Stereoelectronic Effects in Negatively and Positively (Protonated) Charged Species. Ab Initio Studies of the Gauche Effect in 1,4-Dioxa Systems

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A computational study ab initio of the conformational dependence of proton affinities of 2-methoxyethoxide (MEO), dimethoxyethane (DME), and 1,4-dioxane has been carried out at the MP2/6-31+G* level of theory. The results were discussed in comparison with reference systems, from simple alkoxides and ethers to anomeric moieties, in open, cyclic, and bicyclic molecules. The COCCOC species are stronger bases than the COCOC (anomeric) ones and approach regular ethers in their strength. The gauche forms in MEO and DME are altogether stronger bases than the anti forms, and anti (equatorial) protonation is preferred over gauche (axial), unless ditopic protonation is possible, like in *aga*-DME or *cis*-tetraoxadecalin. The *gauche effect* plays a significant role in the formation, relative stability, and reactivity of the charged species.

Introduction

This work was carried out in the wake of an ab initio computational study[1] of the *anomeric effect*[2] in negatively and positively (protonated) charged species, the results of which received experimental concurrence already in contemporary studies.[3] In the present study, we extend this approach to systems exhibiting the *gauche effect*.

The stereoelectronic behavior of RXCCYR containing molecular systems, known as the gauche effect,[2,4−10] consists of the unconventional upgrade in stability of the gauche XCCY (X, Y = N, O, F, Cl) form in its rotational competition with the anti one and certain structural differences between them. The ubiquity and importance of the X = Y = O, i.e., OCCO systems in such areas as carbohydrates, crown ethers, PEG polymers, etc., have made them representative, and the phenomenon received considerable attention during the last two decades.[4−10] For the archetypal dimethoxyethane (DME) COCCOC molecular species, which has been experimentally and computationally investigated on various occasions and with a variety of methods, as recently reviewed,[4] 10 formal conformations are possible: *aaa, aga, agg′, agg, ggg, aag, gag′, gg′g, gag, ggg′*, the first three being the most stable and viable ones (Figure 1) (a = anti, g = gauche; g and g' are of opposite sign, viz., g^+/g^- or g^-/g^+). We had inferred[4] that the gauche effect in DME is largely underestimated by low-level ab initio calculations while MM3(92) somewhat overestimates it, and we have consequently reparametrized the latter (MM3-GE) to reproduce the best contemporary (i.e., highest level ab initio calculated) results for the *aga* − *aaa* energy difference in DME,[4a] namely, 0.5 kcal/mol (vide infra).

Although the significance of the gauche effect in the OCCO moiety is manifested in the conformational behavior of many experimentally studied systems, its origin and magnitude were subject of debate, and they are continuously being probed. The earliest suggested gauche-stabilizing rationalizations were Wolfe's invocation[5] of prevailing (nuclear-electron) attractive over (nuclear−nuclear and electron−electron) repulsive energy terms. Epiotis et al.[6] then proposed that, in the OCHCHO moiety, gauche prevalence is due to σ,σ^* stabilizing interactions between the best σ-donor (a C−H bond) and the best σ^*-acceptor (a C−O bond), which is properly (parallel) oriented only in the gauche conformer; later, they invoked also attractive nonbonded interactions between the oxygen atoms, due to a stabilizing interaction between σ^* and the bonding and antibonding orbital combination of the lone pairs of the oxygens. Wiberg et al.[7] invoked anti destabilization (in 1,2-difluoroethane), due to poorer overlap between the C−C σ-bond forming

