 (1H, m, H_{3ax}); 1.55 (1H, m, H_{4eq}); 1.51 (1H, m, H_{6ax}); 1.49 (1H, m, H_{5ax}); 1.44 (1H, m, H_{4ax}). NMR- ^{13}C (C_3D_6O, 75.46 MHz, δ in ppm): δ 156.3 (C═O); 71.9 (C_1) 49.3 (C_2); 36.6 (N−CH_3); 36.0 (N−CH_3); 31.3 (C_6); 30.9 (C_3); 24.8 (C_5); 23.6 (C_4); and 13.8 (CH_3).

Cis-2-methyselenocyclohexyl-*N*,*N*-dimethylcarbamate. NMR- ^{1}H (C_3D_6O, 300.06 MHz; δ in ppm): δ 4.96 (1H, m, H_1); 3.12 (1H, m, H_2); 2.94 (6H, s, $2CH_3$); 1.99 (3H, m, CH_3) 1.97 (1H, m, H_{6eq}); 1.91 (1H, H_{3eq}); 1.87 (1H, m, H_{3ax}); 1.67 (1H, m, H_{5eq}); 1.61 (1H, m, H_{4eq}); 1.61 (1H, m, H_{6ax}); 1.44 (1H, m, H_{4ax}); 1.39 (1H, m, H_{5ax}). NMR- ^{13}C (C_3D_6O, 75.46 MHz, δ in ppm): δ 156.1 (C═O); 73.4 (C_1) 44.1 (C_2); 36.5 (N−CH_3); 36.0 (N−CH_3); 30.2 (C_6); 29.9 (C_3); 24.9 (C_5); 21.6 (C_4); and 4,8 (CH_3).

Trans-2-methoxycyclohexyl-*N*,*N*-dimethylcarbamate. NMR- ^{1}H (C_3D_6O, 300.06 MHz; δ in ppm): δ 4.67 (1H, m, H_1); 3.39 (3H, m, CH_3) 3.19 (1H, m, H_2); 2.91 (6H, s, $2CH_3$); 1.93 (1H, H_{3eq}); 1.92 (1H, m, H_{6eq}); 1.63 (1H, m, H_{4eq}); 1.62 (1H, m, H_{5eq}); 1.36 (1H, m, H_{3ax}); 1.34 (1H, m, H_{4ax}); 1.31 (1H, m, H_{6ax}); 1.30 (1H, m, H_{5ax}). NMR- ^{13}C (C_3D_6O, 75.46 MHz, δ in ppm): δ 156.4 (C═O); 80.4 (C_2); 75.2 (C_1) 57.4 (CH_3); 36.5 (N−CH_3); 36.0 (N−CH_3); 29.9 (C_6); 29.0 (C_3); 23.1 (C_5); and 23.0 (C_4).

Trans-2-methylthiocyclohexyl-*N*,*N*-dimethylcarbamate. NMR- ^{1}H (C_3D_6O, 300.06 MHz; δ in ppm): δ 4.67 (1H, m, H_1); 2.92 (6H, s, $2CH_3$); 2.65 (1H, m, H_2); 2.11 (3H, m, CH_3); 2.08 (1H, m, H_{6eq}); 2.07 (1H, H_{3eq}); 1.69 (1H, m, H_{5eq}); 1.66 (1H, m, H_{4eq});1.60 (1H, m, H_{3ax}); 1.44 (1H, m, H_{6ax}); 1.37 (1H, m, H_{5ax}) 1.34 (1H, m, H_{4ax}). NMR- ^{13}C (C_3D_6O, 75.46 MHz, δ in ppm): δ 156.3 (C═O); 74.9 (C_1); 48.6 (C_2); 36.6 (N−CH_3); 36.0 (N−CH_3); 31.3 (C_6); 30.9 (C_3); 24.8 (C_5); 23.0 (C_4) and 13.8 (CH_3).

