Conformational Analysis of (*S*)-4-(Cyclohexoxycarbonyl)-2-azetidinone

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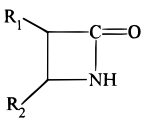
The conformational analysis of (*S*)-4-(cyclohexoxycarbonyl)-2-azetidinone was carried out using quantum mechanical calculations. ^{1}H NMR spectra at different temperatures were used to estimate the relative populations of axial and equatorial chair forms of the cyclohexyl group. Gas-phase energy calculations of the whole molecule rendered two preferred structures, both of them with the cyclohexyl group in equatorial conformation. The azetidinone ring was found to be in a quasi-planar arrangement with endocyclic dihedrals deviating from the ideal planar conformation by 1−2°. Results showed also that the cyclohexoxycarbonyl group is highly flexible and that the stabilization of the molecule is favored by intramolecular interactions between the amide and the ester group. The occurrence of this type of interaction in nonpolar solution was evidenced by FTIR spectroscopy. Additionally, SCRF calculations revealed that solvent effects on the conformational preferences of this compound are small.

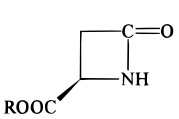
Introduction

C-substituted 2-azetidinones (**1**) are compounds of widely recognized interest due to their inclusion in β-lactam antibiotics like penicillins and cephalosporins.[1] They are also useful as monomers in ring-opening polymerization reactions leading to novel polyamides with unusual properties of technical importance.[2] Specifically, a number of (*S*)-4-(alkoxycarbonyl)-2-azetidinones (**2**) have been recently synthesized from L-aspartic acid and polymerized to poly(α-alkyl-β-L-aspartate)s.[3−5] These polymers are stereoregular nylon 3 derivatives that are distinguished by being able to adopt helical conformations with features similar to the α-helix of polypeptides.[6−9] The reactivity of C-substituted 2-azetidinones has been related with the deviation from planarity of the lactam ring caused by the presence of the substituent.[10] On the other hand, intramolecular interactions of side groups, either among themselves or with amide main chain groups, have been found to be responsible for the outstanding conformational behavior displayed by these poly(β-amide)s.

Whereas the molecular structure of 2-azetidinone has been recently investigated using both experimental[11,12] and theoretical methods,[10,13,14] very little is known about the structural properties of its substituted derivatives. With regard to (*S*)-4-(alkoxycarbonyl)-2-azetidinones (**2**), the methoxy derivative is the unique compound of this family whose structure has been investigated thus far.[10]



(1)



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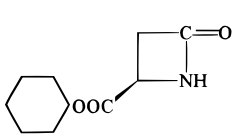
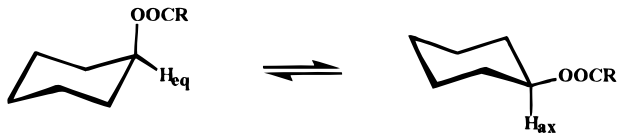


(3)

In this paper we want to report on (*S*)-4-(cyclohexoxycarbonyl)-2-azetidinone (**3**), a compound that is appealing to a structural study because of the number of conformational possibilities that arises from its double-cyclic nature. The conformational description of **3** will provide information about the influence of the cyclohexoxycarbonyl group on the spatial geometry of the quasi-planar β-lactam ring and reciprocally about the effect that the 2-azetidinone-(*S*)-4-carbonyloxy substituent has on the equilibrium between the equatorial and axial chair forms of the cyclohexyl ring.[15] This knowledge is of interest not only for a better understanding of the structural behavior of (*S*)-4-(alkoxycarbonyl)-2-azetidinones in general but for supporting the conformational study of poly(β-L-aspartate)s bearing cycloalkyl side groups. The synthesis and characterization of **3** has been recently described in full detail,[16] and the structural study of the helical polyamide, namely, poly(α-cyclohexyl-β-L-aspartate), that results when **3** is polymerized by ring-opening reaction constitutes the subject of the second part of this work.[17]

CHART 1



I II

The conformational analysis of **3** presented in this paper combines infrared and NMR spectroscopy experiments and quantum mechanical calculations. NMR data obtained in solution were used to estimate the Gibbs free energy difference between the axial and equatorial conformations of the cyclohexyl ring (Chart 1), whereas quantum mechanical calculations were used to predict the conformational preferences around the dihedrals angles χ_1 and χ_2 (Chart 2). Infrared data were used to disclose what type of hydrogen-bonding association is prevailing in CCl_4 solution. These results taken as a whole will allow us to provide a comprehensive picture of the conformational preferences of **3** in nonpolar environments.