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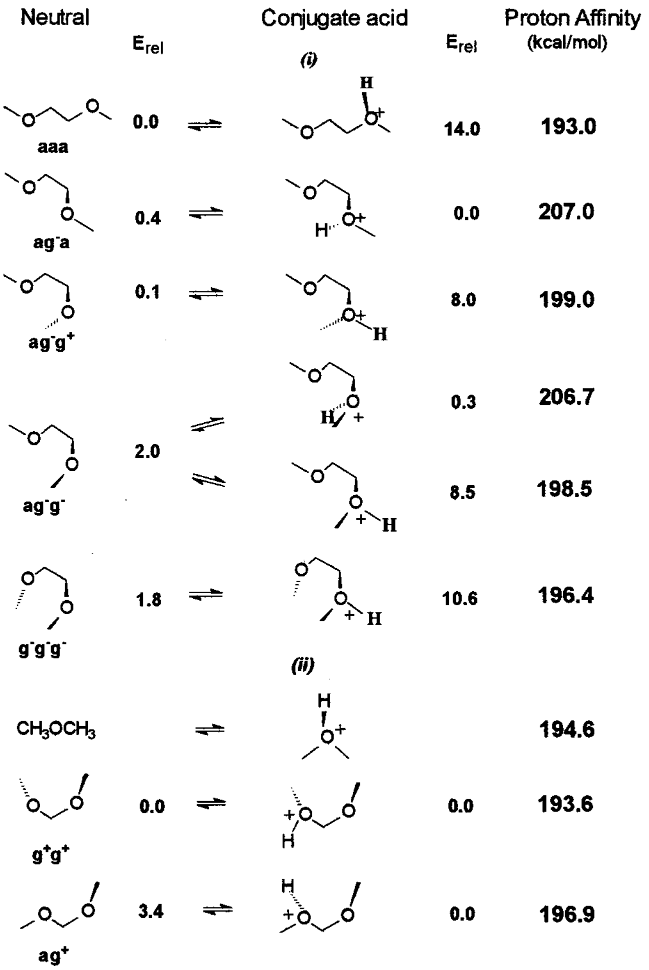

Figure 1. Proton affinities (in kcal/mol) of (i) 1,2-dimethoxyethane (DME) in selected conformations and (ii) related systems to compare with ref 1, as calculated by ab initio methods (MP2/6-31+G*); further details are assembled in Table 1. The relative energies of the neutral and of the charged species are given within different columns.

orbitals caused by bond bending at the carbon nuclei; and recent work by us[4] and others[8] has lent additional support to this view. Altogether, the viability and significance of the phenomenon are evident from the continuous stream of research contributions from various quarters,[8−10] since we reviewed the state of the art.[4]

While the neutral ROCCOR systems have been extensively investigated, the corresponding charged species, viz., the protonated COCCOH$^+$C and the negative COCCO$^-$ ones received no attention, although both are of considerable interest for their theoretical, mechanistic, and synthetic implications (e.g., relative stability of conformers in ground and transition states, structural properties, coordination sites and strength, etc.). We felt compelled to provide answers to this need, as we had recently done for charged anomeric (OCO) species[1] and for related large systems.[11]

Methodology

The stable conformers of the neutral and charged OCCO species, viz., 2-methoxyethoxide (MEO), 1,2-dimethoxyethane (DME), and 1,4-dioxane, were fully optimized at the MP2/6-31+G* level using the Gaussian 94[14] program; the calculations were carried out on Cray J932 and IBM SP-2 supercomputers.

The validity of the basis set, including the influence of polarization and diffuse functions, has been previously checked[1] and shown to approach closely experimental data and earlier pertinent calculations.[12,13] The conformers were defined as true minima by diagonalizing their Hessian (force constant) matrixes at the same level and making sure that all vibrational frequencies are real.

Proton affinities were obtained by difference from the calculated total energies of the neutral molecule and of the derived cation or anion, following Dewar's[13] expression for the proton affinity (PA) of a compound (B): $B + H^+ \rightarrow HB^+$; $PA(B) = E(H^+) + E(B) - E(HB^+)$ (the deprotonation enthalpy of the protonated forms are considered as proton affinity of the corresponding anions).

We regard these as isodesmic processes[1] (e.g., ROCCOH + MeO$^-$ $\rightleftharpoons$ ROCCO$^-$ + MeOH) with internal comparison of energy differences, which should minimize errors caused by the use of differences in total energies instead of heats of formation and by omitting ZPE corrections. Special attention was paid to the geometrical parameters and their changes in consequence of the protonation process, which are bound to be of considerable significance in understanding them.

