Electronic Delocalization Contribution to the Anomeric Effect Evaluated by Computational Methods

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This study proposes the determination of the electronic delocalization contribution to the Anomeric Effect (EDCAE, $\Delta\Delta E_{deloc}$, eq 3) as a computational alternative in the evaluation of the excess of the axial preference shown by an electronegative substituent located at α position to the annular heteroatom of a heterocyclic compound (anomeric position) in both the presence and the absence of electronic delocalization retaining the same molecular geometry. The determination of the EDCAE is computationally accessible through the application of the natural bond orbital analysis (NBO). This type of analysis allows the comparison of hypothetical molecules lacking electronic delocalization (Lewis molecules, in which the electrons are strictly located in bonds and lone pairs) with the fully delocalized molecules retaining the same geometry and the evaluation of the anomeric effect in terms of eq 3. The role of the Lewis molecules is the same as the cyclohexane used experimentally to evaluate the anomeric effect. The advantage of doing this is that Lewis molecules are stereoelectronically inert. Applying this methology to cyclic and acyclic molecules at B3LYP/6-31G(d,p) and HF/6-31G(d,p)//B3LYP/6-31G(d,p) levels of theory, we found that the anomeric effect shown by Cl in 1,3-dioxane; F, Cl, SMe, PH$_3$, and CO$_2$Me groups in 1,3-dithiane is of stereoelectronic nature while the preference of F, OMe, and NH$_2$ in 1,3-dioxane and the P(O)Me$_2$ group in 1,3-dithiane is not. Furthermore, this methodology shows that anomeric effects without stereoelectronic origin can modify the molecular geometry in agreement with the geometric pattern required by the double-bond no-bond model, as recently proposed by Perrin.

Introduction

The anomeric effect[1] (AE) is the excess in the preference for an axial position that electronegative substituents show when they are located at the anomeric position (α position with respect to the annular heteroatom); instead of the equatorial conformation, generally favored in steric terms due to the repulsion that the axial substituents suffer with 4,6-syn-diaxial group. (Scheme 1).

The first attempts to quantify the magnitude of AE were made by Eliel et al.[2] and Anderson and Sepp[3] who determined this quantity according to eq 1.

$$\Delta\Delta G° = AE = \Delta G°_{heterocycle} - \Delta G°_{cyclohexane} = \Delta G°_{heterocycle} + A \text{ value} \quad (1)$$

in which $\Delta G°_{heterocycle}$ corresponds to the conformational free energy of the substituent in the heterocyclic system under study. $-\Delta G°_{cyclohexane}$, also known as *A* value, corresponds to the conformational preference of the same substituent in cyclohexane, which is considered an index of steric interactions.[1,4]

In this approximation, the steric interactions of the substituent in the anomeric position are supposed to remain constant by going from cyclohexane to the heterocyclic system. It is also assumed that cyclohexane is stereoelectronically inert, and the electrostatic interactions that can occur (favored by the introduction of electronegative atoms in the heterocyclic system) are irrelevant.

This way of evaluating the AE has caused several controversies. For example, by applying eq 1, it has been mistakenly determined that 2-carbomethoxy-tetrahydropyran shows a reverse anomeric effect (RAE; excess in preference for equatorial position).[5] This problem is originated when an endocyclic methylene group of a substituted cyclohexane is replaced by an heteroatom, that causes significant changes in geometry (change in bond lengths, bond and dihedral angles). Therefore, changes in the steric environment experienced by the substituents have to be taken into account.[6]

To assess the changes in molecular geometry, Franck[7] linearly correlated the free conformational energy of a

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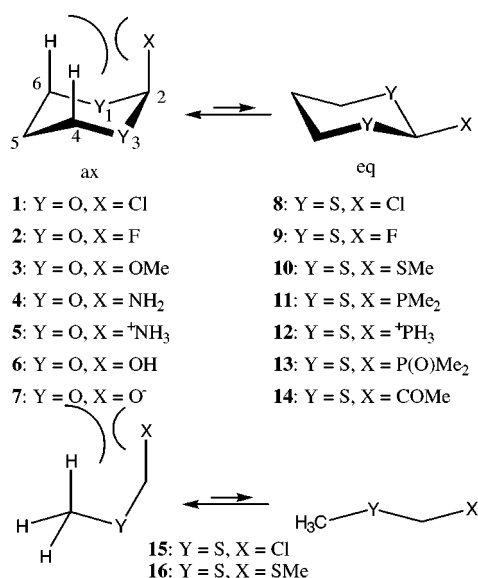
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Scheme 1

1: Y = O, X = Cl   **8**: Y = S, X = Cl

2: Y = O, X = F   **9**: Y = S, X = F

3: Y = O, X = OMe   **10**: Y = S, X = SMe

4: Y = O, X = NH_2 **11**: Y = S, X = PMe_2

5: Y = O, X = $^+NH_3$ **12**: Y = S, X = $^+PH_3$

6: Y = O, X = OH   **13**: Y = S, X = $P(O)Me_2$

7: Y = O, X = O^- **14**: Y = S, X = COMe

15: Y = S, X = Cl
16: Y = S, X = SMe

series of "electronically inert" substituents in cyclohexane (methyl, ethyl, isopropyl, and *tert*-butyl groups) with the $\Delta G°$ of the same substituents in tetrahydropyran. This led to the discovery of the fact that the steric appearance of the methyl group increases 1.53 times when it is transferred from cyclohexane to tetrahydropyran. This approach demonstrated that methylamine and dimethylamine groups show normal AE.[7] The *A* value of the *tert*-butyl group is 4.9 kcal/mol, but when it is a substituent at C2 in 1,3-dithiane, the equatorial conformational preference is only 2.72 kcal/mol.