Methods

Experimental Procedures. Compound **3** was prepared by transesterification of (*S*)-4-(benzyloxycarbonyl)-2-azetidinone

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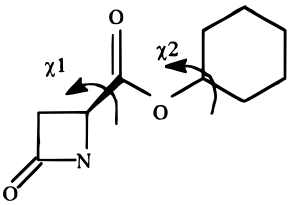
CHART 2



with cyclohexanol as described in detail elsewhere.[16] Infrared spectra were recorded from solution in either $CHCl_3$ or CCl_4 at room temperature on a Perkin-Elmer 2000 FTIR instrument. KBr liquid cells with an optical path length of 1 mm were used. Solvent subtraction was carried out using the reference spectra of the corresponding solvents. Spectra were obtained from 64 scans with a nominal resolution of 4 cm^{-1}. ^1H NMR spectra were recorded at 300.1 MHz in a Bruker AMX-300 fitted with a variable-temperature unit and using tetramethylsilane (TMS) as internal reference. Temperatures were selected at either 10 or 5 K intervals within the range 210.1−333.1 K. The sample was dissolved in deuterated chloroform (1% w/w) and held for 10 min at each temperature to reach thermal equilibrium. The following conditions were applied to record the spectra: pulse angle = 90° (5 μs); spectral width = 4000 Hz; number of transients = 64.

Quantum Mechanical Calculations. Energy calculations were performed in three stages. Firstly, a set of gas-phase calculations were performed on **3** at the semiempirical AM1[18] level. Semiempirical contour maps of the conformational energy *vs* the dihedral angles χ_1 and χ_2 were calculated for the two alternative cyclohexyl chair forms corresponding to the substituent in axial and equatorial positions. At each point the torsional angles χ_1 and χ_2 were held fixed at a given value, while all other geometrical parameters were fully relaxed. A grid step of 20° was used. Secondly, minimum energy conformations were characterized at the ab initio HF/3-21G level.[19] Frequency analyses were performed to verify the nature of the minimum state of the stationary points located during geometry optimizations, as well as to obtain the zero-point energies (ZPE) and thermal corrections to the energy. Single-point calculations were carried out for all the minima characterized at the HF/3-21G level using a 6-31G(d)[20] basis set. The most relevant conformers obtained for both chair forms were reoptimized at the HF/6-31G(d) level.[20] Frequency analyses were subsequently performed at the same level of theory. Finally, solvent effects have been explored by means of a self-consistent reaction-field (SCRF) method developed for the study of dilute CCl_4 solutions.[21] Calculations were performed using a semiempirical AM1 adapted version[21,22] of the method developed by Miertus, Scrocco, and Tomasi (MST/AM1).[23,24] According to this method, the free energy of solvation (ΔG_{solv}) was determined as the addition of electrostatic and steric contributions (eq 1), the latter being computed as the sum of the van der Waals and the cavitation terms.

$$\Delta G_{solv} = \Delta G_{elec} + \Delta G_{vdw} + \Delta G_{cav} \qquad (1)$$

The strategy used to estimate each contribution to ΔG_{solv} has been reported elsewhere.[21] Contour maps of ΔG_{solv} *vs* dihedral angles χ_1 and χ_2 were calculated for the two alternative chair conformations of the cyclohexyl group in a similar way as it was done in the gas phase. Ab initio calculations were performed with the Gaussian-94 program,[25] and AM1 and MST/AM1 calculations were carried out with a modified version of the MOPAC program.[26,27] All calculations were run on a CRAY-YMP of the Centre of Supercomputació de Catalunya (CESCA) and on a Silicon-Graphics RI-4000.

Results and Discussion

NMR Spectra. $\Delta G_{ax\leftrightarrow eq}$ values in chloroform solution for the axial ↔ equatorial equilibrium have been obtained by NMR spectra recorded at low temperature. Under such conditions, the interconversion rate between the chair forms may be slow enough as to make possible the resolution of the axial and equatorial resonances. ΔG for the interchange back and forth process between the two chair conformations has been obtained by means of eq 2, where x_{eq} and x_{ax} are the fractions of molecules bearing the cyclohexyl group with the substituent in the equatorial and axial position, respectively, *i.e.* the fractions of equatorial and axial conformers.

$$\Delta G_{ax\leftrightarrow eq} = -RT \ln \frac{x_{eq}}{x_{ax}} \qquad (2)$$

At room temperature the exchange process is rapid on the NMR time scale and the signals for the proton placed onto C(1) on each of the two alternative cyclohexyl conformers coalesce into a single one which appears at an intermediate position. The chemical shifts of the merging signal (δ_{CH}) and of those corresponding to the axial and equatorial conformers are related by eq 3.

