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Analysis of anomeric effects in some oxa diaza spiro decan derivatives by DFT molecular orbital calculations

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ABSTRACT

The conformational behavior of oxa diaza spiro decan derivative compounds has been investigated using DFT calculations at the B3LYP/cc-pVDZ level of theory. Natural bond orbital (NBO) analysis of the total energy behavior yielded the orbital-interaction factors contributing to the conformational equilibria. The relative energies, NBO analysis and structural parameters predicted that steric and anomeric effects determine the stabilization of the axial and/or equatorial conformers. The dipole moments of the optimized systems were used to estimate the electrostatic contributions to the anomeric effect. The results of calculations indicated that the axial conformers are the most stable in all of the studied compounds. Finally, the strain energy barriers for the most stable conformers were calculated at HF/6-311G*//HF/6-311G* level of theory. Interconversion between chair and twist conformations takes place *via* the half-chair as transition state. The lowest calculated strain energy for this process is 42.41 kJ mol^{-1}.

1. Introduction

The anomeric effect was originally defined as the preference of a polar substituent at the anomeric carbon of a monosaccharide to the axial position over the equatorial one [1]. Currently, the anomeric effect is generally recognized as being of more importance for molecules containing the R–X–C–Y moiety (where X = N, O, or S and Y = Br, Cl, F, N, O, or S) and is to be manifested as follows [2]: (I) structural parameters, for example, shorter or longer anomeric bonds and larger anomeric bond angles; (II) relative energy, that is, greater stability of gauche (axial) forms or anti (equatorial) forms; and (III) stereoselective reactivity. The anomeric effect is no longer an anomaly and proved to be an important factor in the stability of substituted conformers of cyclohexanes and other heterocyclic compounds [3,4]. In this regard; molecules containing the N–C–N moiety have been explored less than the analogous oxygen systems. Only one electron diffraction (ED) study has been performed on *N*,*N*,*N″N″*-tetramethyldiaminomethane, and there are few really reliable (^{13}C NMR) [5] conformational equilibrium studies of the highly relevant 1,3-diazane system [6,7]. The complexity of the systems containing N–C–N moieties is a result of a combination of steric and stereoelectronic effects and hydrogen bond-type interactions. It has been indicated that the anomeric effects in N–C–N systems are smaller than in O–C–O systems, but the structural manifestations were borne out as expected [8]. Salzner has performed *ab initio* HF/6-31G* level calculations on the stability of conformers of 1,3-diazacyclohexane in the light of examining the conformational behavior of 2-hydroxyhexahydropyrimidine [9]. Recently, Locke et al. examined the stability of 1,3-diazacyclohexane with the DFT (B3LYP/6-311 + G**) level while quantifying the contributions and interplay of steric and electronic factors for 5-hydroxyhexahydropyrimidine [10]. Though the studies were limited to N–C–N systems, the 1,3-diazacyclohexane derivatives are nevertheless important for the preparation of neuroblocking-active drugs (such as clothianidin) and high-energy materials [11,12]. The wide application of diazacyclohexane and its derivatives in studies from biology to materials make these compounds candidates for detailed conformational study.

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. 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 of the energetic and geometrical features of the axial/equatorial equilibrium of these compounds. Therefore, we have performed DFT calculations to investigation geometrical structures, energetic properties, and the relative stability of the conformers of various diaza spiro decan compounds, namely: 1-Oxa-6,7-diaza-spiro[4.5]decan (**A**), 1-Oxa-6,8-diaza-spiro[4.5]-decan (**B**), 1-Oxa-6,9-diaza-spiro[4.5]decan (**C**), 1-Oxa-6,10-diaza-spiro[4.5]decan (**D**), 1-Oxa-7,8-diaza-piro[4.5]decan (**E**) and 1-Oxa-7,9-diaza-spiro[4.5]decan (**F**) (see Scheme 1).

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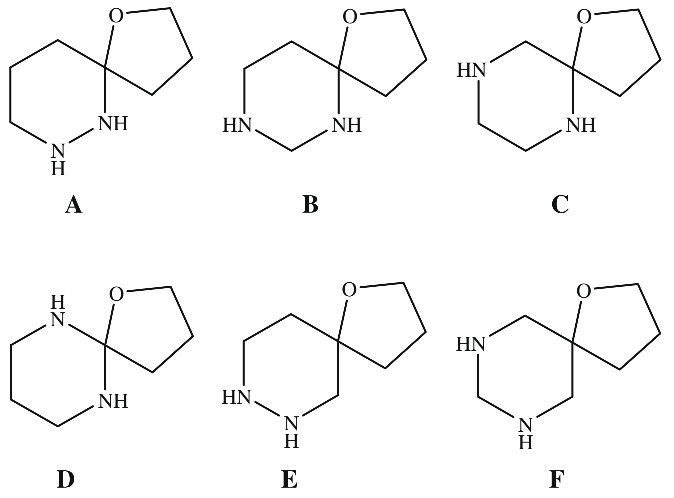


Scheme 1.

Also, to more fully understand the nature and magnitude of anomeric effects, we employed NBO analysis to investigate the hyperconjugative energetic contribution (that can be separated into the steric and electrostatic terms) on conformers of these compounds (**A1–F22**). Moreover, the rotation barrier for ring inversion in these compounds has been studied using the HF method.

