Ab Initio Study of the Axial/Equatorial Equilibrium in N- and O-Containing Rings in Gas Phase and Aqueous Solution: 1-Oxa-3-aza-, 1-Oxa-3,5-diaza-, 1,3-Dioxa-5-azacyclohexanes and *N*-Methyl Derivatives

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The axial and equatorial structures of 1-oxa-3-azacyclohexane, 1-oxa-3,5-diazacyclohexane, and 1,3-dioxa-5-azacyclohexane, which can show anomeric effect, were completely optimized at the HF/6-31G** level. The effects of polarization, diffuse functions, the ZPE, and the electronic correlation as considered at the MP2 level were also discussed. The HF/6-31G** wavefunctions were analyzed according to the NBO method, and it was found that the axial preferences of the R−N−C−O unit are due to hyperconjugation, this contribution being more important than steric effects. The N-methylation reduces the preference for the axial forms by approximately 3−3.5 kcal/mol because the delocalization is increased in the equatorial forms. By means of an ab initio method for the treatment of the solvent as a continuum (PCM), the influence of water on the conformational stability was estimated. It was found that the axial conformers reduce their energetic preference by between 1 and 3.5 kcal/mol mainly due to the interaction between the dipole moment of the solute and the reaction field of the solvent, although local dipolar interactions can also be important.

Introduction

The anomeric effect[1] can be defined in a generalized sense as the preference for sinclinal (*sc* or gauche) over antiperiplanar (*ap* or anti) conformations in a molecular segment R−X−A−Y, where A is an element with an intermediate electronegativity (e.g. C), Y is more electronegative than A (e.g. O or N), X is an element with lone pairs, and R is C or H. The electrostatic model of dipole−dipole interaction suggests that the anomeric effect arises from the repulsion between the dipole of the X lone pairs and the A−Y dipole, which destabilizes the *ap* conformation.[1d] A different explanation is based on the charge delocalization model, according to which the stability of the *sc* conformation is attributed to the delocalization of an X lone pair in the antibonding bicentric orbital of the A−Y bond,[1c] i.e. an $n_X - \sigma^*_{A-Y}$ hyperconjugation takes place. In several papers the charge delocalization model has received theoretical support by means of the natural bond orbital method (NBO).[2,3] Recent experimental work on 2-methoxytetrahydropyran and 2-methoxy-1,3-dimethylhexahydropyrimidine suggested that the dipolar electrostatic interactions in apolar solvents represent the main component of the anomeric effect.[4] However this interpretation has been questioned by means of HF/6-31G** wave functions analyzed according to the NBO method.[5]

The purpose of the present paper is to analyze the characteristics of the axial/equatorial equilibrium in heterocyclic compounds containing N and O, which are susceptible to showing anomeric effect, and on which very little quantitative structural information has been published so far, of either an experimental or theoretical nature. This paper is intended to contribute to the interpretation of the generalized anomeric effect, studying whether the charge delocalization model allows us to provide a satisfactory explanation for the energetic and geometrical features of the axial/equatorial equilibrium of these kinds of compounds.

We have performed ab initio calculations on the following substances: 1-oxa-3-azacyclohexane (**1**), 1-oxa-3,5-diazacyclohexane (**2**), and 1,3-dioxa-5-azacyclohexane (**3**) (see Scheme 1). The choice arose from the presence in these compounds of a H−N−C−O unit which is susceptible to showing anomeric effect, and their study should allow us to establish the influence of the substitution at position 5 on the axial/equatorial equilibrium of the N3-R group. Furthermore, in order to analyze the effect of methylation, the *N*-methyl derivatives (**1m**, **2m**, **3m**) were also considered, as well as the only *N,N*-dimethyl derivative (**2mm**). The experimental information available on the conformation of these compounds is scarce and qualitative. The great predominance of the axial conformer of **1** has been confirmed by ^{1}H-NMR,[6a] IR spectroscopy,[6b] and dipole moment measurements.[6c] The experimental information from magnetic resonance for **1m** and other N3-substituted derivatives shows

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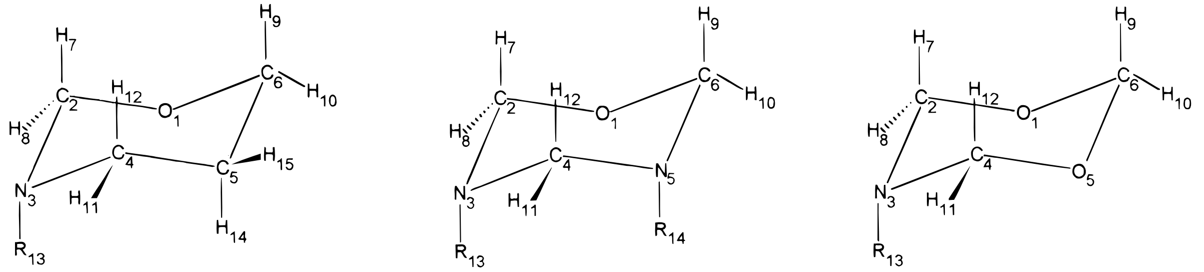
Scheme 1



1   **2**   **3**

Substituents	Conformers	
R_{13} = H	**1A**	**1E**
R_{13} = CH_3	**1mA**	**1mE**

Substituents	Conformers			
R_{13} = H R_{14} = H	**2Aa**	**2Ae**		**2Ee**
R_{13} = CH_3 R_{14} = H	**2mAa**	**2mAe**	**2mEa**	**2mEe**
R_{13} = CH_3 R_{14} = CH_3	**2mmAa**	**2mmAe**		**2mmEe**

Subtituents	Conformers	
R_{13} = H	**3A**	**3E**
R_{13} = CH_3	**3mA**	**3mE**

contradictions,[7] though it indicates a slight preference for the axial conformer of **1m** ($\Delta G_{\mathbf{1mE/1mA}} = -0.16$ kcal/mol at 138 K). Both ^{1}H-NMR and ^{13}C-NMR have proved that the most stable conformer of **2m** has the N-methyl group in axial position,[8] and it must also be the only populated one. From a qualitative point of view, it is known that the most stable conformer of **2mm** contains one axial and one equatorial methyl group.[8] We have previously published a partial theoretical study on compounds **1**, **2**, and **3** at the HF/4-21G level,[9] but it seemed appropiate to complete and revise it, improving the quality of the calculations to take into account the effect of the change of the basis set and the inclusion of polarization and diffuse functions. We also intended to establish the effect of N-methylation. The NBO analysis of the wavefunctions permitted us to interpret the results obtained. Finally, since a reduction of the anomeric effect in polar solvents has been observed experimental[10a] and theoretically,[10b,c] the influence of water on the relative stability of the different conformers was estimated by means of an ab initio method for studying the solvent effect.