$$\delta_{CH} = x_{eq}\delta_{CH_{ax}} + x_{ax}\delta_{CH_{eq}} \qquad (3)$$

On lowering the temperatures to around −60 °C the interconversion rate is slowed and the methine proton in the cyclohexyl ring becomes observed as two well-separated signals at chemical shifts of 4.75 and 5.16 ppm, corresponding to the equatorial and axial conformers, respectively (Figure 1). Under such conditions the relative populations of the two conformers may be readily estimated by intensity integration of their respective signals. At temperatures above −60 °C conformational distributions have to be calculated by chemical shift extrapolation according to eq 3. From the chemical shifts of the separated signals and that observed for the averaged signal, the x_{eq}/x_{ax} ratio was computed for a series of temperatures ranging from 243 to 333 K. At room temperature (298 K) x_{eq} and x_{ax} were estimated to be 0.78 and 0.22, respectively, providing a $\Delta G_{ax\leftrightarrow eq}$ value of −0.75 kcal/mol. This value is similar to those reported earlier for closely related compounds[28] like cyclohexyl methanoate (−0.59 kcal/mol) and cyclohexyl methyl ether (−0.71 kcal/mol). A compilation of the chemical shifts observed for the cyclohexyl methine within the range of temperatures covered in this study with indication of the relative populations of the two conformers and Gibb′s energy increments estimated for every case is given in Table 1.

In order to determine the enthalpy ($\Delta H°$) and entropy ($\Delta S°$) contributions to the free energy driving the conformational equilibrium, we have made use of the van't Hoff plot ($\ln(x_{eq}/x_{ax})$ *vs* $1/T$) (Figure 2). The fact that experimental data points can be well fitted in a straight line gives firm support to the model of a two-state conformational equilibrium for the cyclohexyl ring. $\Delta H°$ and $\Delta S°$ were calculated from the slope and ordinate at the origin of the interpolated straight line according to the expression $\ln(x_{eq}/x_{ax}) = (-\Delta H°/RT) + \Delta S°/R$. $\Delta H°$ and $T\Delta S°$ values resulting for **3** at 298 K are −0.70 and 0.05 kcal/mol, respectively. The preference for the equatorial conformation is definitely reflected in the highly negative value of $\Delta H°$. Although the entropy term also favors the equatorial

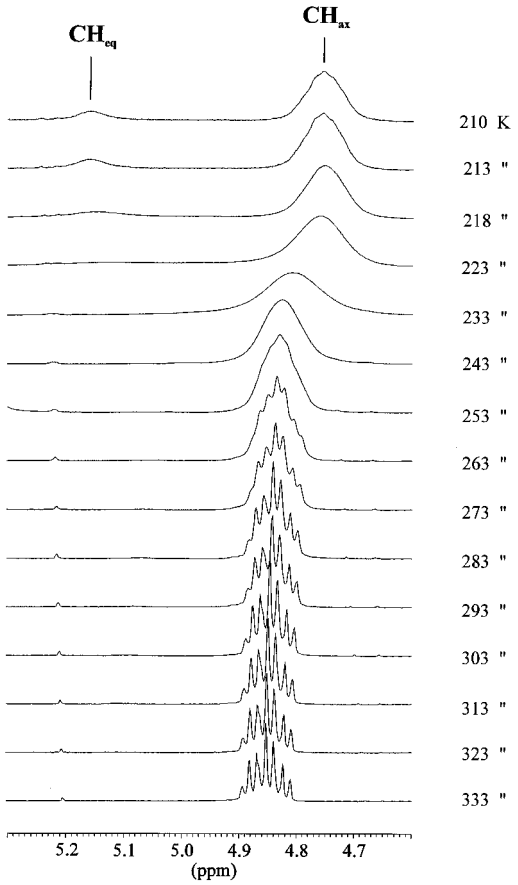


Figure 1. 300.1 MHz ^{1}H NMR in the cyclohexyl CH region of **3** in $CDCl_3$ at the indicated temperatures.

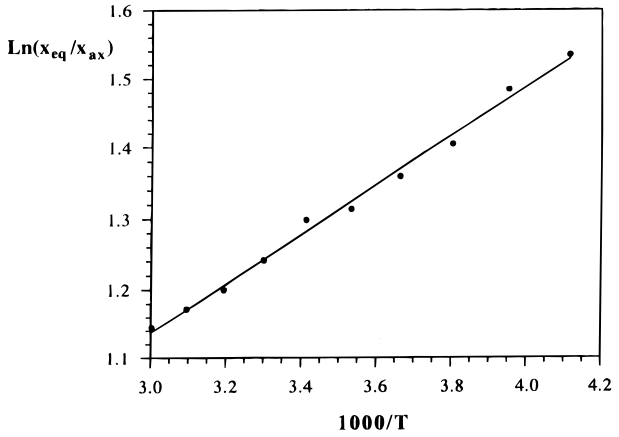


Figure 2. Plot of $\ln(x_{eq}/x_{ax})$ *vs* $1000/T$ for the equatorial−axial chair equilibrium of the cyclohexyl group in **3**.