The introduction of the scaling factor α = 0.6 or (2.72/4.9) to the experimental values allows the assessment of the value of the AE found in 2-diphenylphosphinoyl-1,3-dithiane, which changes from 3.74 kcal/mol to 2.64 kcal/mol when eq 2 is applied.[8]

$$\Delta\Delta G° = EA = \Delta G°_{\text{heterocycle}} - \alpha\Delta G°_{\text{cyclohexane}} \quad (2)$$

$$\Delta\Delta G° = AE = 1.0 - [0.6\,(-2.74)] = 2.64$$

Equation 2 also allows the estimation of the AE in terms of enthalpy as 3.39 kcal/mol. This eliminates entropic contributions in the evaluation of conformational preferences.[9] However, since the relative changes in the $\Delta G°$ value of stereoelectronically inert groups going from cyclohexane to other heterocyclic systems are not linear[7] (α value depends on both heterocycle and the substituent), the method presented in eq 2 cannot be generalized. Particularly, it cannot be easily applied to the experimental evaluation of the AE in acyclic systems in which this effect is manifested as the preference for the gauche conformation with respect to the anti. In this case, the scaling factor would be difficult to obtain experimentally due to the small conformational barriers. For example, the α factor for the methyl group in the *n*-butane/ethyl methyl ether system is 1.7. From this value, the α factor of the OMe group in the MeO−CH_2 segment is deter-

mined as 1.23, the value originated in the interpolation procedure suggested by Franck.[10] This may cause some interpretation problems, but from the experimental point of view this is the best alternative to date.

As demonstrated by Eliel and Giza,[6] the incorporation of heteroatoms causes electronic, stereoelectronic, and electrostatic changes. Therefore, if only stereoelectronic contributions are considered, they do not account for the difference shown in eqs 1 and 2.[2]

From the computational point of view,[1] the AE has been defined as the positive difference between the energy of the axial (or gauche) conformer and the equatorial (or antiperiplanar). This way of measuring the AE, though quite simple, does not keep the original aim of the definition in terms of an excess for the axial or gauche preference. On the other hand, *A* values have been calculated by the introduction of atom−atom steric potentials[11,12] determined through molecular mechanics[13,14] as well as semiempirical and ab initio methods.[15]

The analysis that uses natural bond orbitals (NBO) allows a unique approach to the evaluation of the AE from the computational standpoint. The NBO analysis has been widely used to study not only wave functions but also electronic densities obtained through ab initio calculations[7] employing the Hartree−Fock and Kohn−Sham approximations.[16] This analysis allows the separation of the molecular energy into two fundamental contributions: the total energy (where delocalization is present), and the energy of the Lewis molecule (E_{Lew}) which corresponds to the hypothetical molecule of Lewis, where the hyperconjugation is absent. Therefore, the electrons are strictly located in bonds and in lone pairs.

The NBO program orthogonalizes the atomic orbitals basis set and transforms the canonical delocalized Hartree−Fock molecular orbitals into the so-called natural bond orbitals (NBOs). This is possible because the Fock matrix is diagonal in the basis of the canonical MOs, and the elements outside the diagonal correspond to interactions between occupied orbitals or lone pairs and empty orbitals (stereoelectronic interactions).[17] The energy of the hypothetical Lewis molecule with strictly localized bonds is obtained by removing all off-diagonal elements from the Fock matrix and computing one SCF cycle. This information is useful in order to determine the delocal-

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ization energy: $E_{\text{deloc}} = E_{\text{total}} - E_{\text{Lew}}$. The properties of Fock's matrix in natural orbitals terms has been previously discussed and reviewed.[18]

These concepts were applied by Salzner and Schleyer[19] to study several oxane derivatives such as hydroxy-, methoxy-, fluoro, etc., confirming the hyperconjugative origin of the AE of these segments. The same authors[20] investigated the origin of the generalized AE in $CH_2(XH_2)$ compounds (X = O, S, Se, Te) finding smaller anomeric effects going down the group.