TABLE 1: Percentages of Conformers of Each Isomer of Compounds 1−3 Obtained Experimentally through ^{1}H and ^{13}C Spectra Signal Integration at Low-Temperature Experiments (DNMR)[a]

	cis		trans	
compound	ae	ea	aa	ee
1	80	20	12	88
2	90	10	10	90
3	81	19	*b*	*b*

[a] Experiments performed at 203 K in Acetone-d_6. [b] Isomer not isolated.

Computational Details

The theoretical calculations were performed with Gaussian03.[23] The most-stable conformers of compounds **1**−**3** were obtained by calculating the potential energy surface (PES) through the HF[24]/6-31G(d,p)[25] level of theory. The conformational equilibrium of compounds **1**−**3** is shown in Figure 1. The most-stable structures of each conformer of **1**, **2**, and **3** were determined through potential energy surface calculation (PES) by varying two dihedral angles $C_6-C_1-O-C_{C=O}$ and $C_3-C_2-X-C_{CH_3}$ (Figure 2) in increments of 10° ranging from 0° to 360° with partial optimization at each point.

The geometries for the most-stable conformers obtained from PES were optimized applying the MP2 method.[26] Dunning's basis set (cc-pVDZ) was used to carry out these calculations because this basis set describes the atoms present in the studied compounds satisfactorily. This basis set is defined as a consistent correlation that contains all of the correlating functions that lower the correlation energies by similar amounts as well as all correlation functions that lower the energy by large amounts.[27] Stationary points were fully optimized and characterized by vibrational frequency calculations, which also provided zero

TABLE 2: Energy Difference (kcal mol^{-1}) and Percentages of Each Conformer of Compounds 1−3 Obtained through Theoretical Calculations in the Vapor Phase

	cis						trans					
	1		**2**		**3**		**1**		**2**		**3**	
	ae	**ea**	**ae**	**ea**	**ae**	**ea**	**aa**	**ee**	**aa**	**ee**	**aa**	**ee**
	ΔE/%	ΔE/%	ΔE/%	ΔE/%	ΔE/%	ΔE/%	ΔE/%	ΔE/%	ΔE/%	ΔE/%	ΔE/%	ΔE/%
MP2/cc-pVDZ	0/83	0.94/17	0/82	0.89/18	0.64/25	0/75	0/94	1.62/6	0/84	0.97/16	0.61/26	0/74
B3LYP/cc-pVDZ	0/66	0.40/34	0/82	0.89/18	0/72	0.54/28	0.06/47	0/53	0.40/34	0/66	0.88/18	0/82
B971/cc-pVDZ	0/74	0.60/26	0/83	0.92/17	0/57	0.16/43	0/56	0.14/44	0.20/43	0/57	1.0/15	0/85

TABLE 3: Energy Difference (kcal mol^{-1}) and Percentages of Each Conformer of Compounds 1−3 Obtained through Theoretical Calculations with Solvent Effect with the Onsager Model at B3LYP/cc-pVDZ

Compound	cis		trans	
	ae	**ea**	**aa**	**ee**
	ΔE/%	ΔE/%	ΔE/%	ΔE/%
1	0/70	0.49/30	1.15/13	0/87
2	0/67	0.40/33	1.94/4	0/96
3	0/87	1.13/13	1.26/10	0/90

point vibrational energy (ZPE). Natural bond orbital (NBO)[28] analyses were performed applying the B3LYP[29] hybrid functional and the cc-pVDZ basis set. These calculations were performed using NBO version 3.0[30] for the delocalization interaction and NBO version 5.0[31] for the steric interactions using Gaussian03.[23]

Results and Discussion

Low-temperature experiments to determine the conformer preferences of all compounds were carried out successfully, except for the trans isomer of compound **3**, which was not isolated. Both ^{1}H and ^{13}C NMR spectra were run as a function of temperature in acetone-d_6. The ratios of each conformer in conformational equilibrium shown in Table 1 were obtained through ^{1}H and ^{13}C signal integration at low-temperature experiments. These experiments were also useful to identify the obtained conformers through the measurement of *w* (half-height line width) for ^{1}H resonance, which corresponds to the sum of the vicinal couplings plus any long-range couplings.[20]