Methods

Although Hartree–Fock theoretical calculations are applied to isolated molecules at 0 K, numerous studies[5] have proved that ab initio calculations succeed in reproducing the energetic trends and the effects in bond lengths and bond angles related to the anomeric effect. Therefore, as the axial/equatorial equilibrium is not influenced by apolar solvents, theoretical studies were performed in the gas phase. The compounds were completely optimized, without restrictions, at the HF/6-31G** level, and single point calculations on the optimized geometries were performed using the 6-31++G** basis set to establish the effect of the diffuse functions because of the presence of lone electron pairs. Furthermore, MP2/6-31G** and MP2/6-31++G** single point calculations were performed to analyze the effect of electronic correlation. The IR frequencies and the zero point energy (ZPE) were also evaluated at the HF/6-31G** level. Throughout the whole study the computing program Gaussian 94[11] was used. The puckering coordinates, as defined by Pople and Cremer,[12] were evaluated for the optimized geometries.

NBO calculations[3] were also performed with Gaussian 94 on the HF/6-31G** geometries. The NBO program transforms the HF canonical molecular orbitals into a set of localized orbitals, called natural bond orbitals (NBOs), which form a hypothetical Lewis structure with electron pairs perfectly localized. The delocalization effects, according to NBO, are due to the interactions between occupied bonds and antibonds and are represented by off-diagonal terms in the Fock matrix, written on the basis of the NBOs. To evaluate these contributions of hyperconjugation energy, a procedure was used to simultaneously disregard all the off-diagonal elements in the Fock matrix and perform only one SCF cycle, which results in the Lewis energy ($E_{\rm Lew}$) that should correspond to the hypothetical molecule with localized bonds. $E_{\rm Lew}$ includes steric and electronic (i.e. dipole repulsion) effects that cannot be separated by means of the NBO procedure. The interpretation of $E_{\rm Lew}$ is not completely direct, since it is likely to be influenced by geometrical changes induced by interactions between orbitals, which cannot be manifested because no geometrical reoptimization is performed for determining $E_{\rm Lew}$. The difference between total SCF and $E_{\rm Lew}$ energies corresponds to the energetic contributions arising from all the possible interactions between orbitals, i.e. to the delocalization energy, $E_{\rm del}$. The familiar interactions of the type $n_X-\sigma^*_{C-Y}$, where X and Y are heteroatoms, are dominant, but others such as $n_X-\sigma^*_{C-H}$, $n_X-\sigma^*_{C-C}$ and additional smaller bond–antibond interactions could have different relative contributions to $E_{\rm del}$. The dependence of the $n_X-\sigma^*_{C-Y}$ interactions with geometrical differences between conformers and the balance between the different types of interactions have been discussed in detail.[2]

The influence of water was estimated using an ab initio solvation procedure based on a continuous description of the solvent (polarized continuum model, PCM),[13] the reliability of which has been widely tested and which was successfully

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Table 1. Relative Energies (kcal/mol) for the Conformers of Compounds 1, 2 and 3 and Their N-Methylated Derivatives at Several Computational Levels

	1A	**1**E	**2**Aa	**2**Ae		**2**Ee	**3**A	**3**E
HF/4-21G//HF/4-21G [9a]	0.00	4.75	0.00	5.48		15.09	0.00	–
HF/6-31G**//HF/6-31G**	0.00	3.19	0.00	3.69		10.58	0.00	7.16
HF/6-31G**//HF/6-31G**+ZPE	0.00	2.98	0.00	3.44		9.88	0.00	6.68
HF/6-31++G**//HF/6-31G**	0.00	2.95	0.00	3.51		9.97	0.00	6.78
MP2/6-31G**//HF/6-31G**	0.00	3.83	0.00	4.33		12.03	0.00	8.12
MP2/6-31++G**//HF/6-31G**	0.00	3.35	0.00	4.10		11.20	0.00	7.66
	1mA	**1m**E	**2m**Aa	**2m**Ae	**2m**Ea	**2m**Ee	**3m**A	**3m**E
HF/6-31G**//HF/6-31G**	0.00	0.31	0.00	0.89	3.77	7.80	0.00	4.36
HF/6-31G**//HF/6-31G**+ZPE	0.00	0.04	0.00	0.60	3.48	7.07	0.00	3.89
HF/6-31++G**//HF/6-31G**	0.09	0.00	0.00	0.54	3.64	7.03	0.00	3.76
MP2/6-31G**//HF/6-31G**	0.00	1.21	0.00	1.86	4.36	9.57	0.00	5.74
MP2/6-31++G**//HF/6-31G**	0.00	0.55	0.00	1.47	4.23	8.63	0.00	5.09
			2mm Aa	**2mm**Ae		**2mm**Ee		
HF/6-31G**//HF/6-31G**			1.41	0.00		4.15		
HF/6-31G**//HF/6-31G**+ZPE			1.60	0.00		3.71		
HF/6-31++G**//HF/6-31G**			1.41	0.00		3.51		
MP2/6-31G**//HF/6-31G**			0.80	0.00		5.43		
MP2/6-31++G**//HF/6-31G**			0.57	0.00		4.68		

applied for other systems with anomeric effect.[10c] The 6-31G** basis set was used, with the gas phase optimized geometries at the same level. According to this model, the solvation energy for a solute M, ΔG_{sol}, which has the status of free energy, can be split into the following terms:

$$\Delta G_{\mathrm{sol}}(\mathrm{M}) = W(\mathrm{M}) + \Delta G_{\mathrm{ther}} + \Delta(PV) \qquad (1)$$