TABLE 1: Chemical Shifts, x_{eq}/x_{ax}, and ΔG Values at Different Temperatures

T (K)	δ (ppm)	x_{ax}	x_{eq}	x_{eq}/x_{ax}	$-\Delta G$ (kcal/mol)
333.1	4.852	0.24	0.76	3.15	0.76
323.1	4.850	0.23	0.76	3.23	0.75
313.1	4.848	0.23	0.77	3.31	0.75
303.1	4.845	0.22	0.78	3.46	0.75
293.1	4.841	0.21	0.79	3.67	0.76
283.1	4.840	0.21	0.79	3.72	0.74
273.1	4.837	0.20	0.80	3.90	0.74
263.1	4.834	0.20	0.80	4.08	0.74
253.1	4.829	0.19	0.81	4.40	0.75
243.1	4.826	0.18	0.82	4.65	0.74

conformation, its contribution to the free energy in the studied range of temperatures is far weaker than that provided by enthalpy.

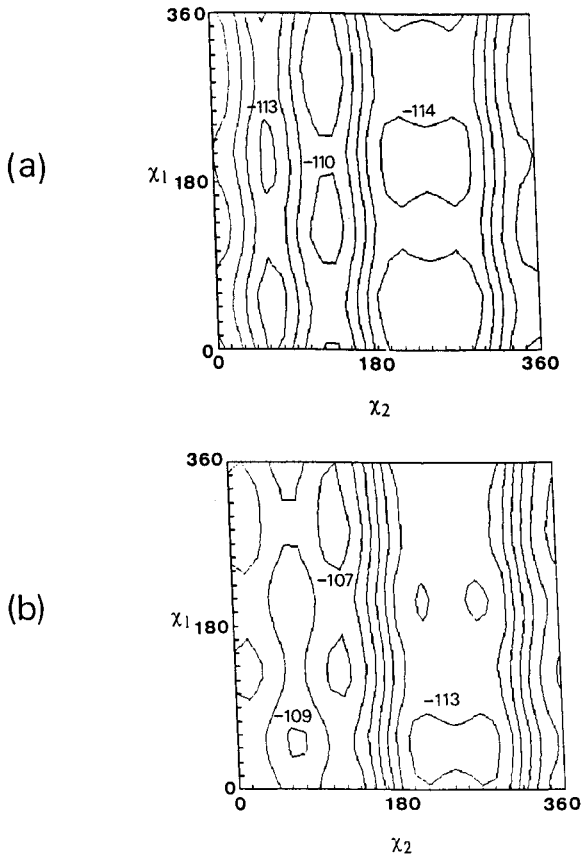


Figure 3. $\chi_1-\chi_2$ gas-phase conformational energy maps (in kcal/mol) of (*S*)-4-(cyclohexoxycarbonyl)-2-azetidinone (**3**) with the cyclohexyl ring in either equatorial (a) or axial (b) conformation. Contour lines are drawn for energy increments of 1 kcal/mol.

Conformational Analysis of 3. The $\chi_1-\chi_2$ gas-phase conformational energy maps of **3** with the cyclohexyl ring in equatorial and axial conformation are shown in Figure 3. Contour lines are drawn for energy increments of 1 kcal/mol, revealing the presence of very flat low-energy regions. Thus, contour lines from 1 kcal/mol upward enveloping a continuous range of favored conformations are found for both cases. Comparison between the two energy maps indicates that the equatorial conformation is favored by about 1 kcal/mol with respect to the axial one. In order to provide a better description of the potential energy surface of **3**, minimum energy conformations were characterized at the ab initio level. For this purpose, the low-energy structures located in the AM1 energy maps were used as starting geometries for HF/3-21G optimizations. Single-point energy calculations at the HF/6-31G(d) level were then performed for all the minima characterized in previous stages. Results are described in Table 2.

The two lowest energy structures resulting from the energy analysis have the cyclohexyl ring in equatorial conformation and are almost isoenergetic. They correspond to dihedral angles $\chi_1, \chi_2 = -175.8°, -78.9°$ (**I**) and $\chi_1, \chi_2 = -177.1°, -160.7°$ (**II**), and they are schematically depicted in Figure 4. Nevertheless, it is noticed that, with the exception of **X**, the relative energy of minima ranges between 0 and 3.1 kcal/mol at the best theoretical level. Such small energies suggest a large conformational flexibility around the bonds defined by χ_1 and χ_2. Minimum **X** is 9.2 kcal/mol unfavored with respect to the lowest energy structure due to the occurrence of steric interactions between the carbonyl oxygen and the hydrogens attached to the C3 and C5 atoms of the cyclohexyl ring. In order to verify the reliability of our calculations, geometry optimizations