Results and Discussion

The calculated proton affinities along the possible directions of protonation of COCCOC (DME) in its most relevant conformations are given in Figure 1i. The relative stabilities of conformers within the neutral and protonated series are incorporated in special columns. To understand the order of stabilities in the first column of the neutral species, we reckon that we deal with three main interactions, superimposed on the gauche effect: steric, electrostatic, and intramolecular H-bonding (each with its basic contributors[10]). The *aaa* form of DME is reasonably the most stable one and the *aga* is only 0.4 kcal/mol higher, in spite of the higher dipole moment and steric effect; this is, in our opinion, the best way to conceive the gauche effect (next to an energy decomposition scheme,[10a] which cannot be standardly performed). A further alleviation of this energy is seen in the *agg′* form (0.1 kcal/mol), due to the weak but finite O1C1H$_2$H- - -O4 H-bond. The latter are inexistent in the less stable *agg* and *ggg* forms; all other forms (see Introduction) are of higher energy.

As anticipated, protonation induces significant changes in the bond lengths and torsion angle of the COCCOC moieties, and these geometric parameters are displayed in Table 1. To establish a frame of reference, we included in Figure 1ii the proton affinities of three of the earlier reported systems,[1] namely, the basic dimethyl ether (a

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Table 1. Energies (E), Proton Affinities (PA), and Geometries (Bond Lengths in Å, Torsion Angles in deg) of Selected Dimethoxyethane (DME) Conformers and Their Protonated Forms (cf. Figure 2), As Calculated by ab Initio Methods; Energies Are Compared with Previous Studies (AI and MM)

DME (C1-O1-C2-C3-O4-C4)

ggg

	neutral	H$^+$*anti*[a]
O1-C2	1.419	1.513
C2-C3	1.528	1.516
C3-O4	1.419	1.408
O1-C2-C3-O4	-43.0	-46.3
C1-O1-C2-C3	-58.6	-47.1
C4-O4-C3-C2	-58.6	-88.6
H$^+$-O1-C2-C3		183.6

a) The *gauche* H$^+$ form converged to an **agg** species.

E(hartree)	-307.87077	-308.18373
PA (kcal/mol)		196.38

agg

	neutral	H$^+$*gauche*	H$^+$*anti*
O1-C2	1.419	1.497	1.511
C2-C3	1.515	1.521	1.505
C3-O4	1.417	1.429	1.407
O1-C2-C3-O4	-43.0	-38.6	-50.1
C1-O1-C2-C3	-58.6	-92.4	-50.2
C4-O4-C3-C2	179.4	-181.6	190.2
H$^+$-O1-C2-C3		28.5	179.8
E(hartree)	-307.87041	-308.19988	-308.18676
PA (kcal/mol)		206.74	198.51

aaa

	neutral	H$^+$*gauche*
O1-C2	1.423	1.510
C2-C3	1.513	1.516
C3-O4	1.422	1.406
O1-C2-C3-O4	180.2	185.9
C1-O1-C2-C3	180.2	187.9
C4-O4-C3-C2	180.3	186.0
H$^+$-O1-C2-C3		61.2
E(hartree)	-307.87356	-308.18110
PA (kcal/mol)		192.98

aga

	neutral	H$^+$*gauche*
O1-C2	1.420	1.491
C2-C3	1.507	1.518
C3-O4	1.420	1.432
O1-C2-C3-O4	-74.8	-43.9
C1-O1-C2-C3	174.0	156.4
C4-O4-C3-C2	173.9	173.2
H$^+$-O1-C2-C3		32.5
E(hartree)	-307.87292	-308.20276
PA (kcal/mol)		206.97

ag^-g^+

	neutral	H$^+$*anti*[a]
O1-C2	1.422	1.516
C2-C3	1.513	1.502
C3-O4	1.424	1.412
O1-C2-C3-O4	-73.8	-64.9
C1-O1-C2-C3	85.4	88.4
C4-O4-C3-C2	178.0	184.5
H$^+$-O1-C2-C3		215.4

a) The *gauche* H$^+$ form converged to an **aga** species.