The first term represents the dipole−solvent interactions, and the remaining terms are contributions due to the motion of solute molecules and should require the evaluation of vibrational, rotational, and translational partition functions of the solute M in the gas phase and in solution. These last terms in eq 1 remain approximately constant when considering energy differences between conformations and can be disregarded.[14] In this way, ΔG_{sol} reduces to the solute−solvent interaction term, which can be split as follows:

$$\Delta G_{\mathrm{sol}} = \Delta G_{\mathrm{el}} + \Delta G_{\mathrm{noel}} = \Delta G_{\mathrm{el}} + \Delta G_{\mathrm{cav}} + \Delta G_{\mathrm{dis-rep}} \qquad (2)$$

A detailed description of each term is beyond the scope of this paper, but it can be indicated that ΔG_{el} represents the electrostatic interaction between solute and solvent, the nonelectrostatic term, ΔG_{noel}, is formed by the cavitation energy, ΔG_{cav}, calculated for a cavity defined in terms of Van der Waals spheres, according to Pierotti equations,[15] and a dispersive−repulsive interaction, $\Delta G_{\mathrm{dis-rep}}$, calculated according to atom−atom coefficients.[16]

Results and Discussion

The relative energies, the energetic contributions in the NBO model, selected values of the HF/6-31G** geometrical parameters, and the puckering coordinates for the different optimized conformers of each compound are detailed in Tables 1−5. In Table 2 the dipole moments are also included because it has been suggested that the most stable conformers in the gas phase correspond with those with the lowest dipole, although it has been proved that this not always the case.[4d] The stabilities in water are shown in Table 6. The difference between these relative energies and the gas phase values is a consequence of the different solvation energies, which are also included in Table 6, together with their separation into electrostatic and nonelectrostatic terms, according to eq 2. Scheme 1 shows the unified numbering employed throughout the study, and the nomenclature of the conformers, where the capital letters indicate the axial (A) or equatorial (E) orientation of the N3-R13 group. For **2** and its derivatives, the lower case letters indicate the axial (a) or equatorial (e) disposition of the N5-R14 group.

The analysis of the energy values of Table 1 permits us to establish a series of general considerations on the influence of the basis set, electron correlation, and ZPE on the stability of the conformers. For comparison, HF/4-21G results have been included.[9] Although at any level the same energy ordering is predicted, the small 4-21G basis set notably overestimates the axial preferences, even being unable to characterize the **3**E conformer as a minimum. This fact suggests the necessity of incorporating polarization functions into the basis set for a correct description of this kind of system. The incorporation of diffuse functions slightly lowers the relative energies of the equatorial conformers (by 0.7 kcal/mol at the most), and the effect of ZPE acts in the same direction and magnitude. The MP2 partial treatment of the electron correlation acts in the opposite direction, stabilizing the axial forms (1.7 kcal/mol at the most).

The simultaneous inclusion of ZPE, diffuse functions, and MP2 correction predicts energies which are close to those obtained at the HF/6-31G**//HF/6-31G** level, so this calculation level can be considered sufficient, and it will be taken as the reference in the following. All these tendencies agree with the research carried out on a wide range of systems with axial/equatorial equilibria analogous to those in this study.[5,17] It was shown that the correlation effects at the MP2 level tend to cancel each other out when the basis set is increased, and the MP2 corrections with the 6-31G* basis set, which tend to increase the axial preferences, can be considered artifacts.

The energetic effect of the N3-methylation is practically constant and independent of the atom in position 5. The axial forms are still the most stable, but E_{rel} of the

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Table 2. HF/6-31G Relative Energies (E_{rel}) and Lewis Energies (E_{Lew}), and Hyperconjugation Contributions (E_{del}), According to the NBO Method, for the Conformers of 1, 2, and 3 and Their N-Methylated Derivatives (see Scheme 1), Piperidine[17] (4) and Hexahydropyrimidine[5a] (5) in kcal/mol. Dipole Moments in Debyes Are Also Shown**

	E_{rel}	E_{Lew}	E_{del}	Dip.		E_{rel}	E_{Lew}	E_{del}	Dip.		E_{rel}	E_{Lew}	E_{del}	Dip.
1A	0.00	0.00	0.00	1.44	**1m**A	0.00	0.00	0.00	1.38					
1E	3.19	-0.65	3.84	2.29	**1m**E	0.31	-0.43	0.74	2.01					
2Aa	0.00	0.00	0.00	0.80	**2m**Aa	0.00	0.00	0.00	0.80	**2mm**Aa	1.41	9.14	-7.73	0.86
2Ae	3.68	-3.61	7.29	1.89	**2m**Ae	0.89	-3.66	4.56	1.58	**2mm**Ae	0.00	0.00	0.00	1.58
					2mEa	3.77	-4.60	8.37	1.89					
2Ee	10.57	-2.21	12.78	3.28	**2m**Ee	7.80	-1.70	9.50	2.95	**2mm**Ee	4.15	3.63	0.52	2.63
3A	0.00	0.00	0.00	0.92	**3m**A	0.00	0.00	0.00	1.06					
3E	7.16	-0.55	7.71	3.07	**3m**E	4.36	0.82	3.54	2.74					
4A	0.00	0.00	0.00	1.25										
4E	-0.76	-1.35	0.59	0.94										
5Aa	0.00	0.00	0.00	1.78										
5Ae	-0.16	-4.07	3.91	1.33										
5Ee	2.79	-2.87	5.65	2.03										

Table 3. Selected HF/6-31G Geometrical Parameters for 1 and Its N-Methylated Derivative 1m (bond lengths in angstroms and bond angles in degrees for the axial (A) conformers and relative values for the equatorial forms). Pople and Cremer's Puckering Coordinates (Q in angstroms, θ and ϕ_2 in degrees)**

	1A	**1**E	**1m**A	**1m**E
C2−O1	1.4020	-0.0130	1.4027	-0.0159
C2−N3	1.4335	0.0092	1.4334	0.0108
C5−C4	1.5315	-0.0049	1.5339	-0.0085
H7−C2	1.0892	0.0088	1.0893	0.0106
H12−C4	1.0880	0.0079	1.0881	0.0098
R13−N3	1.0013	-0.0015	1.4518	-0.0077
N3−C2−O1	113.82	-3.24	113.65	-1.91
C4−N3−C2	111.61	0.34	110.06	1.22
C5−C4−N3	111.90	-3.86	112.37	-2.88
C6−O1−C2	112.73	0.29	112.39	0.90
C6−C5−C4	109.27	0.12	109.23	0.19
C5−C6−O1	110.75	0.06	110.79	-0.55
H7−C2−N3	108.32	3.77	108.41	2.72
H12−C4−N3	107.84	4.44	107.75	3.55
R13−N3−C2	109.35	1.10	113.62	-1.77
N3−C2−O1−C6[a]	-59.25	1.04	-61.38	-1.15
C4−N3−C2−O1	54.66	6.32	57.10	1.62
C5−C4−N3−C2	-50.42	7.03	-51.77	3.50
C6−C5−C4−N3	49.57	3.32	49.51	3.09
O1−C6−C5−C4	-52.66	0.48	-51.39	1.85
C5−C6−O1−C2	57.75	-0.54	57.55	0.07
R13−N3−C2−O1[b]	-67.17	-174.04	-72.25	-174.10
Q	0.525	0.558	0.533	0.549
θ	176.78	177.61	177.11	179.32
ϕ_2	213.60	57.20	165.39	61.28