The NBO analysis has been successfully used to study delocalization energies in several systems such as 1,3-oxolane,[21] 1,3-dithianes,[22] 1-oxo-aza-cyclohexanes,[23] aminoketals,[24] thionucleosides,[25] and 1,3-diazanes.[26,27] Very recently, two papers regarding the study of the AE through NBO analysis were published.[28] Carballeira and Pérez-Juste[28a] described the interpretation of the AE in $CH_2(XH_2)_2$ (X = N, P, As) compounds, concluding, in agreement with Schleyer, that the AE decreases considerably for the higher row substituents. The second paper by Alabugin[28b] described the stereoelectronic interactions in cyclohexane with the use of the Natural Resonance Theory (NRT). These theoretical results should be taken with care because the NRT analysis does not meet the requirements of a formal theoretical approach. It cannot be justified even by using "chemically reasonable" numerical results. Thus, NRT analysis was not used in our study.[29]

The NBO analysis allows us to estimate the AE according to Eliel's proposal (eq 1). It is possible to estimate the energy of the molecule with the same geometry but in the absence of electronic delocalization. Moreover, only the steric and electrostatic interactions through the E_{Lew} are taken into account. The delocalization contribution to the AE (EDCAE, $\Delta\Delta E_{\text{deloc}}$) can be calculated for an equilibrium between two components according to:

$$\text{EDCAE} = \Delta\Delta E_{\text{deloc}} = (E_{\text{total}} - E_{\text{Lew}})_{\text{eq. or anti}} - (E_{\text{total}} - E_{\text{Lew}})_{\text{ax. or gauche}} \quad (3)$$

This equation satisfies the initial purpose of considering the AE as an electronic delocalization index, avoiding problems of geometric origin. However, the electrostatic interactions would be enhanced due to the fact that this procedure increases punctual charges that could be taken into account since calculations are performed on isolated molecules at 0 K. This paper shows the results obtained from the evaluation of the EDCAE in the heterocyclic systems shown in Scheme 1.

Computational Methods

Full geometry optimization (no symmetry constraints) of all structures was carried out by using Density Functional Theory (DFT). Energy and geometry of methylthiomethyl-substituted derivatives were calculated by using the semilocal (generalized gradient corrected) exchange-correlation energy functional, which included the exchange functional of Becke[30] and the correlation energy functional of Perdew[31] (BP), incorporating the semilocal corrections self-consistently.[32] The orbital basis set was double-ζ plus polarization (DZVP2), and the auxiliary basis set used to fit the charge density and the exchange-correlation potential was A1.[33] A FINE grid was selected for the numerical integration. The calculations were performed with the Dgauss 1.1 package.[33] Cyclic compounds were determined at B3LYP/6-31G(d,p) level and at HF/6-31G(d,p)// B3LYP/6-31G(d,p). The calculations at B3LYP/6-31G(d,p) level were carried out with the Gaussian 92 (G92) program.[34] NBO analysis[35] was carried out with version 4.0 included in G92. The keyword NOSTAR was used in the NBO input to determine the energy of the hypothetical Lewis molecule.[36]

Results and Discussion

There are two manifestations of the AE originated by the participation of the unshared electron pairs of the annular heteroatoms: energy and molecular geometry. Table 1 shows the main geometric parameters generated by the full geometry optimization of the studied systems at the B3LYP/6-31G(d,p) level.

The first rationalitazion of the AE was given by Edward,[37] who stated that the equatorial conformations of sugars might be destabilized by repulsion between the lone pairs of the endo- and exo-cyclic oxygens and/or by an unfavorable dipole orientation. However, its apparent incapability to explain the experimental geometric patterns motivated the proposition of the double bond-no bond model which is supported by the delocalization of the lone pair of the heteroatom Y into the σ^*_{C-Y} bond.[38,39] (Figure 1). The participation of these interactions in the axial conformer was observed in the C−X bond elongation, in the C−Y bond shortening, and in the increment of the Y−C−C angle.[30,38] Perrin et al.[41,42] have recently

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Table 1. Optimized Geometric Data of Molecules 1−12 at B3LYP/6-31G(d,p) Level of Theory. Bond Lengths Are in Angstroms and Bond and Dihedral Angles in Degrees

