Stereoelectronic Effects in Negatively and Positively (Protonated) Charged Species. Ab Initio Studies of the Anomeric Effect in 1,3-Dioxa Systems

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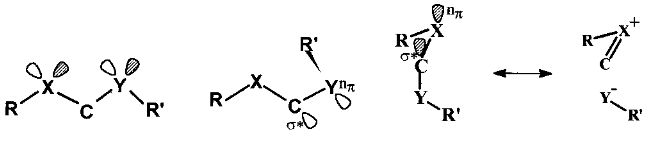
A systematic computational ab initio study of the conformational dependent proton affinities of methoxymethoxide, tetrahydropyran 2-oxide, methoxymethanol, dimethoxymethane, 1,3-dioxane, and tetrahydropyran has been carried out at the MP2/6-31+G* level of theory. In addition, methoxide, propoxide and methanol, propanol, and dimethyl ether have been computed at the same level as reference systems. Methoxymethoxide and tetrahydropyran 2-oxide exhibit a strong *anomeric effect*, e.g., the equatorial oxide is a stronger base than the axial one and all are weaker bases than the simple alkoxides. Axial (n_π) protonation is preferred over equatorial (n_σ) by 2–3 kcal/mol. The COCOC acetals are stronger bases (at the acceptor O) then the simple ethers. The structural changes between bond lengths and bond angles for different conformers correlate well with the $On_\pi-\sigma^*_{C-O}$ lone pair delocalization interactions. Thus, the anomeric effect plays an important role in the charged species and in the process of their formation.

Introduction

The stereoelectronic behavior of C–X–C–Y–C-containing molecular systems, known as the *anomeric effect*, has been extensively studied and documented,[1–5] including by ourselves,[2] and is fairly well understood. It is now well accepted[1] that the anomeric effect in a R–X–C–Y–R′ system consists of a difference of properties and behavior between its anti (**a**) and gauche (**g**) forms. This



aa **ag** **gg**

is due to an $Xn_\pi-\sigma^*_{C-Y}$ two-electron–two-orbital interaction[3] (or a negative hyperconjugation[4] in valence bond terms) and is manifest in (1) structural parameters, e.g., shorter anomeric bonds at the donor O–C and longer ones at the acceptor C–O and wider anomeric bond angles; (2) relative energy, i.e., greater stability of gauche (axial) forms over anti (equatorial) ones; and (3) stereoselective reactivity, i.e., variation of rates of attack at or around the anomeric center, all those as a function of torsion angles in R–X–C–Y–R′. In symmetrical R–X–C–Y–R moieties with X = Y, e.g., C–O–C–O–C, four conformations have to be considered: *aa*, *ag*$^+$, g^+g^+, and g^+g^-. This number decreases to two when one terminal substituent is removed (e.g., Y = Hal or O$^-$) and increases for every additional substituent (e.g., Y = NHR or OH$^+$R). In the latter cases, the unequal donor and acceptor give rise to two unequal anomeric effects. The ubiquity and importance of the X = Y=O systems have made them paradigmatic; the energy and structural manifestations of the anomeric effect are well established and unequivocal, but less so is the reactivity criterion. Earlier experimental studies had led to the conclusion that acid-catalyzed, *i.e.*, protonation-initiated hydrolysis of acetals, ortho esters, and glycosides, etc., are subject to stereoelectronic control.[1c,3] While this interpretation has been

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challenged,[6] there has been little theoretical evidence one way or another.

While the neutral O−C−O systems have been extensively investigated, the corresponding charged species, viz., the protonated $C-O-C-OH^{+}-C$ and the negative $C-O-C-O^{-}$ ones were less so, although both are of considerable interest for their theoretical, mechanistic, and synthetic implications (e.g., relative stability of conformers, structural properties, coordination sites and strength, relative reactivity: acetal formation and hydrolysis, glycosidation, nucleophilic reactions, etc.).

There are the early, pioneering but necessarily low level treatments by Wipff[7a] and Lehn[7b] of acetal and amide hydrolysis. More recently, Andrews, Bowen, and Fraser-Reid reported computational studies of the conformational dependence of protonated dimethoxymethane (at 6-31G* level)[8a] and of 2-methoxytetrahydropyran as a model for glycopyranosides hydrolysis.[8b] Woods, Szarek, and Smith investigated protonated methanediol (at MP2/6-311++G** level, with constrained torsion angles),[9] and recently, Grein and Deslongchamps used a simple decomposition model for acetals and protonated acetals to analyze the anomeric effect;[10a,b] these were carried further to second-row systems.[10c]

The computational approaches to anion proton affinities and their pitfalls have been succinctly but admirably reviewed in Chandrasekhar, Andrade, and Schleyer's thorough study,[11] and a comprehensive AM1 study and review of proton affinities and deprotonation enthalpies has been published by Dewar and Dieter.[12] Negatively charged anomeric species, however, have received practically no explicite attention, to the best of our knowledge.