[a] Differences in torsional angles are calculated as differences in absolute values. [b] Calculated values for all the conformers, not differences.

equatorial forms decreases in 2.8 kcal/mol with respect to the nonmethylated compounds. The second N-methylation in compound **2** has a cumulative effect: it notably reduces the energy of the conformer **2mm**Ee with respect to **2m**Ee, and the form **2mm**Aa is no longer the most stable.

The selection of geometrical parameters listed in Tables 3−5 permits us to deduce that **1**, **2**, and **3** show the tendencies associated with the anomeric effect, which were previously described in detail at the 4-21G level.[9] Briefly, the bonds are elongated when they are in *anti* to the lone pair of the nitrogen, and the angles which these bonds form are widened. Thus, due to the delocalization of the lone pair, C2−O1 and X5−N4 (X = C, N, or O) bonds are longer in the axial conformers and the angles N3−C2−O1 and X5−C4−N3 are wider in the axial forms than in the equatorial ones. In the same way, H7−C2 and H12−C4 bonds are longer in the equatorial forms because of being placed in *anti* to the N3 lone pair, and the angles H7−C2−N3 and H12−C4−N3 are wider than those of the axial forms. Furthermore, the data from Tables 3−5 will permit us to analyze individually the effect of the N-methylation on the optimized geometries (see below).

1-Oxa-3-azacyclohexane (1) and 3-methyl-1-oxa-3-azacyclohexane (1m). 1-oxa-3-aza-cyclohexane (**1**) is the simplest six-membered heterocycle containing the H−N−C−O unit (Scheme 1). In agreement with the experimental information,[6] Tables 1 and 2 show a great predominance of the stability of **1**A. The dipole moments empirically estimated for **1**A (1.03 D) and **1**E (2.16 D)[6c] correspond well with the calculated ones (Table 2). The dipole repulsion model correctly assigns **1**E as less stable, since assuming that N−H causes polar repulsions smaller than those of the lone pairs, the interactions N−H/C−H and n_O/N−H in **1**A are smaller than the n_N/C−H and n_O/n_N ones occurring in **1**E. However, the NBO decomposition permits a different interpretation: In **1**E, n_N is antiperiplanar to the adjacent axial C−H bonds, while in **1**A n_N is antiperiplanar to C−O and C−C. As the interactions n_N−σ^*_{C-O} and n_N−σ^*_{C-C} are larger than n_N−σ^*_{C-H}, the predominance of **1**A is due to hyperconjugation, as reflected by E_{del} (Table 2). On the other hand, the E_{Lew} column indicates that, disregarding the hyperconjugative effects, **1**A should have a higher energy, which indicates interaction between the bonds N−H and C−H which should be separated in the same way as n_N and C−H in **1E**. Therefore, according to NBO, the different contributions included in E_{Lew} which imply n_N are less than those of N−H, in opposition to the dipole repulsion model. The higher energy of **1**E can be attributed to its lower stabilization by hyperconjugation.

We have incorporated into Table 2 the results of the HF/6-31G** NBO analysis of piperidine (**4**).[17] The comparison of **4** with **1** shows that substitution of O1 for C1 makes very little difference (0.7 kcal/mol) to the relative value of E_{Lew}, while a significant change is produced in E_{del} (3 kcal/mol), which produces a clear instability of **1**E, the order being reversed respect to piperidine. This means that substitution of O for C stabilizes **1**A by hyperconjugation due to n_N−σ^*_{C-O}, and that the change in E_{Lew} is due to the fact that the interactions n_N/n_O or N−H/n_O are smaller than n_N/C−H or N−H/C−H.

Also in agreement with the experiment,[7] there is a slight predominance of the **1m**A conformer over **1m**E. The difference in Lewis energy between the forms **1m**A

Table 4. Selected HF/6-31G Geometrical Parameters for 2 and Its N-Methylated Derivatives 2m and 2mm (bond lengths in angstroms and bond angles in degrees for the Aa conformers and relative values for the other forms). Pople and Cremer's Puckering Coordinates (*Q* in angstroms, θ and ϕ_2 in degrees)**