TABLE 2: HF/3-21G Minimum Energy Conformations of 3

		dihedral angles (deg)		ΔE (kcal mol^{-1})			amide−ester interactions		
conformer	cyclohexyl	χ_1	χ_2	HF/3-21G*[a]	HF/6-31G(d)	HF/6-31G(d)[a]	atoms	d(H···O) (Å)	∠N−H···O (deg)
I	equatorial	−175.8	−78.9	0.1	0.0[c]	0.0[d]	N−H···O=C−	2.97	71.7
II	equatorial	−177.1	−160.7	0.1	0.0	0.0	N−H···O=C−	2.98	71.3
III	equatorial	67.5	−79.4	0.8	1.0	1.0	N−H···O−C=	2.94	77.1
IV	equatorial	68.4	−160.7	0.8	1.0	1.0	N−H···O−C=	2.93	76.5
V	axial	−176.9	−161.6	0.0[b]	0.9	1.3	N−H···O=C−	2.97	71.4
VI	axial	−178.6	−78.0	0.0	0.9	1.3	N−H···O=C−	2.98	71.1
VII	axial	68.1	−78.3	0.7	1.9	2.2	N−H···O−C=	2.95	77.0
VIII	axial	66.0	−164.4	0.5	2.0	2.4	N−H···O−C=	2.93	76.5
IX	equatorial	−176.1	62.8	1.6	2.8	3.1	N−H···O−C=	2.96	71.7
X	axial	−175.8	65.3	6.6	8.7	9.2	N−H···O=C−	2.95	71.8

[a] ZPE and thermal corrections computed at the HF/3-21G level. [b] $E = -662.221\,308$ au. [c] $E = -666.470\,144$ au. [d] $E = -665.929\,718$ au.

TABLE 3: HF/6-31G(d) Minimum Energy Conformations of 3

		dihedral angles (deg)		ΔE (kcal mol^{-1})		amide−ester interactions		
conformer	cyclohexyl	χ_1	χ_2	HF/6-31G(d)	HF/6-31G(d)[a]	atoms	d(H···O) (Å)	∠N−H···O (deg)
I	equatorial	−176.3	−84.0	0.0[b]	0.0[c]	N−H···O=C−	2.76	82.0
II	equatorial	−175.9	−154.0	0.0	0.0	N−H···O=C−	2.76	82.0
V	axial	−176.1	−154.3	0.7	0.5	N−H···O=C−	2.76	82.1
VI	axial	−177.6	−84.5	0.7	0.5	N−H···O=C−	2.77	81.7

[a] ZPE and thermal corrections computed at the HF/3-21G(d) level. [b] $E = -666.476\,703$ au. [c] $E = -665.932\,860$ au.

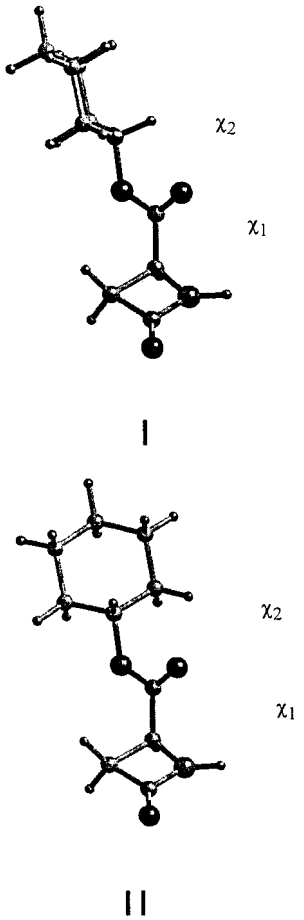


Figure 4. Two lowest energy structures (**I** and **II**) of (*S*)-4-(cyclohexoxycarbonyl)-2-azetidinone (**3**) computed at the HF/3-21G level.

and frequency analyses were performed at the HF/6-31G(d) level on the two lowest energy structures with the substituent at both axial and equatorial positions, *i.e.* models **I**, **II**, **V**, and **VI**. Results are displayed in Table 3. They are very similar to those obtained from HF/6-31G(d) single-point calculations on HF/3-21G molecular geometries. These overall results indicate that this level is appropriate to perform geometry optimizations, although calculations at the HF/3-21G(d) level are required in order to attain reliable energy values. The present results are in full agreement with the NMR data presented in the previous section and are consistent with the conformational flexibility attributed to the alkoxycarbonyl side group of 2-azetidinones in earlier theoretical studies.[10]

On the other hand, deviation from planarity is likely the most relevant feature concerning the molecular geometry of β-lactam rings. In this regard it should be reminded that the nitrogen atom tends to adopt a pyramidal structure in β-lactam moieties included in the structure of penicillins.[29,30] The values obtained for the N−C(=O)−C−C dihedral angle of the 2-azetidinone cycle in **3** range from 0.6° to 2.3°, which is in contrast with the ideally planar conformation previously obtained for the unsubstituted β-lactam. However, such deviations are about 2° smaller than those reported for **2** with R = Me indicating that the distorting effect of the cyclohexoxycarbonyl substituent is even weaker than that exerted by the methoxycarbonyl group.