From this background, we sought a reliable and unified treatment of positively and negatively charged model anomeric species at a high enough level, that is, using a high enough basis set, including polarization and diffuse functions, with electron correlation (mainly to offset the strong C−O bond shortening caused by the polarization functions) and full geometry optimization. Until recently, jobs of this size were beyond our reach.

With the advent of supercomputer technology, we were able to carry out and we describe here a detailed and systematic, high-level ab initio analysis of the anomeric effect on the geometry and conformational behavior of acyclic and monocyclic charged 1,3-dioxa systems, consisting of the protonated species of methoxymethanol, dimethoxymethane, and 1,3-dioxane, as well as the proton affinities of negatively charged 1,3-dioxa species, methoxymethoxide and tetrahydropyran 2-oxide.

Table 1. Experimental vs Computed Proton Affinities (in kcal/mol) for Methanol and Dimethyl Ether

	MeOH	Me_2O
MP2/6-31G**	192.9	203.4
MP2/6-31+G**	188.0	199.8
MP2/6-31+G*	183.4	194.6
experiment[16,17]	181.8	192.1

Methodology

The stable conformers of each species have been fully optimized at the MP2/6-31+G* level using the Gaussian 92[13] and Gaussian 94[14] programs. The latter calculations were carried out on Cray J932 and IBM SP-2 supercomputers.

To probe the relative validity of the basis sets and to evaluate on site[11] the influence of polarization and diffuse functions, we calculated the proton affinities of methanol and dimethyl ether with different basis sets: MP2/6-31G**, MP2/6-31+G**, and MP2/6-31+G*. The results (Table 1) showed that MP2/6-31+G* calculations are in line with previous high-level calculations[11,15,18] and approach most closely the experimental data;[16,17] in any case, the observed small deviations are in the same direction. 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[12] definition of the proton affinity (PA) of a compound (B): $B + H^{+} \rightarrow HB^{+}$; $PA(B) = E(H^{+}) + E(B) - E(HB^{+})$. For the sake of simplicity, we define the deprotonation enthalpy of the protonated forms as proton affinity of the negatively charged species.

Essentially, we can regard the cases we are dealing with as isodesmic processes[19] (e.g., $ROH + MeO^{-} \rightarrow RO^{-} + MeOH$) and internal comparisons of energy differences. This should minimize if not cancel errors caused by the approximation introduced by using differences in total energies instead of heats of formation. At the same time, the geometrical parameters are highly trustworthy at this level of theory and their changes in consequence of the protonation process are bound to be of considerable significance in understanding the reactivity implications.

Results and Discussion

The calculated conformation dependent proton affinities are given in Figures 1−7, with the relative stabilities of conformers within each series included in separate