E(hartree)	-307.87344	-308.19062
PA (kcal/mol)		199.03

Conform.†:	*aaa*	*aga*	*agg′*	*agg*	*ggg*
a. i.[a]	0.00	0.40	0.08	1.98	1.75
a. i.[b]	0.00	0.14	0.23	1.51	1.64
a. i.[c]	0.00	0.51	0.53	2.24	1.97
MM3(92)	0.00	0.05	1.21	1.97	3.71
MM3-GE[d]	0.00	0.56	1.78	2.48	4.18

a) MP2/6-31+G*- this work; b) MP2/D95+(2d,f,p)[8a]; c) MP3/6-311+G*//6-311+G[8b]; d) MM3-GE is MM3(92) reparametrized for the *gauche effect.*[3]

higher dialkyl ether is available as THP in Figure 2) as well as *gg*- and *ag*-dimethoxymethane, which exhibit a two- and one-directional anomeric effects, respectively. The results are very interesting and instructive: (i) the *aaa* conformer has the lowest proton affinity (193 kcal/mol), comparable only to that of *gg*-dimethoxymethane with its delocalized electron pairs due to the anomeric effect; (ii) the gauche manifold, exhibits altogether higher proton affinities; the anti protonation of the *agg* and *agg′* forms (~ 199 kcal/mol) being of diagnostic value and approaching the strength of THP; (iii) yet, the highest proton affinities (~ 207 kcal/mol) belong to the *agg* (gauche protonated) and *aga* forms, which achieve extra stability through ditopic protonation; i.e., they are reinforced by internal hydrogen bonding. These findings are in line with the increased atomic charges on the oxygens in the gauche form, as we had calculated in our previous study.[3]

A compelling application of this approach was that to ring systems. We calculated the proton affinities of 1,4-dioxane (Figure 2i and Table 2), in an instructive juxtaposition (Figure 2ii) with the previously calculated[1] tetrahydropyran (THP) and 1,3-dioxane, as well as those of the diastereomeric 1,3,5,7-tetraoxadecalins.[11] An interesting trend, and its turn, were observed: 1,4-dioxane is a weak base, relative to its 1,3-isomer and much more so in relation to THP. It prefers equatorial protonation, in analogy to THP but in contrast to 1,3-dioxane. Evidently, THP and 1,4-dioxane exhibit two strong 1,3-diaxial H- -H interactions due to the short C−O bonds in the ring, whereas in 1,3-dioxane there is only one such interaction and a second order anomeric effect in its g^+g^- moiety (i.e., a hyperconjugatively delocalized equatorial lone-pair); hence, the axial protonation is preferred. There seems to be no experimental observations to date to verify these results (other than tetrahydropyran−HCl[15] and −HOH[16] complexes and 1,4-dioxane-HOH ones,[17] in which the axial approach prevails), and we are presently seeking mass-spectrometric methods to scrutinize the gas-phase protonated species.

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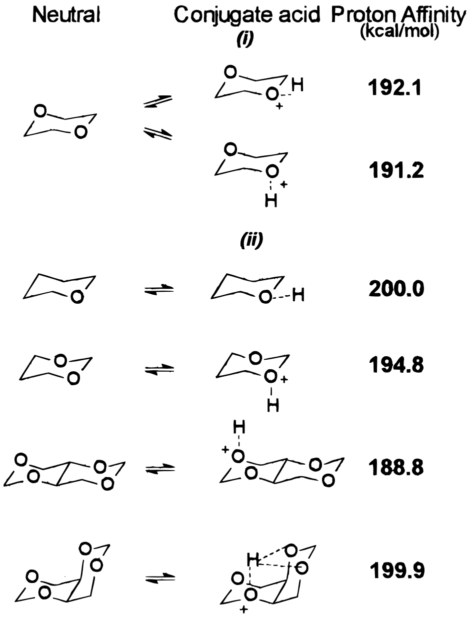

Figure 2. Proton affinities (in kcal/mol) of (i) 1,4-dioxane in its two possible modes and (ii) related systems in their most stable form, to compare with ref 1, as calculated by ab initio methods (MP2/6-31+G*); cf. Table 2.