Recent studies have shown that solvent effects are able to invert the conformational preferences of certain flexible compounds.[21,31−34] Therefore it was considered of interest to investigate the influence that organic solvents have on the conformational pattern of **3**. For this purpose, we selected the MST/AM1 method, which has been recently adapted to study CCl_4 dilute solutions.[21] The $\chi_1-\chi_2$ solvation free energy maps are shown in Figure 5 for the equatorial and axial conformations of the cyclohexyl ring. Contour lines are drawn for solvation free energy increments of 0.1 kcal/mol. They show that the solvent does not introduce any significant change on the conformational preferences of **3**. The largest computed value of $\Delta\Delta G_{solv}$ was 1.0 kcal/mol for both equatorial and axial $\chi_1-\chi_2$ maps, which reveals the scarce influence that the solvent has on the configuration of the potential energy surfaces. The effect of CCl_4 solvent on the axial ↔ equatorial equilibrium was found to be also very small, with a $\Delta\Delta G_{solv}$ for the minima of only 0.3 kcal/mol. This is a very reasonable result provided that the peculiar nonpolar bulky nature of the CCl_4 solvent makes the steric contribution the leading attractive term for ΔG_{solv}.[21,34] This term includes the cavitation and van der Waals contributions which mainly depend on the molecular surface area. It may be concluded that variations in the dihedral angles χ_1 and χ_2 as well as in the conformation of the cyclohexyl ring

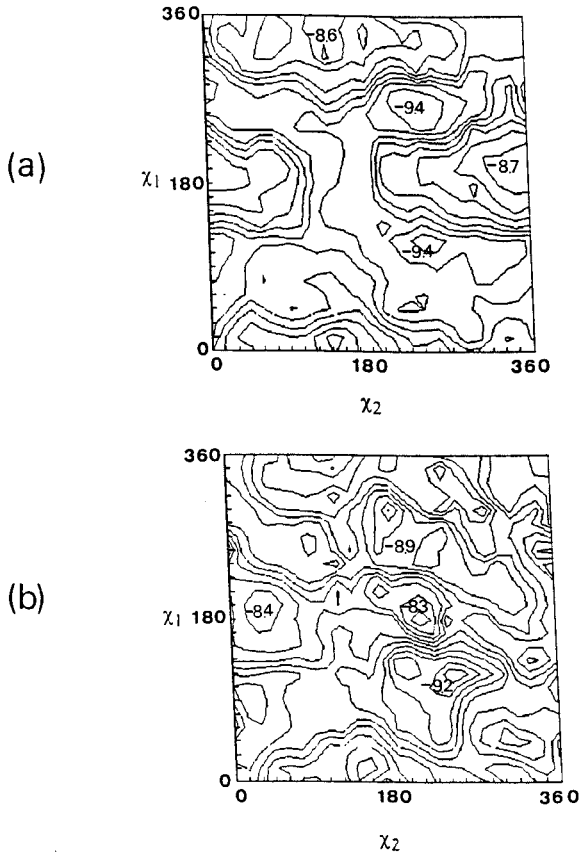


Figure 5. $\chi_1-\chi_2$ solvation free energy maps (in kcal/mol) of (*S*)-4-(cyclohexoxycarbonyl)-2-azetidinone (**3**) in CCl_4 solution with the cyclohexyl ring in either equatorial (a) or axial (b) conformation. Contour lines are drawn for energy increments of 0.1 kcal/mol.