2. Computational details

In the present study, density functional theory methods were used to optimize the conformations of oxa-diaza-spiro[4.5]decan analogues (**A–F**). The restricted Hartree–Fock (RHF) *ab initio* method with 6-311G* basis set, and Becke's three parameter exact exchange functional (B3) [13] combined with the gradient corrected correlation functional of Lee–Yang–Parr (LYP) [14] DFT method with the cc-pVDZ basis sets have been employed to optimize these molecules. The nature of optimized geometries at the HF and B3LYP levels has been checked with frequency calculations. The NBO calculations have been carried out employing the HF/6-311 + G** level using B3LYP/cc-pVDZ geometries.

Total energy, relative energy, dipole moment and anomeric effect have been calculated for all optimized geometries. The structural parameters of the stable conformers were optimized by minimizing the energy with respect to the geometrical parameters. The calculated structural parameters, energies, total dipole moments and orbital interactions of these molecules are given in Tables 1–8. All calculations were performed using GAUSSIAN 2003W computational package [15].

3. Results and discussions

The results obtained from theoretical calculations will be discussed in the light of the effects of the lone-pairs on the heteroatom of the rings (steric effects), the relative stability of axial/equatorial conformers and the effects of anomeric interactions derived from the NBO analysis on the molecular properties.

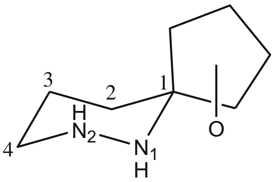
The results indicated that both hyperconjugative and steric effects are important in determining the relative stability of axial and equatorial conformers of compounds **A–F** (Scheme 1). The most stable conformers in these compounds are axial conformers, with stereoelectronics and/or steric interactions determining the stability of these conformers.

3.1. Stereoelectronic effects

*3.1.1. 1-Oxa-6,7-diaza-spiro[4.5]decan (**A**)*

The investigation of 1-Oxa-6,7-diaza-spiro[4.5]decane (**A**) by DFT calculation, revealed that it has eight conformers (Scheme 2). It is expected that the **A1ax** conformer is more stable than the others due to equatorial orientations of lone-pair electrons on nitrogen atoms. But the results of DFT calculations indicated that the **A4ax** conformer is more stable than other **A** conformers (Table 1). The orbital interactions can explain the stability of the **A4ax** conformer over **A1ax** (Table 7). NBO analysis indicated that in the **A4ax** conformer the highest stabilization energy of the orbital interactions are the endo-anomeric ($N \rightarrow \sigma^*_{C-O}$) interaction of 82.63 $kJ\,mol^{-1}$ and the exo-anomeric ($O \rightarrow \sigma^*_{C-N}$) interaction of 55.10 $kJ\,mol^{-1}$. While in **A1ax** conformer, the exo-anomeric ($O \rightarrow \sigma^*_{C-N}$) interaction is the greatest orbital interaction at 58.78 $kJ\,mol^{-1}$, the value of endo-anomeric orbital interaction is only 23.47 $kJ\,mol^{-1}$. These results are confirmed by values of bond lengths and bond angles in which the $C–N_1$ bond is lengthened (1.477 Å) and the C–O bond is shortened (1.429 Å) in the **A1ax** conformer. But in the **A4ax** conformer both endo- and exo-anomeric interactions are active and therefore an intermediate bond length is observed for C–O and $C–N_1$ (Table 1). Also, it was worth noting

Table 1
Selected geometries parameters, calculated total and zero-point vibrational energies, relative energy (including zero-point energy, $kJ\,mol^{-1}$) and dipole moment for various conformations of **A**.



		A1ax	**A1eq**	**A2ax**	**A2eq**	**A3ax**	**A3eq**	**A4ax**	**A4eq**
B3LYP/cc-pvdz/// B3LYP/ cc-pVdz		−459.8817126	−459.8801659	−459.8753544	−459.8728983	−459.87764	−459.8819681	−459.88419266	−459.8764075
ZPE		0.21458	0.21451	0.21479	0.21476	0.21454	0.21470	0.21493	0.21444
E_{rel} = $kJ\,mol^{-1}$		5.58	9.48	22.84	29.21	16.20	5.24	0.0	19.17
$C_1–N_1$	r_1/Å	1.477	1.488	1.463	1.476	1.482	1.484	1.458	1.475
$N_1–N_2$	r_2/Å	1.430	1.426	1.477	1.476	1.428	1.430	1.436	1.428
$N_2–C_4$	r_3/Å	1.470	1.468	1.466	1.469	1.461	1.463	1.466	1.465
$C_1–O$	r_4/Å	1.429	1.425	1.453	1.434	1.416	1.423	1.459	1.433
$N_1–C_1–O$	θ_1/°	107.64	105.95	111.42	106.20	109.73	106.57	111.94	105.93
$C_1–N_1–N_2$	θ_2/°	115.31	116.71	110.50	107.64	109.90	109.35	113.48	114.97
$N_1–N_2–C_4$	θ_3/°	113.98	115.20	107.87	106.39	112.75	112.79	107.93	108.27
μ		1.385	1.685	1.352	1.548	1.935	1.036	1.919	2.77