The results of the calculations performed in the gas phase and including solvent (acetone) effects through the Onsager model[32] are important tools to describe the conformational behavior of compounds **1**−**3**. The energy minimums localized to each conformer were fully optimized in the gas phase and in solvent (acetone), yielding the energies listed in Tables 2 and 3. The conformer populations N_I and N_{II} were calculated through eq 1. In this equation, *N* is the molar fraction of either **ae** and **ea** or **aa** and **ee** (Figure 1), and ΔE is the conformational energy difference determined previously. The results are shown in Tables 2 and 3.

$$N_I / N_{II} = e^{-\Delta E/RT} \quad (1)$$

It can be observed from Table 2 that the energy difference between conformers for cis or trans isomers calculated at the MP2/cc-pVDZ level in some cases are smaller than 1 kcal mol^{-1}. In addition, this level of theory (MP2/cc-pVDZ) did not reproduce the experimental results for the trans isomer of compounds **1** and **2** or the cis isomer of compound **3**. Therefore, we performed single-point energy calculations, using geometries optimized at the MP2/cc-pVDZ level with two hybrid functionals (B3LYP[29] and B971[33]). The energy difference and percentages for each functional and for each conformers of compounds **1**−**3** are listed in Table 2. The hybrid functional methods reproduced the experimental results for the cis isomer of compounds **1**−**3**. In the particular case of trans isomers, there are energy differences smaller than 0.5 kcal mol^{-1} (**1**−**2**) in both hybrid functional methods. However, a good correlation was observed between the experimental and theoretical energy difference for the cis isomer of compound **3**. As can be seen in Table 3, the results obtained by solvation calculation at the MP2/cc-PVDZ level are in agreement with the experimental results (Table 1), showing that the solvent effect plays an important role in the conformational preference for all compounds studied here.

TABLE 4: Sum of Main Hyperconjugative Interactions from Second-Order Perturbation Energy Matrix (kcal mol^{-1}) Obtained through NBO Analyses at B3LYP/cc-pVDZ for Compounds 1−3

isomers	conformers	**1**	**2**	3
cis	**ae**	96.3	91.4	89.9
	ea	94.1	89.0	87.8
trans	**aa**	85.3	81.7	80.7
	ee	83.9	82.7	81.0

To find out which effects are responsible for the stabilization of each conformer, we performed a study of attractive (hyperconjugative interaction) and repulsive (steric interaction) stereoelectronic effects through NBO[28,30−31] analysis for all conformers. To simplify the NBO analysis, the most-important hyperconjugative (attractive) and steric (repulsive) interactions were summed and are summarized in Tables 4 and 5, respectively.

For the cis isomer, compound **1**−**2**, the results suggest that hyperconjugative interactions are responsible for the larger stabilization of conformer **ae** in relation to conformer **ea**. In Table 4, it can be observed that the sums of the main second-order stabilization energies for **ae** conformers are around 2.0 kcal mol^{-1} higher than those of conformers **ea**. Note that the steric interaction energies between **ae** and in **ea** are quite similar (Table 5) for the cis isomer of compounds **1**−**2**, which, as mentioned before, corroborates the hyperconjugative interactions as the main factor driving the conformational preference of compounds **1** and **2**.

However, for compound **3**, the difference between steric interactions in **ae** and in **ea** is around 8 kcal mol^{-1}(Table 5). This energy difference is more significant than that observed for hyperconjugative interactions (Table 4). These results indicate that for compound **3** both steric and hyperconjugative interactions drive the conformational preferences.