cmpd	Y−C2	Y−C4,6	C4,6−C5	C2−X	X−H4,6	Y−C−Y	C−Y−C	Y−C−X	Y−C−Y−C	C−Y−C−C	Y−C−C−C	X−C−Y−C
1-ax	1.366	1.441	1.527	1.923	2.857	116.4	115.0	109.3	50.5	51.6	52.4	73.8
1-eq	1.393	1.437	1.528	1.792		113.2	110.9	107.4	61.5	56.7	52.6	180.0
2-ax	1.381	1.439	1.528	1.396	2.548	114.8	113.3	108.8	55.8	54.1	52.7	66.4
2-eq	1.391	1.432	1.529	1.349		112.9	111.6	106.8	60.8	56.5	52.4	177.8
3-ax	1.389	1.436	1.528	1.407	2.628	113.5	113.1	111.7	55.9	54.7	53.2	66.5
	1.407	1.436	1.528		2.563			108.0	56.2	55.2	53.1	68.2
3-eq	1.395	1.428	1.579	1.373		112.2	111.7	105.7	60.9	57.1	52.7	177.7
	1.414	1.428	1.5300				111.7	109.2	60.3	56.6	52.5	177.2
4-ax	1.407	1.435	1.528	1.454	2.623	113.8	113.4	109.5	54.8	54.5	53.8	68.0
4-eq	1.409	1.427	1.531	1.431		112.8	111.2	106.9	60.7	56.5	52.7	178.0
5-ax	1.332	1.463	1.520	1.785	3.149	122.2	118.7	105.5	27.9	41.0	53.6	92.1
5-eq	1.373	1.462	1.526	1.523		115.9	111.7	103.4	58.6	54.2	52.5	171.1
6-ax	1.388	1.437	1.528	1.410	2.631	113.9	113.2	110.9	55.1	53.9	53.2	67.2
	1.409	1.436	1.528		2.559		113.5	108.1	55.9	55.4	53.6	67.9
6-eq	1.411	1.429	1.529	1.369		112.6	110.8	108.8	59.7	57.1	52.5	179.5
7-ax	1.536	1.404	1.540	1.259	1.455	101.9	108.8	115.4	69.6	64.1	53.3	56.3
7-eq	1.542	1.396	1.536	1.240		103.6	113.0	113.2	59.8	61.2	54.7	117.2
8-ax	1.819	1.837	1.531	1.857	3.123	115.8	100.2	111.9	56.3	56.7	65.4	73.5
8-eq	1.835	1.841	1.530	1.800		115.2	97.7	108.2	60.7	58.5	66.1	177.9
9-ax	1.824	1.840	1.531	1.390	2.786	115.9	98.8	109.5	58.6	57.6	66.2	65.8
9-eq	1.837	1.841	1.531	1.371		115.1	97.6	106.9	61.2	58.7	66.2	179.8
10-ax	1.835	1.837	1.531	1.850	3.167	114.0	100.3	108.7	57.0	58.6	66.6	70.4
	1.839	1.839	1.531		3.115		100.7	116.0	56.2	56.4	65.6	74.9
10-eq	1.839	1.840	1.530	1.831		114.6	99.3	109.7	59.1	59.0	66.4	179.9
	1.842	1.841	1.530				99.0	107.3	57.8	57.2	65.8	179.9
11-ax	1.841	1.839	1.531	1.900	3.174	113.5	100.1	112.5	56.6	58.0	66.1	72.7
11-eq	1.840	1.838	1.531	1.898		113.3	98.9	109.1	60.4	58.9	65.1	177.9
12-ax	1.829	1.846	1.527	1.856	3.480	119.9	107.6	109.8	43.6	51.6	68.7	85.4
12-eq	1.846	1.846	1.528	1.825		116.7	99.0	105.5	55.6	56.5	67.4	172.4
13-ax	1.840	1.844	1.531	1.869	3.146	114.1	100.5	112.3	56.4	57.8	66.8	72.9
13-eq	1.839	1.838	1.532	1.873		113.7	97.9	100.9	62.1	59.0	65.2	173.0
14-ax	1.848	1.842	1.531	1.534	2.480	115.1	101.3	107.7	54.9	55.1	65.3	73.2
	1.830	1.840	1.532		2.542		99.7	114.7	56.2	58.7	67.9	70.9
14-eq	1.851	1.838	1.531	1.537		114.7	97.8	109.3	60.3	59.3	66.4	176.2
	1.830		1.531				98.5	109.6	60.2	57.8	65.4	176.5
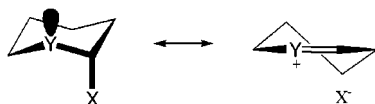
Figure 1. Double bond−no bond hybrid.

described that the shortening of the C−Y bond might be explained in terms of electrostatic interactions. Thus, the modification in the geometry is not a necessary condition to achieve the model suggested by Altona et al.[39]

Table 1 shows that this pattern is observed by all the equilibria studied except for entries **11** and **13**. In the former, there are negligible differences between both conformers, while the equilibrium of the latter is the only system in which the double bond−no bond model pattern completely breaks, in agreement with what was experimentally found.[1d,e,4,8,43]

The energy of these systems at the B3LYP/6-31G(d,p) level is included in Table 2. The axial conformer is expected to be more stable than the equatorial one as a manifestation of the AE. It is accepted that the preference of the substituents for the equatorial position in cyclohexane is due to steric effects although it is not stereoelectronically inert. At B3LYP/6-31G(d,p) level, the total energy of cyclohexane is −235.89717 Hartrees, while the corresponding Lewis molecule is −235.59751 Hartrees, which produces a difference of 188.03 kcal/mol of delo-

Table 2. Total Energies and Lewis Energies (in Hartrees), and Electronic Delocalization Contribution to the AE ($\Delta\Delta E_{deloc}$ in kcal/mol) of Molecules 1−14 at B3LYP/6-31G(d,p)

compd	total energy	Lewis energy	ΔE_{total}	ΔE_{Lewis}	$\Delta\Delta E_{deloc}$
1-ax	−767.28160	−766.78631			
1-eq	−767.27078	−766.80653	6.79	−12.69	19.45
2-ax	−406.92591	−406.41664			
2-eq	−406.91954	−406.41399	4.00	1.66	2.34
3-ax	−422.21187	−421.66152			
3-eq	−422.20821	−421.65327	2.30	5.17	−2.87
4-ax	−363.03748	−362.57080			
4-eq	−363.03469	−362.56122	1.75	6.01	−4.26
5-ax	−363.40416	−362.86516			
5-eq	−363.40626	−362.94910	−1.32	−52.67	51.35
6-ax	−382.90597	−382.41531			
6-eq	−382.90753	−382.41203	−0.98	2.06	−3.04
7-ax	−382.31016	−381.62079			
7-eq	−382.30642	−381.57231	2.34	30.42	−28.08
8-ax	−1413.22146	−1412.86154			
8-eq	−1413.21641	−1412.86773	3.17	−3.88	7.05
9-ax	−1052.85817	−1052.46327			
9-eq	−1052.85202	−1052.46847	3.86	−3.26	7.12
10-ax	−1391.13176	−1390.73707			
10-eq	−1391.12819	−1390.74276	2.24	−3.57	5.81
11-ax	−1374.22036	−1373.79374			
11-eq	−1374.21775	−1373.79759	1.64	−2.42	4.06
12-ax	−1295.91271	−1295.52437			
12-eq	−1295.90799	−1295.54096	2.96	−10.41	13.37
13-ax	−1449.47686	−1448.70865			
13-eq	−1449.46757	−1448.55852	5.83	94.21	−88.38
14-ax	−1106.27561	−1105.72568			
14-eq	−1106.27037	−1105.72879	3.29	−1.95	5.24