	2Aa	**2**Ae	**2**Ee	**2m**Aa	**2m**Ae	**2m**Ea	**2m**Ee	**2mm**Aa	**2mm**Ae	**2mm**Ee
C2−O1	1.4034	0.0003	-0.0131	1.4040	0.0011	-0.0150	-0.0157	1.4045	-0.0008	-0.0174
C2−N3	1.4367	-0.0017	0.0066	1.4375	-0.0025	0.0089	0.0062	1.4355	-0.0022	0.0062
N5−C4	1.4525	0.0011	-0.0055	1.4525	0.0021	-0.0100	-0.0070	1.4542	0.0003	-0.0094
H7−C2	1.0890	-0.0002	0.0088	1.0890	-0.0001	0.0106	0.0109	1.0893	-0.0005	0.0105
H12−C4	1.0856	0.0075	0.0164	1.0856	0.0076	0.0095	0.0186	1.0863	0.0089	0.0199
R13−N3	1.0016	0.0000	-0.0018	1.4521	0.0036	-0.0082	-0.0088	1.4522	0.0035	-0.0086
R14−N5	1.0017	-0.0010	-0.0019	1.0005	-0.0002	0.0010	-0.0007	1.4522	-0.0087	-0.0086
N3−C2−O1	113.05	-0.03	-3.11	112.89	0.07	-1.78	-1.78	112.78	-0.23	-2.11
C4−N3−C2	110.57	-0.11	0.71	108.92	0.00	1.41	1.84	109.41	-0.40	1.36
N5−C4−N3	114.14	-4.11	-6.64	114.20	-4.05	-2.96	-5.48	115.54	-4.22	-5.58
C6−O1−C2	111.73	0.56	0.69	111.48	0.52	0.92	1.14	110.85	1.29	1.95
C6−N5−C4	110.56	0.27	0.73	110.56	0.22	-0.03	0.74	109.41	0.81	1.37
N5−C6−O1	113.04	-3.09	-3.11	113.09	-3.23	-0.48	-3.59	112.78	-1.74	-2.11
H7−C2−N3	108.32	0.11	3.92	108.38	0.13	2.71	2.85	108.63	-0.01	2.74
H12−C4−N3	107.89	-0.38	3.52	107.84	-0.32	3.51	2.60	107.01	0.99	3.79
R13−N3−C2	109.40	-0.52	1.28	113.30	-0.01	-1.22	-1.20	113.93	-0.63	-1.68
R14−N5−C6	109.38	1.36	1.31	109.85	1.11	-0.90	1.04	113.93	-1.77	-1.67
N3−C2−O1−C6[a]	-56.62	-0.69	1.58	-58.33	-0.73	-1.49	-0.55	-59.26	-1.58	-1.29
C4−N3−C2−O1	52.16	1.30	5.76	54.91	0.80	1.00	0.86	52.87	2.97	3.07
N5−C4−N3−C2	-48.87	4.59	8.06	-51.17	4.03	3.29	3.81	-48.64	6.35	6.10
C6−N5−C4−N3	48.88	7.64	8.06	49.71	7.56	3.39	7.05	48.64	6.71	6.10
O1−C6−N5−C4	-52.17	5.78	5.75	-51.13	6.15	2.47	6.95	-52.87	2.40	3.07
N5−C6−O1−C2	56.63	0.49	1.58	55.94	0.93	0.21	2.39	59.26	-2.77	-1.29
R13−N3−C2−O1[b]	-69.11	-65.78	-178.19	-72.82	-71.24	-177.42	-177.61	-79.52	-71.20	-174.44
R14−N5−C6−O1[b]	69.06	177.52	178.15	71.24	177.96	65.90	178.03	79.53	178.02	177.43
Q	0.500	0.535	0.556	0.511	0.526	0.545	0.547	0.513	0.536	0.538
θ	175.88	176.58	178.45	175.86	178.14	178.02	178.28	173.72	179.12	179.86
ϕ_2	180.16	288.87	359.61	139.71	83.20	320.97	301.02	179.98	8.13	1.29

[a] Differences in torsional angles are calculated as differences in absolute values. [b] Calculated values for all the conformers, not differences.

Table 5. Selected HF/6-31G Geometrical Parameters for 3 and Its N-Methylated Derivative 3m (bond lengths in angstroms and bond angles in degrees for the axial (A) conformers and relative values for the equatorial forms). Pople and Cremer's Puckering coordinates (*Q* in angstroms, θ and ϕ_2 in degrees)**

	3A	**3**E	**3m**A	**3m**E
C2−O1	1.4045	-0.0115	1.4059	-0.0153
C2−N3	1.4363	0.0066	1.4370	0.0064
H7−C2	1.0885	0.0087	1.0885	0.0108
R13−N3	1.0015	-0.0016	1.4566	-0.0130
N3−C2−O1	112.19	-3.12	112.07	-1.80
C4−N3−C2	109.97	0.66	108.33	1.84
C6−O1−C2	111.80	0.39	111.62	0.61
O5−C6−O1	111.83	0.07	111.84	-0.32
H7−C2−N3	108.54	3.86	108.64	2.78
R13−N3−C2	109.29	2.27	113.14	-0.49
N3−C2−O1−C6[a]	-54.62	1.64	-55.99	-0.09
C4−N3−C2−O1	51.78	4.74	54.40	0.07
O1−C6−O5−C4	56.38	0.27	55.65	1.20
R13−N3−C2−O1[b]	-68.19	-178.65	-71.89	-178.82
Q	0.510	0.535	0.523	0.526
θ	178.50	177.49	178.81	179.20
ϕ_2	240.14	60.78	60.01	61.31

[a] Differences in torsional angles are calculated as differences in absolute values. [b] Calculated values for all the conformers, not differences.

and **1m**E does not differ from that between **1**A and **1**E, which seems to indicate a compensation of the electrostatic and steric effects included in E_{Lew}. That is, despite the extra steric repulsion introduced by N−CH$_3$, the E_{Lew} changes only slightly because previously a major distortion is produced in decisive geometric elements (see angle R13−N5−C2 in Table 3) which reduces the impediment. According to NBO and compared with **1**E, **1m**E is stabilized about 3 kcal/mol exclusively by hyperconjugation, being almost as stable as **1m**A. As the delocalization of the n_N pair is similar in **1**E and **1m**E, the origin of the stabilization is the increase of the bond−antibond interactions in **1m**E with the N-methylation, in particular those between σ_{N3-C13} and σ^*_{C-O} or σ^*_{C-C}. This fact was previously observed in methylcyclohexane[5a] and *N*-methylpiperidine.[17]

The values of the puckering coordinates of **1** (Table 3) show the same tendencies as those previously calculated for HF/4-21G geometries,[9] even though the magnitudes differ. According to θ, both **1**A and **1**E are nearly ideal chairs, and the values of *Q* indicate that **1**A is flatter than **1**E. It was interpreted that the decrease in the experimental and calculated values of *Q* for cyclohexane (Q = 0.56−0.57) when compared to the expected value for an ideal chair with standard C−C bonds, all internal C−C−C angles being tetrahedral and all endocyclic dihedral angles being 60° ($Q = 0.629$), is associated with the 1,3-diaxial repulsive interactions which lead to the flattening of the ring.[18] Thus, the order *Q*(ideal chair) > *Q*(cyclohexane) > *Q*(**1**E) > *Q*(**1**A) suggests larger steric repulsions in **1**A than in **1**E, that is, 1,3-diaxial repulsions with participation of the n_N pair are smaller than those where N−H is involved, as it was indicated above by NBO. The N-methylation does not distort the near ideal nature of the chair forms, since θ is almost unaffected. *Q* increases in **1m**A (more puckered than **1**A) and decreases in **1m**E (flatter than **1**E), but *Q*(**1m**E) is still larger than *Q*(**1m**A), showing that here also the 1,3-diaxial interactions predominate in **1m**A. This behavior of *Q* is parallel to what happens when piperidine **4** is N-methylated,[17] that is, the substitution of O for C has no influence.