Table 2. Energies (E), Proton Affinities (PA), and Geometries (Bond Lengths in Å, Torsion Angles in deg) of 1,4-Dioxane and Its Protonated Forms (cf. Figure 3), As Calculated by ab Initio Methods (MP2/6-31+G*)

1,4-dioxane	neutral	(H^+_{ax})	(H^+_{eq})
O1−C2	1.432	1.517	1.518
C2−C3	1.515	1.500	1.509
C3−O4	1.431	1.422	1.422
C2−O1−C6	109.9	113.0	113.5
O1−C2−C3−O4	58.5	56.5	58.9
H^+−O1-C2−C3		73.5	177.4
E(hartree)	−306.714 30	−307.018 93	−307.020 42
PA (kcal/mol)		191.15	192.09
		0.94	0.0

One can understand now better the order found in the 1,3,5,7- tetraoxadecalin diastereomers,[11] which are depicted in Figure 3ii along with their most stable protonated forms. Both prefer axial protonation, but the trans isomer is a very weak base while the cis form returns to the 200 kcal/mol range, due mainly to the tritopic protonation.

To conclude this analysis, we felt bound to probe the directionality of protonation in charged species. The proton affinities of 2-methoxyethoxide (MEO) in its two conformations (*aa* and *ag*) were calculated and the resulting 2-methoxyethanol conformations devoid of internal hydrogen bonding are listed (Figure 3i). These were compared with the earlier calculated[1] proton affinities of methoxide, propoxide and methoxymethoxide (MMO) (Figure 3ii), which decrease in this order, the lowest being MMO, because of mutual electron withdrawing, mainly due to the anomeric effect.[1]

This trend is reversed in MEO (Figure 3i); i.e., $COCCO^-$ has higher proton affinities, resembling the aliphatic oxides, and among the two conformers, *ag* is the stronger base, in line with the results for the analogous neutral species (vide infra).

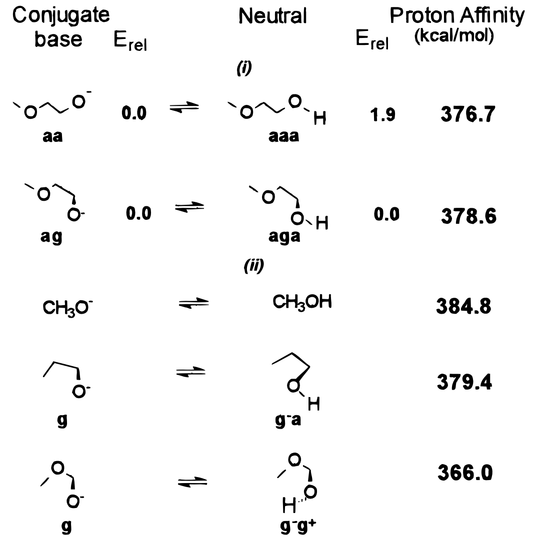

Figure 3. Proton affinities (in kcal/mol) of (i) 2-methoxyethoxide (MEO) in selected conformations and (ii) related systems to compare with ref 1, as calculated by ab initio methods (MP2/6-31+G*). The relative energies of the neutral and of the charged species are given within different columns.

Conclusion

We have performed calculations ab initio (MP2/6-31+G*) of the proton affinities of dimethoxyethane (DME), 1,4-dioxane, and 2-methoxyethoxide (MEO), focusing on their conformational dependence. The results were compared with reference systems, from simple ethers and alkoxides to *anomeric* systems, in open, cyclic, and bicyclic molecules. The COCCOC systems are altogether stronger bases than the COCOC (anomeric) ones: the neutral species approach regular ethers in their strength, while the charged ($COCCO^-$) ones resemble aliphatic oxides. The gauche forms in 1,2-dimethoxyethane and 2-methoxyethoxide are stronger bases than the anti forms. Generally, anti (equatorial) protonation is preferred over gauche (axial), unless ditopic protonation is possible (like in *aga*-DME or *cis*-tetraoxadecalin). 1,4-Dioxane prefers equatorial protonation (like tetrahydropyran), due to the short C−O bonds in the ring and strong 1,3-diaxial H- -H interactions. 1,3-Dioxane, however, prefers axial protonation, since it has only one such interaction and a second-order anomeric effect in its g^+g^- moiety (i.e., a hyperconjugatively delocalized equatorial lone pair). Clearly, the gauche effect plays a notable role in the formation, relative stability, and reactivity of charged species of OCCO systems (like the anomeric effect in OCO-containing systems[1]).

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