calization energy, equal to 0.13% of the total energy. At HF/6-31G(d,p) level, since the energies are: −234.22537 and −233.89234 Hartrees respectively, the delocalization energy is 208.98 kcal/mol, equal to 0.14%. These energy

(42) Perrin, C. L.; Armstrong, K. B.; Fabian, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 715. Perrin, C. L.; Fabian, M. A.; Brunckova, J.; Ohta, B. K. *J. Am. Chem. Soc.* **1999**, *121*, 6911.

(43) Juaristi, E.; Valle, L.; Valenzuela, B. A.; Aguilar, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 2000. Juaristi, E.; Cuevas, G. *J. Am. Chem. Soc.* **1993**, *115*, 1313.

values are small and imply a molecule with small electronic delocalization energy. In contrast, benzene, calculated at B3LYP/6-31G(d,p) has a total energy of −232.25821 Hartrees while the Lewis energy is −231.63154, with 393.24 kcal/mol of difference, that is 0.27% of the total. The difference $\Delta E_{del} = E_{total} - E_{Lew}$ measures the loss of stabilization (variational energy raising of E_{Lew} relative to E_{total}) associated with the deletion of all hyperconjugative interactions such as n → σ*, σ → σ*, etc.[36] The participation of stereoelectronic interactions in cyclohexane is demonstrated experimentally by $^1J_{C-H}$ coupling constants since this molecule shows a normal Perlin effect.[44]
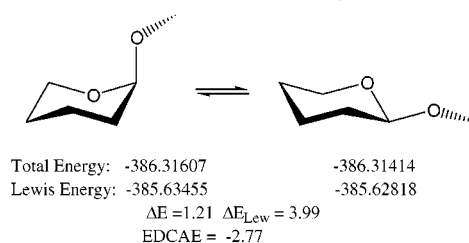
From these results, it is possible to think that if electronic delocalization is removed from the substituted heterocyclic systems under study, the steric effect would be dominant in axial or gauche conformer and an equatorial or anti preference would predominate. The Lewis energy difference is a measure of molecular stability in the absence of stereoelectronic interactions. The steric and electrostatic interactions between other terms would account for the observed conformational preference. Writing the chemical equilibria with the axial conformer on the left-hand, a positive sign in the total energy means conformational preference for the axial conformer. The same is true for the Lewis energy. According to eq 3, if a positive total energy difference and a negative Lewis energy difference are determined, a positive $\Delta\Delta E_{deloc}$ is obtained, originated by the dominant participation of stereoelectronic effects. In other words, the axial conformer is favored when electronic delocalization is dominant and equatorial is preferred when the steric effect predominates.

When the substituent prefers the axial position in the absence of electronic delocalization and interactions such as $n_Y \rightarrow \sigma^*_{C-X}$ (Figure 1) are only an additional stabilizing contribution to the axial preference if any, the Lewis energy is positive and a negative value of the $\Delta\Delta E_{deloc}$ is determined. This result implies an AE of a non-stereoelectronic nature; therefore, an electrostatic contribution would be relevant. In the same sense, when the equatorial preference is of a stereoelectronic origin, a negative value for ΔE_{total} and ΔE_{Lewis} would be determined.

For the cases studied here (Table 2), an AE of stereoelectronic origin is determined when 1,3-dioxane is substituted by Cl and for 1,3-dithiane when it is substituted by Cl, F, SMe, PMe₂, PH₃, and COMe. For example, for equilibrium **1**, **1**-ax is favored in the presence of electronic delocalization and **1**-eq in the absence of stereoelectronic interactions, as would be expected for an AE of stereoelectronic origin. 1,3-Dioxanes substituted at the anomeric position with F, OMe, NH₂, and O⁽⁻⁾ and 2-dimethylphospinoyl-1,3-dithiane have a negative difference when eq 3 is applied. This corresponds to an AE in which the stereoelectronic factors are not responsible for the conformational behavior.