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(18) (a) Cremer, D. *Acta Crystallogr.* **1984**, *B40*, 498. (b) Cremer, D.; Binkley, J. S.; Pople, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 6863.

Table 3 shows the effect of the N-methylation on the geometrical parameters (i) increasing the average differences in bond lengths between **1m**A and **1m**E, with respect to the differences between **1**A and **1**E; (ii) slightly reducing the average value of the endocyclic bond angles, primarily through the reduction of the angle most affected by the methylation, C4−N3−C2; (iii) reducing the average differences in the bond angles between **1m**A and **1m**E with respect to **1**A and **1**E; (iv) increasing the average value of the six dihedral endocyclic angles, and reducing the average value of their differences between **1m**A and **1m**E, with respect to **1**A and **1**E; (v) opening R13−N−C and R13−N−C−O, when H13 is replaced by C13, to reduce the steric repulsions. In all the cases, a perfect mathematical correlation can be observed between the average values of the endocyclic bond and torsion angles given in any ring.[19] This correlation has also been proved in the conformers of **2, 2m, 2mm, 3**, and **3m**. Moreover it is interesting to point out that N-methylation does not alter the general tendencies associated with the anomeric effect.

1-Oxa-3,5-diazacyclohexane (2), 3-methyl-1-oxa-3,5-diazacyclohexane (2m), and 3,5-dimethyl-1-oxa-3,5-diazacyclohexane (2mm). In 1-oxa-3,5-diazacyclohexane (**2**) the substitution of C5 for N5 increases the number of conformers due to the different orientations of the N−H groups (Scheme 1). The calculated energy order, **2**Aa < **2**Ae < **2**Ee, agrees with that predicted by the dipole repulsion model, since this assigns **2**Ee as less stable, assuming that n_N/n_N axial polar repulsions are larger than n_N/N−H axial repulsions in **2**Ae, and that these in turn are larger than the N−H/N−H axial ones in **2**Aa.

According to NBO, E_{del} in **2**Aa is much lower than in **2**Ae and **2**Ee due to a larger hyperconjugation, since two n_N-σ^*_{C-N} and two $n_N-\sigma^*_{C-O}$ interactions are stronger than the $n_N-\sigma^*_{C-N}$, $n_N-\sigma^*_{C-O}$, and two $n_N-\sigma^*_{C-H}$ occurring in **2**Ae and the four $n_N-\sigma^*_{C-H}$ interactions in **2**Ee. Disregarding hyperconjugation, the highest E_{Lew} corresponds to **2**Aa, which points to the interactions between N−H axial bonds, so that NBO indicates that the interactions due to the lone pairs are smaller than those due to N−H bonds.

In Table 2 the NBO analysis of hexahydropyrimidine (**5**) performed by Salzner[5b] at the HF/6-31G* level was included. Comparison of **5** with **2** shows that substitution of C1 for O1 clearly differentiates—and even reverses—the energy ordering of the conformers Aa, Ae, and Ee, because according to NBO the stabilization by hyperconjugation of **2**Aa is largely increased with respect to that of **2**Ae and **2**Ee, because the $n_N-\sigma^*_{C-O}$ interactions are stronger than $n_N-\sigma^*_{C-C}$ due to the larger polarity of the C−O bond, while the E_{Lew} energies are basically equal. It is interesting to observe that E_{Lew} varies in passing from **2** to **5** in the order of 0.5−0.7 kcal/mol, as occurred when it passed from **1** to **4**. In both cases, the only difference between the compounds is the substitution of O for C, so that the substitution of a pair n_O for a bond C−H behaves systematically, which in addition appears to contradict the assumptions based on the dipole repulsion model. However it is important to bear in mind that E_{Lew} cannot be separated into its components and, for this reason, interactions in this energetic contribution do not have an exclusive dipolar character.

N-Methylation makes a very slight change in the Lewis energies of the conformers of **2m** with respect to those of **2**, which indicates that the steric factors within E_{Lew} eclipse the dipolar ones. Thus, the increase in the stability of **2m**Ae and **2m**Ee, with respect to **2**Ae and **2**Ee, is due to bond−antibond interactions between σ_{N3-C13} and σ^*_{C-N} or σ^*_{C-O} that cannot occur in **2m**Aa. This increase in stability is of the same order (3 kcal/mol) as that observed for **1m**E/**1**E, which reinforces the explanation given previously and indicates that the $\sigma_{N3-C13}-\sigma^*_{C-C}$ interactions are similar to $\sigma_{N3-C13}-\sigma^*_{C-N}$.

The energy ordering of the conformers of the **2mm** compound agrees with the experimental estimate,[8] with **2mm**Ae being the most stable conformer. The double N-methylation alters the importance of factors conditioning the stability according to NBO, and now the predominance of E_{Lew} leads to a reversed order in E_{rel} in comparison with the other compounds. As the dipole moments of the conformers of **2mm** are very similar to those of **2m**, and even to those of **2**, it is possible to conclude that the high values of E_{Lew} are due to steric factors. **2mm**Aa is still the most stabilized conformer by hyperconjugation, but this effect is not sufficient to compensate its high E_{Lew}. In **2mm**Ee there are more bond−antibond interactions in which N3−C13 and N5−C14 take part than those in **2mm**Ae, so E_{del} is similar for both forms, in such a way that the higher energy of **2mm**Ee is due to E_{Lew}.

The puckering coordinates of **2** calculated with the 6-31G** basis set (Table 4) and 4-21G[9] show similar trends. The values of θ indicate almost perfect chairs for all three conformers. According to Q, **2**Aa is flatter than **2**Ae, and the latter is flatter than **2**Ee, so that the 1,3-diaxial repulsions decrease when one or two n_N pairs adopt an axial position, in agreement with NBO predictions. N-Methylation does not alter the quasi-ideal nature of the chairs and approximates the values of Q for the conformers of **2m**, increasing Q for the totally axial conformer and decreasing it for those which are partially or totally equatorial. The double N-methylation comes even nearer to the Q values, though the puckering of **2mm**Ae and **2mm**Ee is now very similar but different to that of **2mm**Aa, which differs much more ($\theta = 173.72°$) from the ideal than any other conformer. All this is coherent with the behavior of E_{Lew} described above for **2mm**.