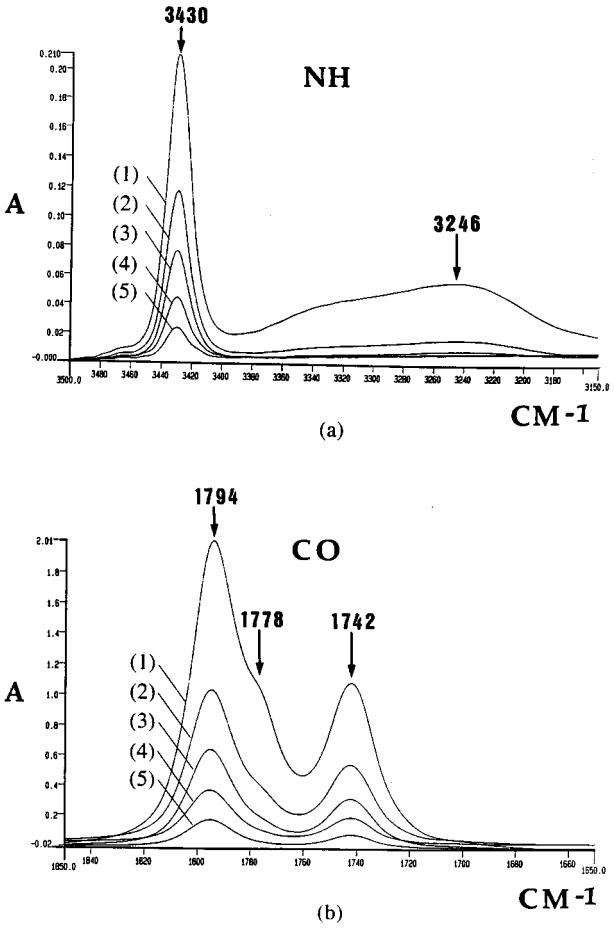


Figure 6. NH (a) and CO (b) regions of the FTIR spectra of **3** registered in carbon tetrachloride solution at different concentrations: (1) 25 mM; (2) 12.5 mM; (3) 6.2 mM; 3.1 mM; (5) 1.5 mM.

do not introduce drastic modifications on the molecular surface area, and therefore the value of ΔG_{solv} remains essentially unchanged.

Hydrogen Bond Interactions. It is known that self-aggregation of unsubstituted 2-azetidinones into dimeric forms takes place in nonpolar solution via intermolecular hydrogen bonding between amide groups.[35] On the other hand, the characteristics of the ester−amide interaction has been recently investigated using high-level ab initio calculations.[36] Results obtained thereof revealed that the interaction of the NH with the alkoxy oxygen is much less favorable than with either the amide or the ester carbonyl oxygen and that these two are of similar strength.

We have analyzed **3** by infrared spectroscopy (Figure 6) in order to see what type of interactions are operating in this compound. The NH region of the infrared spectrum of a 0.025 M solution of **3** in CCl_4 shows a sharp peak at 3430 cm^{-1} and a broad band centered around 3200−3300 cm^{-1}. They clearly correspond to the stretching absorption of the NH in the free and associated state, respectively. The CO region of the spectrum displays the ester and amide carbonyl peaks at 1794 and 1742 cm^{-1}, respectively, the former with a shoulder of medium intensity at 1778 cm^{-1}, which is attributed to the fraction of ester being in the associated state. Absorption peaks arising from associated species were found to disappear on dilution revealing that CO···HN interactions entail different molecules rather than taking place within the same molecule. When similar experiments were carried out in $CHCl_3$ solution, no traces of absorption attributable to association were detected at any concentration, whereas peaks corresponding to the free state appeared in exactly the same positions as in carbon tetrachloride. These results demonstrate that ester−amide hydrogen-bonding interactions take place in **3** when it is in a nonpolar environment and evidence at the same time the weakness of such interactions.

The occurrence of intramolecular interactions via hydrogen bonding between amide and ester groups should be also considered. In fact, weak interactions of this nature were assumed in a preceding work to describe the conformational preferences of certain 2-azetidinones bearing alkoxycarbonyl groups.[10] In the conformational analysis of **3** described above, it was found that all the energy minimum conformations characterized at the ab initio level involved weak intramolecular interactions between the amide group and either the carbonyl or the alkoxy oxygens. Specifically, the two most stable conformations of **3** (**I** and **II**) appear stabilized by an intramolecular interaction between the N−H group and the carbonyl oxygen of the ester group with an H···O distance of 2.97−2.98 Å. It is the ability of oxygen atoms of the ester group to interact favorably with the amide group within the same molecule that is in part responsible for the flat potential energy hypersurfaces found for **3**. According to the nature of the participating atoms, these interactions could be viewed as hydrogen bonds, although their geometry parameters are clearly out of the standard ranges of values. H···O distances and N···H···O angles describing the geometry of such interactions are given in Table 2. We have searched for experimental evidence in support of this prediction, but no indications could be detected in either infrared or NMR spectra. Apparently the interactions are too weak to produce perceivable spectroscopy changes, at least at the resolution level we are using in this work.

TABLE 4: Theoretical and Experimental Values (kcal /mol) of the Energy Contributions to the Axial ↔ Equatorial Equilibrium.

	$\Delta H_{gas-phase}$	$T\Delta S_{gas-phase}$[a]	ΔG_{CCl4}	$\Delta G_{ax\leftrightarrow eq}$
AM1	−1.3	0.1	−0.34	−1.7
HF/6-31G(d)	−1.4			−1.8
experimental[b]	−0.70	0.05		−0.75

[a] At 298 K. [b] Solvent contributions included in the enthalpy and entropy terms.