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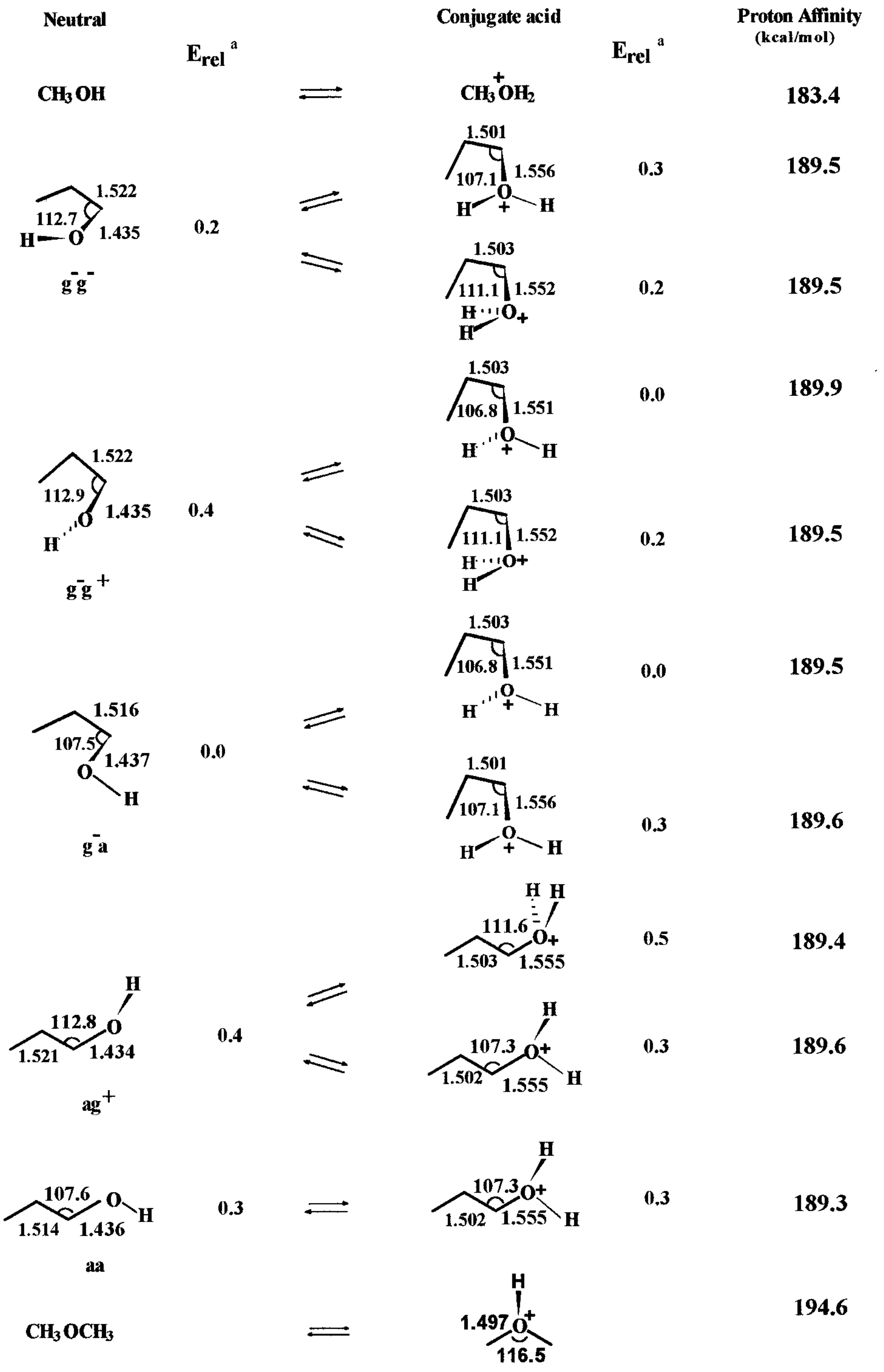
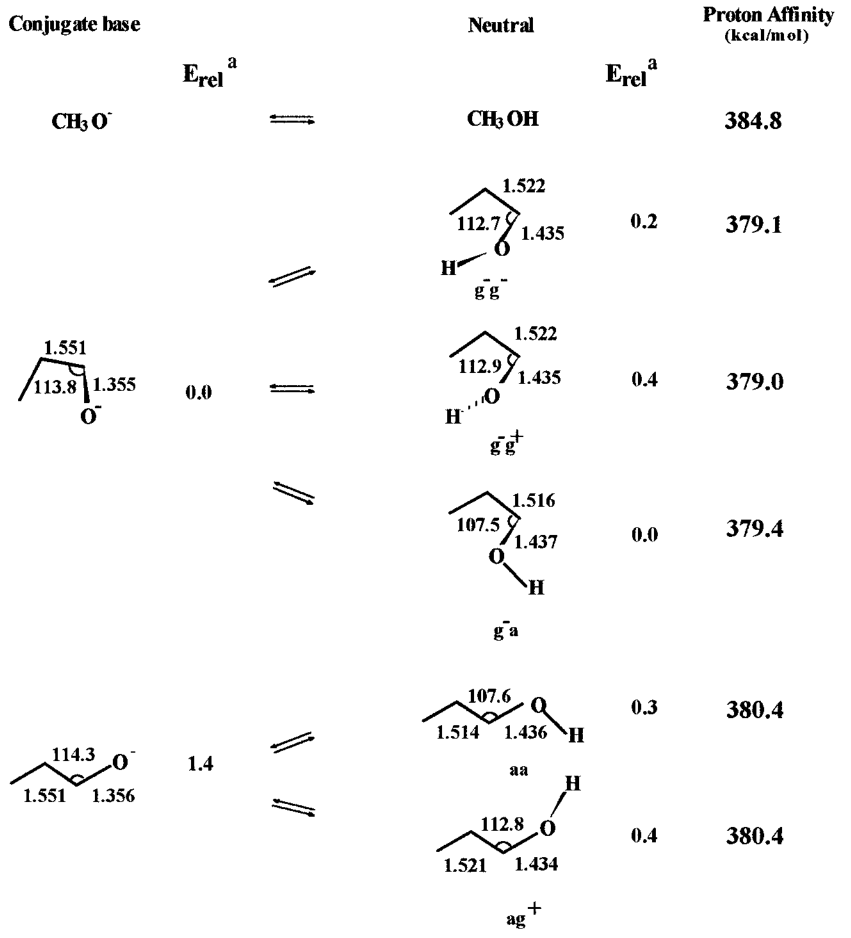