With regard to geometry, N-monomethylation does not alter the bond lengths of the most stable conformer, **2m**Aa, with respect to **2**Aa, nor does it alter the general tendencies of the anomeric effect. There is a slight reduction in the average value of the endocyclic bond angles of **2**m with respect to **2** (due fundamentally to C4−N5−C2), and also in the differences of these angles between the conformers of **2**m, with respect to those of **2**. Also the average value of the endocyclic dihedral angles increases, but the average value of the differences of these angles between the conformers decreases, with respect to the angles of **2**. The bond angles R13−N3−C2 and R13−N3−C2−O1 are widened when R13 is CH_3 to reduce tension. Double methylation increases the bond lengths of **2mm**Aa, compared with **2**Aa, and reduces the average value of the endocyclic bond angles with respect to **2,** but not with respect to **2**m, although the bond angle N5−C4−N3 must widen to accommodate two axial methyl groups. The average differences in bond lengths between the conformers of **2mm** increase with respect to **2** and **2m**, while there is a clear reduction in

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[19] Altona, C.; Geise, H. J.; Romers, C. *Rec. Trav. Chim. Pays-Bas* **1966**, *85*, 1197.

Table 6. HF/6-31G Relative Energies in Water (E_{wat}) Calculated with the PCM Method (see text for computational details). Solvation Energies (ΔG_{sol}) and Its Electrostatic (ΔG_{el}) and Nonelectrostatic (ΔG_{noel}) Contributions Are Also Shown. All Values Are in kcal/mol**

	E_{wat}	ΔG_{sol}	ΔG_{el}	ΔG_{noel}		E_{wat}	ΔG_{sol}	ΔG_{el}	ΔG_{noel}		E_{wat}	ΔG_{sol}	ΔG_{el}	ΔG_{noel}
1A	0.00	-1.92	-6.36	4.44	**1m**A	0.00	1.20	-4.94	6.14					
1E	2.20	-2.91	-7.35	4.44	**1m**E	-0.27	0.62	-5.43	6.05					
2Aa	0.00	-5.67	-9.31	3.64	**2m**Aa	0.00	-1.72	-7.02	5.30	**2mm**Aa	1.49	1.18	-5.60	6.78
2Ae	3.20	-6.16	-9.76	3.60	**2m**Ae	0.11	-2.50	-7.77	5.27	**2mm**Ae	0.00	1.10	-5.94	7.04
					2mEa	3.09	-2.40	-7.69	5.29					
2Ee	7.29	-8.96	-12.54	3.58	**2m**Ee	4.32	-5.20	-10.44	5.24	**2mm**Ee	1.74	-1.31	-8.17	6.86
3A	0.00	-5.07	-8.16	3.09	**3m**A	0.00	-1.38	-6.11	4.73					
3E	5.00	-7.23	-10.28	3.05	**3m**E	2.58	-3.16	-7.82	4.66					

the average differences in the endocyclic bond angles. As always, the average differences of the endocyclic dihedrals between the conformers of **2mm** decrease. R13−N3−C2, R14−N5−C6, R13−N3−C2−O1 and R14−N5−C6−O1 widen, when R14 is CH_3, to avoid nonbonded interactions between methyl groups.

1,3-Dioxa-5-azacyclohexane (3) and 5-Methyl-1,3-dioxa-5-azacyclohexane (3m). The last case of this study is 1,3-dioxa-5-azacyclohexane (**3**) and its N-methylated derivative which show C_s symmetry because of the introduction of an oxygen in position 5 (see Scheme 1). According to the dipole model, the repulsion between the N3 axial lone pair and the axial lone pairs of the oxygen makes the **3**E form a very unstable conformer, in contrast with **3**A where the N−H axial dipole interacts with the oxygen's pairs.

The NBO analysis suggests a different view. Two $n_N-\sigma^*_{C-O}$ interactions are present in **3**A, and two $n_N-\sigma^*_{C-H}$ in **3**E, that is, the smaller hyperconjugation term in **3**E is responsible for its higher energy. On the other hand, E_{Lew} is just slightly larger in **3**A, which indicates again that the interactions with N−H are larger than with n_N. The comparison of **3** with **1** leads to the conclusion that substitution of O5 for C5 increases the stability of the A forms by about 4 kcal/mol, and that the effect arises from the stronger delocalization due to the presence of a polar C4−O5 bond instead of C4−C5 in *trans* to the N3 lone pair. Unlike what occurred with the pairs **1** and **4** and **2** and **5**, where E_{Lew} varied constantly with the substitution of O for C, the identical values of E_{Lew} for **1** and **3** are due to the fact that this substitution now takes place in the presence of another oxygen, that is, in the absence of an axial bond C−H or N−H in that position, now occupied by a pair n_O. This is coherent with the aforementioned fact that in NBO analysis, the interactions produced by n_O are less then those of C−H or N−H.

The instability of **3m**E coincides with the experimental estimate.[8] The difference in Lewis energy between the forms **3m**A and **3m**E differs from that between **3**A and **3**E (Table 2). Taking into account that **3m** is related to **1m**, by substitution of C5 for O5, and considering that the dipole moments of **3m**A and **3m**E differ from each other much more than those of **1m**A and **1m**E, it could be concluded that the relative increase of E_{Lew} when going from **3**E to **3m**E would be justified by electrostatic rather than steric interactions. However, the determining factor is E_{del}, and **3m**E is stabilized by hyperconjugation with respect to **3**E in a similar amount, about 3.5 kcal/mol, to what happened between **1m**E and **1**E. Since the delocalization of the n_N pair is similar in **3**E and **3m**E, again the explanation resides in that the N-methylation increases the bond−antibond interactions in **3m**E, in particular those between N3−C13 bond and C−O antibonds, which are similar to those in **1m**E. As before, this indicates that the $\sigma_{N3-C13}-\sigma^*_{C-C}$ interactions are of the same order as the $\sigma_{N3-C13}-\sigma^*_{C-O}$ ones.