Simulation of the Axial ↔ Equatorial Equilibrium. The $\Delta G_{ax\leftrightarrow eq}$ value in CCl_4 solution has been estimated taking advantage from the semiempirical and ab initio calculations presented above. Thus, the $\Delta G_{ax\leftrightarrow eq}$ has been decomposed into the gas-phase and solution contributions (eq 4).

$$\Delta G_{ax\leftrightarrow eq} \approx \Delta G_{gas-phase} + \Delta G_{CCl_4} \tag{4}$$

The $\Delta G_{gas-phase}$ term can be in turn separated into the enthalpy and entropy contributions. For a rigorous determination of the latter, an exploration of the whole conformational space of **3** should be required. Fortunately, an acceptable approach to estimate approximately the entropy contribution consists of making use of the $\chi_1-\chi_2$ energy maps computed at the AM1 level for the axial and equatorial conformers of the cyclohexyl ring. Thus, calculations were performed using eq 5,

$$T\Delta S_{AM1} = \Delta H_{AM1} - \Delta G_{AM1} \tag{5}$$

where

$$\Delta G_{AM1} = -RT \ln \frac{x_{eq}}{x_{ax}} \tag{6}$$

and

$$\Delta H_{AM1} = \Delta H^{eq}_{AM1} - \Delta H^{ax}_{AM1} \tag{7}$$

The molar ratios x_{ax} and x_{eq} were calculated as

$$x_{ax} = \frac{\sum_{i}^{ax} \exp(-\Delta H_i/RT)}{\sum_{j}^{ax+eq} \exp(-\Delta H_j/RT)} \tag{8}$$

$$x_{eq} = 1 - x_{ax} \tag{9}$$

and the enthalpies $\Delta H^{ax}{}_{AM1}$ and $\Delta H^{eq}{}_{AM1}$ as

$$\Delta H^{ax}_{AM1} = \frac{\sum_{i}^{ax} \Delta H_i \exp(-\Delta H_i/RT)}{\sum_{j}^{ax} \exp(-\Delta H_j/RT)} \tag{10}$$

The 324 grid points computed for building each one of the two $\chi_1-\chi_2$ energy maps were used in the estimation of $T\Delta S_{AM1}$. Results are summarized in Table 4. The values obtained for ΔH_{AM1} and $T\Delta S_{AM1}$ were −1.31 and 0.1 kcal/mol at 298 K, respectively. Note that AM1 calculations are able to predict correctly the stability of the equatorial conformer with respect to the axial one, although ΔH and $T\Delta S$ appear overestimated by −0.6 and 0.05 kcal/mol, respectively, with regard to those obtained on the basis of NMR data. In this regard it should be taken into account that since experimental values include the solvent contributions, direct comparison with theoretical data is not adequate. On the other hand, the enthalpy term was reevaluated at the ab initio level using the energies displayed in Table 2. Application of eqs 7 and 10 provides a $\Delta H_{6-31G(d)}$ value of −1.4 kcal/mol, giving confidence to the results obtained at the AM1 level. Finally, the solvent contribution was estimated by applying eqs 6 and 8 to the 324 conformers used to compute $\chi_1-\chi_2$ ΔG_{CCl4} maps. The final value was −0.34 kcal/mol, indicating that the preference for the equatorial conformer is retained. Since the use of SCRF does not permit the separation of the solvent contribution into the enthalpy and entropy terms, the direct comparison between theoretical and experimental data is not feasible at this stage.

Conclusions

The conformational preferences of **3** have been investigated by NMR spectroscopy and quantum mechanical calculations. Results show that, according to expectations, the equatorial conformer of the cyclohexyl ring is favored with respect to the axial one, the experimental $\Delta G_{ax\leftrightarrow eq}$ being −0.76 kcal/mol. Semiempirical and ab initio estimations of $\Delta G_{ax\leftrightarrow eq}$ are in agreement with this value. It was concluded therefore that the 2-azetidinone-(*S*)-4-carboxyloxy group does not have any special effect on the axial ↔ equatorial equilibrium of the cyclohexyl ring. Reciprocally, no particular distorting effect on the planarity of the 2-azetidinone ring is exerted by the cyclohexoxycarbonyl group. SCRF calculations indicate that the contribution of solvation effects to $\Delta G_{ax\leftrightarrow eq}$ is small. On the other hand, quantum mechanical calculations reveal a large conformational flexibility around the χ_1 and χ_2 dihedral angles of the alkoxycarbonyl side chain. This behavior, although rather unexpected given the bulkiness of the cyclohexyl group, is consistent with results recently provided for other (*S*)-4-alkoxycarbonyl-2-azetidinones bearing linear alkyl groups.[10]

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