Especially remarkable is the negative $\Delta\Delta E_{deloc}$ for 2-methoxy-1,3-dioxane (**3**) which is paradigmic for AEs that are generally thought to be due to delocalization. Axial 1,3-dioxane is 2.30 kcal/mol more stable than the equatorial conformer at B3LYP/6-31G(d,p), 2.74 kcal/mol at HF/6-31G(d,p)//B3LYP/6-31G(d,p), 2.27 at BLYP/cc-PVDZ, and 2.17 at BLYP/6-31G(d,p) levels of theory, in

Scheme 2.   Total and Lewis Energies (in Hartrees) of 2-Methoxyoxane

Total Energy:	-386.31607	-386.31414
Lewis Energy:	-385.63455	-385.62818

$\Delta E = 1.21$ $\Delta E_{Lew} = 3.99$
EDCAE = -2.77

good agreement with the 2.9 kcal/mol previously described.[19] In the absence of electronic delocalization (Lewis molecule), the equatorial conformer is again higher in energy than the axial. In this case, by 5.17 and 5.38 kcal/mol at the levels B3LYP/6-31G(d,p) and HF/6-31G(d,p)//B3LYP/6-31G(d,p), respectively. Salzner and Schleyer found 4.8 kcal/mol for this difference.[19]

To obtain information about this conformational behavior, we studied the conformers of 2-methoxyoxane shown in Scheme 2. Booth et al.[45] found the following thermodynamic parameters: $K = 0.26$, $\Delta H° \approx 0.0$, and $\Delta S° = -2.7$ cal/K mol for the equilibrium. They indicated that the observed axial preference in 2-methoxyoxane is due to favorable entropy but not enthalpic contribution.

In agreement with experimental results, the axial conformer is favored in terms of total energy by 1.21 kcal/mol, and in the absence of electronic delocalization again the axial one is preferred by 3.99 kcal/mol at B3LYP/6-31G(d,p) level. Our results suggest an AE of non-stereoelectronic origin.

For comparison purposes, a recent calorimetric study of the AE for 2-methoxyoxane[46] allowed an energy difference to be established between the axial and equatorial forms of 4,6-dimethyl-2-methoxyoxane equal to 1.21 ± 0.07 kcal/mol in the gas phase, with the axial form being more stable (our value is 1.21 kcal/mol). These numbers are also in good agreement with the results of ab initio calculations for 2-methoxyoxane reported by Schleyer[19] and Wiberg.[10]

The O⁻ in the 1,3-dioxane shows a preference for the axial position (**7**, Table 2). The difference in the total energy between the axial and equatorial conformer of this compound based on higher levels of theory [B3LYP/6-311+G(d,p)//B3LYP/6-31G(*d,p*) and [B3LYP/6-311++G-(2df,2dp)//B3LYP/6-31G(d,p)] is 2.03 and 1.65 kcal/mol, respectively, in favor of axial conformer. The $\Delta\Delta E_{deloc}$ shown in **7** implies a non-stereoelectronic origin, because an $n_O \rightarrow \sigma^*_{C-O^-}$ interaction is not possible even if the geometric pattern corresponds to a double bond−no bond model. This is due to the bad acceptor properties of O⁻. Perrin et al.[41,42] have demonstrated that electrostatic effects can modify the molecular geometry in the same way as the stereoelectronic interactions do. Indeed the Edwards model justifies this conformational preference.

It is also possible that an electrostatic attraction between hydrogens at 4,6-syn-diaxial positions and the O⁻ substituent at C2 can be the origin of this preference. Due to the nature of electrostatic interactions, the distance between the atoms involved is relevant. Table 1 includes the X−H4,6ₐₓ distance values, which vary from 2.54 to 2.62 Å in 1,3-dioxanes **1**−**7** (Scheme 1) and 1.146

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(45) Booth, H.; Grindley, T. B.; Khedhair, A. K. *J. Chem. Soc., Chem. Commun.* **1982**, 1047.

(46) Wiberg, K. B.; Marquez, M. *J. Am. Chem. Soc.* **1994**, *116*, 2197.
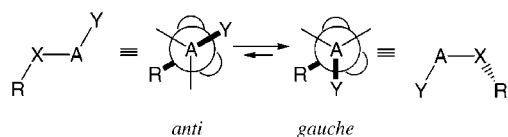
Figure 2. Generalized AE.

Å in dithiane **13**. Nevertheless, in this case, the interaction is not with the atom which is directly bonded to C2, but with the oxygen atom of the phosphoryl group located at a distance of 2.489 Å from H4,6$_{ax}$. Considering the H−O distances and the sum of the van der Waals radii, one would expect a stabilizing interaction between the two atoms involved.[47] Recently, Cuevas[48] studied the electron density of **13**-ax in the frame of Atoms in Molecules Theory, finding two C−H···O−P bond trajectories and the associated critical points. These interactions were characterized as having a small value of ρ and a small and positive value of $\nabla^2\rho$, as well as a strong dependence with respect to the annular substituent. This type of interaction can contribute as a stabilizing factor to the AE shown in these systems.