The puckering coordinates show that all the conformers of **3** and **3m** are almost perfect chairs. The smaller values of Q indicate flatter rings when the N3−R13 groups are axial, that is, 1,3-diaxial steric repulsions involving the n_N pair are smaller, and the N-methylation makes the values of Q in **3m**A and **3m**E get closer. The behavior of Q and E_{Lew} is slightly different from that found in **1**, **1m**, **2**, and **2m,** because in this case the 1,3-diaxial interactions in which n_N or N3−R13 are involved are not those with C−H but with n_O. On the other hand, the influence of methylation on the geometrical parameters (Table 5) shows the same features as those already described for **1** and **1m**, even from a quantitative point of view, so that the endocyclic substitution of C5 for O5 has no repercussion on these parameters.

Solvation. In agreement with previous findings,[10] PCM calculations predict that the preference for the N3−R13 axial forms is reduced in the presence of a polar solvent such as water (Table 6), but to an extent that is not sufficient to eliminate the anomeric effect, except in **1m** where the equatorial form, **1m**E, becomes more stable. The influence of the solvent on the variation of the stabilities is slightly larger (~0.5 kcal/mol) in **1**, **2**, and **3** than in their *N*-methyl derivatives, with the exception of **2m**.

The greater influence of the solvent occurs in those conformers with a larger dipole moment, although a proportional relationship between the variations in relative energies and the variations in dipole moments is not observed (see the case of **2**, **2m**, and **2mm**). This suggests that the interaction of the total dipole of each conformer with the solvent is not the only factor responsible for the electrostatic component of the solvation energy and that local dipolar interactions or even multipole components can be important.[20]

A comparison of ΔG_{el} for **1**, **2**, and **3** can throw some light on this. Since the nonelectrostatic components of ΔG_{sol} are practically constant for the conformers of each of the species studied, the variations of the relative energies are mainly due to the electrostatic component. According to Table 6, $\Delta G_{el}(\mathbf{2}) > \Delta G_{el}(\mathbf{3}) > \Delta G_{el}(\mathbf{1})$ and there is no correlation between the values of ΔG_{el} and the total dipole of the conformers of each molecule. This tendency in ΔG_{el} could be related to some local interaction due to the type of substitution in position 5 and would indicate that the interaction of the solvent with the local dipoles of the N3−H13 bond and the lone pair of N5 in **2** is more favorable than with the lone pairs of two O in **3** and even more so than with two C−H bonds in **1**.

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(20) Alagona, G.; Ghio, C. *J. Mol. Struct. (THEOCHEM)* **1992**, *254*, 287.

The same interpretation would also explain the reduction in ΔG_{el} when each substance is N-methylated. In every case, N-methylation reduces ΔG_{el} by approximately 2 kcal/mol, and the effect seems additive as can be seen when comparing **2**, **2m**, and **2mm**. This reduction, which could not be explained by the interaction of the total dipole of the molecule with the solvent because the dipole is almost unaffected by the N-methylation in each case, could be due to the substitution of the local dipolar interaction between the N−H bond and the solvent by the local interaction between $N-CH_3$ and the solvent. The latter is less important because the $N-CH_3$ group is not as polar as N−H.

The mentioned decrease in ΔG_{el} and the increase of 1.5 kcal/mol in ΔG_{noel}, principally due to its cavitation component, are responsible for the decrease of ΔG_{sol} in approximately 3.5−4 kcal/mol for each methyl group introduced. The effect of the N-methylation on the solvation energies seems to be independent of the substituent in position 5, since it is observed in **1m**, **2m**, and **3m**, and it is furthermore additive because the second *N*-methyl in **2mm** also follows the trend mentioned.

Conclusions

The axial/equatorial equilibrium of compounds containing the N−C−O endocyclic unit can be considered acceptably described at the HF/6-31G**//HF/6-31G** level, since other effects tend to compensate. For all the molecules studied, axial preferences of the N3−R13 group have been determined as a consequence of the anomeric effect present at the R−N−C−O unit. The N-methylation ($R13 = CH_3$) shows a systematic influence, independent of the atom at position 5 (C, N, or O), that consists in approaching the relative stabilities for the axial and equatorial forms.

According to the NBO analysis, the reason for the preference for the axial forms, in which the generalized anomeric effect takes place, is the contribution due to hyperconjugation, that is always larger than the energy of these forms considered as hypothetical Lewis structures. Substitution of C5 for O5 produces a systematic increase (3 to 4 kcal/mol) of the preference for the axial forms, due to the increase of hyperconjugation when the polar C4−O5 bond is present. The effect of N3-methylation increases constantly (3−3.5 kcal/mol), and independent of the atom in position 5, the delocalization energy of the equatorial forms, with respect to the nonmethylated compounds, while the Lewis energies do not suffer appreciable changes. The second N5-methylation reverses the importance of these terms.

The results of this and our previous work[9] indicate that the tendencies of the puckering coordinates of **1**, **2**, and **3** are independent of the basis set used. According to these coordinates, the atom in position 5 does not alter the ideal nature of the chairs but increases the flattening of the rings in the order $C < O \leq N$. The N-methylation does not alter it either (except for double axial conformers) and tends to equal the puckering of the conformers of each compound, in agreement with the approaching of the stabilities.

The geometrical tendencies associated to the anomeric effect are fulfilled for the 6-31G** basis set. On the other hand, methylation has a systematic influence on the main geometrical parameters. It does not alter the tendencies associated to the anomeric effect, and it tends to reduce the average value of the endocyclic bond angles as well as the average differences between conformers. Consequently, given the mathematical correlation between the endocyclic bond angles and dihedrals of a ring, there is an average increase in the latter and an average decrease in the differences between conformers. The endocyclic substitution of N or O for C does not essentially affect the behavior of the differences of the geometric parameters between conformers. The substitution of N for C produces a slight increase in the average value of the endocyclic bond angles, and reduction of the average value of the endocyclic dihedral angles, while the substitution of O for C is indiscernible. The double N-methylation systematically reinforces the geometric effects previously described.

The influence of water on the relative stabilities of the studied conformers was estimated. As in other substances showing anomeric effect, the axial forms reduce their preferences between 1 and 3.5 kcal/mol, the influence of water being slightly smaller in the N-methylated forms. The electrostatic contribution of ΔG_{sol}, the main factor responsible for these variations, could be related to the interaction between the dipole moment of the solute and the reaction field of the solvent, although the possible importance of local dipolar interactions has also been pointed out.

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