For the trans isomer, only the hyperconjugative interactions do not explain the conformational preferences of compounds **1**−**3**, especially in the case of compound **1**. For this compound, NBO analysis showed that the sum of most-important second-order stabilization energies for conformer **aa** is higher than that for conformer **ee** by 1.4 kcal mol^{-1} (Table 4), in contrast to the experimental result. However, by analyzing the data in Table 5, it can be observed that there are strong repulsive steric

TABLE 5: Sum of Main Steric Interaction Energies (kcal mol^{-1}) Obtained through NBO Analysis at B3LYP/cc-pVDZ

		1	2	**3**
		ae		
σ_{C1-C2}	LP_{O7}	12.58	11.72	7.93
σ_{C1-Heq}	LP_{O7}	8.55	8.05	4.97
σ_{C2-Hax}	LP_{O7}			0.56
σ_{C1-C2}	LP_x	14.05	6.59	2.73
σ_{C1-Heq}	LP_x			1.34
σ_{C2-Hax}	LP_x	11.00	7.5	3.10
TOTAL		46.18	33.86	20.63
		ea		
σ_{C1-C2}	LP_{O7}	12.94	12.46	12.32
σ_{C1-Hax}	LP_{O7}	10.09	10.12	10.84
σ_{C2-Heq}	LP_{O7}			
σ_{C1-C2}	LP_x	13.81	7.72	1.65
σ_{C1-Hax}	LP_x			
σ_{C2-Heq}	LP_x	8.77	3.87	3.94
TOTAL		45.61	34.17	28.75
		aa		
σ_{C1-C2}	LP_{O7}	13.95	12.31	11.95
σ_{C1-Heq}	LP_{O7}	10.10	10.07	9.96
σ_{C2-Heq}	LP_{O7}		0.74	0.74
σ_{C1-C2}	LP_x	12.67	7.95	5.84
σ_{C1-Heq}	LP_x		1.65	2.03
σ_{C2-Heq}	LP_x	9.04	3.96	1.58
TOTAL		45.76	36.68	32.10
		ee		
σ_{C1-C2}	LP_{O7}	7.43	11.86	11.61
σ_{C1-Hax}	LP_{O7}	9.59	8.07	8.15
σ_{C2-Hax}	LP_{O7}	0.52		
σ_{C1-C2}	LP_x	13.79	6.50	4.24
σ_{C1-Hax}	LP_x	0.65		
σ_{C2-Hax}	LP_x	8.15	3.64	2.82
TOTAL		40.13	30.07	26.82

interactions for conformer **aa**, which are around 5 kcal mol^{-1} higher than those of conformer **ee**. This repulsive interaction can be invoked to explain the higher stability of conformer **ee** in comparison to that of conformer **aa** of compound **1**.

For compounds **2** and **3**, the differences between the sums of the most-important second-order stabilization energies of conformers **ee** and **aa** are 1.0 and 0.8 kcal mol^{-1}, respectively. Alternatively, the steric repulsive interaction (Table 5) of conformer **aa** is around 6 kcal mol^{-1} higher than that of conformer **ee.** Therefore, for the trans isomers of compounds **2** and **3**, it was observed that both interactions drive the conformational preference for conformer **ee**. Both interactions work in the same way: while the attractive hyperconjugative interaction stabilizes conformer **ee**, the repulsive steric interaction destabilizes conformer **aa**, leading to a higher stabilization of conformer **ee**.

Conclusions

The conformational equilibrium of compounds **1**−**3** was investigated through theoretical and experimental methods. The amounts of conformers in equilibrium determined through DNMR spectroscopy were in agreement with those determined theoretically. The cis isomers of compounds **1**−**2** present a small difference between steric interactions; therefore, the hyperconjugative interactions lead to the stabilization of **ae** conformers. For compound 3, both effects, steric and hyperconjugative interactions, are important in conformational rule.

The conformational preference of the **ee** conformer for the trans isomer of compounds **2** and **3** is dictated by hyperconjugative and steric interactions, while the stability of conformer **ee** for the trans isomer of compound **1** is dictated by steric interactions.

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Supporting Information Available: Most important interaction energies, calculated to each conformer through the NBO method. This material is available free of charge via the Internet at http://pubs.acs.org.

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