The case of equilibria **14** stands out. The oxygen atom of the carbonyl group could show a similar behavior with respect to **13**. Regarding **14**-ax, the oxygen atom of the carbonyl group does not point toward the center of the ring, but rather toward one of the axial hydrogen atoms.[49] From the electrostatic point of view, this arrangement is less efficient, and also, the charge over the oxygen atom of the phosphinoyl group is larger than that of the carbonyl group. Experimentally,[50] it has been determined that hydrogen bonds involving the phosphoryl group are stronger with respect to ketones.
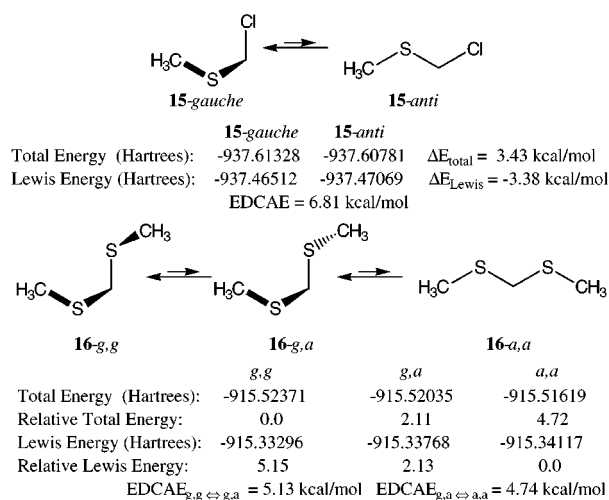
Concerning **5**-ax, one hydrogen atom of the $^+NH_3$ group is located at 2.714 Å from the 4,6-syn-diaxial hydrogens increasing steric repulsion. The equatorial conformer is favored by a small stereoelectronic contribution but with a large contribution of non-stereoelectronic origin. This fact could be closely related to the RAE that is experienced by these molecules and agrees with a recent explanation postulated by Perrin et al.[51]

In 2-hydroxy-1,3-dioxane (**6**, Scheme 1), the equatorial conformer is stabilized when stereoelectronic interactions are considered. On the other hand, the axial one is stable when these interactions are removed. A RAE would be implied through an $n_{Oexo} \rightarrow \sigma^*_{C-Oendo}$ stereoelectronic interaction. It is important to note that the relative magnitude of the $\Delta\Delta E_{deloc}$ for the systems in which the origin is stereoelectronic increases according to the substituent's electronegativity, as is concluded from equilibria **8**, **10**, **11**, **12**.

The energies obtained for the molecules involved in equilibria **2**, **3**, **4**, **9**, and **13** at the HF/6-31G(d,p)//B3LYP/6-31G(d,p) level of theory are shown in Table 3. These results confirm the non-stereoelectronic origin of the preference for the axial conformer of these compounds which was previously discussed in the frame of Density Functional Theory.

(47) Mikolajczyk, M.; Graczyk, P. P. Wieczorek, M. W. *J. Org. Chem.* **1994**, *59*, 1672.
(48) Cuevas, G. *J. Am. Chem. Soc.* **2000**, *122*, 692.
(49) (a)Mikolajczyk, M.; Graczyk, P. P.; Wieczorek, M. W.; Blaszczyk, J. *Heteroatom Chem.* **1992**, *3*, 625. (b) Juaristi, E.; Cuevas, G. *Tetrahedron* **1999**, *55*, 359.
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(51) Perrin, C. L.; Armstrong, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 6825.

Table 3. Total Energies and Lewis Energies (Hartrees), and Electronic Delocalization Contribution to the AE ($\Delta\Delta E_{deloc}$ in kcal/mol) of Molecules 2−5, 7, 9, 13 at HF/6-31G(d,p)//B3Lyp/6-31 g(d,p) Level

compd	total energy	Lewis energy	ΔE_{total}	ΔE_{Lewis}	$\Delta\Delta E_{deloc}$
2-ax	−404.71614	−404.19761			
2-eq	−404.70971	−404.19455	4.03	1.92	2.11
3-ax	−419.74253	−419.17273			
3-eq	−419.73817	−419.16416	2.74	5.38	−2.64
4-ax	−360.88508	−360.39851			
4-eq	−360.88133	−360.38802	2.35	6.58	−4.23
5-ax	−361.24683	−360.69977			
5-eq	−361.25670	−360.77737	−6.19	−48.69	42.5
7-ax	−380.10440	−379.43301			
7-eq	−380.09743	−378.85023	4.37	365.68	−361.31
9-ax	−1052.85817	−1052.46327			
9-eq	−1052.85202	−1052.46847	3.86	−3.26	7.12
13-ax	−1445.43529	−1444.68939			
13-eq	−1445.42618	−1444.67922	5.72	6.38	−0.66

Scheme 3

	15-gauche	**15**-anti	
Total Energy (Hartrees):	-937.61328	-937.60781	ΔE_{total} = 3.43 kcal/mol
Lewis Energy (Hartrees):	-937.46512	-937.47069	ΔE_{Lewis} = -3.38 kcal/mol
	EDCAE = 6.81 kcal/mol		

	g,g	g,a	a,a
Total Energy (Hartrees):	-915.52371	-915.52035	-915.51619
Relative Total Energy:	0.0	2.11	4.72
Lewis Energy (Hartrees):	-915.33296	-915.33768	-915.34117
Relative Lewis Energy:	5.15	2.13	0.0

EDCAE$_{g,g \leftrightarrow g,a}$ = 5.13 kcal/mol   EDCAE$_{g,a \leftrightarrow a,a}$ = 4.74 kcal/mol

Like any population analysis performed in the Hilbert space partitioning,[52] the NBO analysis employed here is sensitive to the level of theory. Nevertheless, for all cases studied, energy trends are the same. A comparison of the results in Tables 2 and 3 reveals a substantial difference in the Lewis energy between equilibria **5**, **7**, and **13**. This relationship can be expected because of the overestimation of electrostatic interactions due to electronic localization that increases punctual charges.

The AE is not restricted to heterocycles. An acyclic molecular fragment can also experience the so-called "generalized AE".[1,4] This term was introduced to describe the synclinal (gauche) conformational preference over the antiperiplanar (anti) arrangement in R−X−A−Y fragments, where A is an element of intermediate electronegativity (C, P, S), Y is an electronegative element, X is an atom with lone pairs, and R is an H or alkyl group[1,53,54] (Figure 2).

Scheme 3 includes the determination of the $\Delta\Delta E_{deloc}$ for methylthiomethyl derivatives **15** and **16** (Scheme 1) evaluated at the B3LYP/6-31G(d,p)//BP/DZVP2 level. The

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Table 4.   Experimental ΔH° versus Theoretical ΔE values for 1,3-Dithiane Derivatives

group at C2	$\Delta H^{\circ}_{experim}$	ref	group at C2	ΔE calcd[a]	ΔE calcd[b]
P⁺Me₃Cl⁻	0.0	43	P⁺Me₃	−0.9	−0.6
P(O)Ph₂	2.21	43	P(O)Me₂	6.53	5.91
Cl	>3.5	54	Cl	4.59	3.23
SPh	1.51[a], −2.68[b]	48[b]	SMe	2.87	2.49

[1] At (BP+NLSCF)/DZVP2 level [2] At Becke3LYP/6-31G(*d,p*)//(BP + NLSCF)/DZVP2 level 2. [a] In acetone-d_6. [b] In toluene-d_8.

total energy pattern obtained with the pure functional is similar to that calculated with the hybrid functional. As expected, in the presence of stereoelectronic interactions, **15**-gauche is more stable than **15**-anti due to a $n_S \rightarrow \sigma^*_{C-Cl}$ stereoelectronic interaction. However, this trend is reversed when stereoelectronic interactions are deleted in the Lewis molecule because steric interactions are dominant. Evidently, due to the spherical nature of chloride atom, in both conformers an interaction of type $n_{Cl} \rightarrow \sigma^*_{C-S}$, analogous to RAE in cyclic systems is possible. However, it appears that, in this case, this interaction is of the same magnitude in both conformers.

This is not true for the equilibria between the three conformers of dithiomethylmethane (**16**, Scheme 3) because of the different geometry of the substituent. In conformer gauche,gauche (g,g Scheme 3) two $n_S \rightarrow \sigma^*_{C-S}$ stereoelectronic interactions are possible, but this arrangement brings about steric crowding, a factor that impacts the total energy and the energy of the Lewis molecule. In conformer anti,gauche (a,g), only one $n_S \rightarrow \sigma^*_{C-S}$ is possible, but the steric crowding is diminished with respect to g,g, and finally, the anti,anti (a,a) conformer, where no stereoelectronic stabilizing interactions are possible and the steric interactions are avoided. The EDCAE between g,g and a,a conformer is 9.87 kcal/mol, which is larger than the $\Delta\Delta E_{deloc}$ between g,g and g,a conformers and g,a and a,a that would correspond to the combined magnitude of both effects.

Unfortunately, not many experimental enthalpic conformational preferences are known for comparison with the calculated energies for the compounds discussed here, but there are some values for closely related compounds. These values are summarized in Table 4.

Of course, theoretical calculations are not expected to quantitatively reproduce experimental results because the energetic properties are calculated for an isolated molecule in gas phase and at 0 K. In this case, it is important to notice that all phenyl groups in the original compounds were changed by methyl groups in the calculated molecules (for computational reasons). Nevertheless, the values are very close and reproduce the energetic trends expected when the AE takes place. This speaks for the accuracy of density functional methods for the kind of molecules studied here.[56,57]

Conclusions

The electronic delocalization contribution to the AE (EDCAE, $\Delta\Delta E_{deloc}$) obtained through the determination of the energy of the hypothetical Lewis molecules, calculated with NBO program,[19] allows the determination of the electronic delocalization contribution to the conformational equilibria of several 1,3-dioxanes and 1,3-dithianes. With this analysis, it is possible to differentiate the nature of the AE, whether of stereoelectronic or electrostatic origin. In all cases, the theoretical results agree with the experimental ones in terms of predicting the more stable conformer.

Thus, the determination of $\Delta\Delta E_{deloc}$ (which includes only stereoelectronic interactions) differs from that obtained experimentally by the comparison with cyclohexane derivatives. This is because in cyclohexane derivatives, the geometry is modified, the stereoelectronic interactions decrease, and electrostatic interactions are substantially diminished. Applying eq 3 to the theoretical evaluation of conformational preferences, the aim of AE definition as an excess in the preference for the axial conformation is preserved. Finally, the use of EDCAE facilitates the study of cyclic and acyclic molecules. Thus, it proves to be a good index of stereoelectronic participation.

Supporting Information Available: The Cartesian coordinates with the computed total energies (Hartrees) for axial and equatorial conformers of compounds **1**−**14** and anti,gauche conformers of compounds **15** and **16**.

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