a) The energies of neutral and charged species are given in different columns and are relative only within each column (see also Table 5). b) *cf.* Table 2 for torsion angles.

Figure 1. Proton affinities (in kcal/mol) and selected geometrical parameters (bond lengths, Å, and angles, deg) of methanol, propanol (in its stable conformations), and dimethyl ether.

columns. The most significant anomeric geometric parameters (O−C−O internal bond lengths and angles) are shown on the conformers in the figures. Protonation induces considerable changes in the torsional geometry of the C−O−C−O−C moieties, and hence, the torsion angles in the protonated species are tabulated in Tables 2−4. Such a large amount of data cannot possibly be discussed *all* in this limited framework; since the neutral species have been the subject of numerous papers in the past, they are only briefly mentioned and linked to previous references for ready retrieval, comparison, and discussion by the interested reader.

To establish a frame of reference, we calculated the proton affinities of four reference systems: methanol, propanol, dimethyl ether (Figure 1), and tetrahydropyran (Figure 7). The results are in good agreement with experimental[16,17] and available theoretical[12,15] results. The proton affinities of methoxide and propoxide were calculated as well (Figure 2). The lower proton affinity of propoxides compared to that of methoxide may be



a) The energies of neutral and charged species are given in different columns and are relative only within each column (*cf.* Table 5). b) *cf.* Table 2 for torsion angles

Figure 2. Proton affinities (in kcal/mol) and selected geometrical parameters (bond lengths, Å, and angles, deg) of propoxide in its stable conformations.

Table 2. Torsion Angles (deg) in Various Conformers of Neutral and Negatively Charged Species, As Calculated ab Initio (MP2/6-31+G*)

	gg	g^-g^+	g^-a	ag^+	ag^-	*aa*
propanol[a]						
CCCO	−60.2	−63.9	−62.3	183.3		180.1
CCOH	−64.5	68.8	179.2	−61.3		179.8
methoxymethanol[b]						
COCO	−66.8	−67.3		177.0		180.0
OCOH	−62.8	84.6		−55.4		180.0
2-hydroxy-THP[c]						
COCO	64.4	68.8	65.0	179.1	175.3	
OCOH	56.3	−87.7	186.8	−49.5	51.6	
dimethoxymethane[d]						
COCO	−65.6	−117.1		178.3		180.0
OCOC	−65.6	64.3		−64.8		180.0
methoxymethoxide[a]						
$COCO^-$		**g**: 50.2		**a**: 180.0		
THF 2-oxide[c]						
$COCO^-$		**g**: 54.0		**a**: 173.2		

[a] Cf. Figures 1 and 2. [b] Cf. Figures 3 and 5. [c] Cf. Figure 4. [d] Cf. Figure 6.

due[16a] to the former's higher polarizability, although negative hyperconjugation may already play a role. The similarity of the structural parameters of the two propoxide conformers is in accord with the involvement of O^-n_π–σ^*_{C-C} interactions in both anti and gauche propoxide. The latter's somewhat higher stability could be attributed mainly to nonbonded terminal attractive interaction due to weak C–H---O^- hydrogen bonding (the distance between oxygen and the nearest methyl hydrogen is 2.57 Å). The proton affinities are also weakly conformation dependent, and altogether, the differences of both the energies and the proton affinities of the propanol conformers are slight, as expected.[18]

Turning now to the anomeric systems, we start with the proton affinities of methoxymethoxide given in Figure 3. The relative stabilities of the protonation products, i.e., the conformers of methoxymethanol show that the *gg* form is the most stable one, followed by g^-g^+, ag^+, and (high up) *aa*. This is in accord with earlier findings[2j,20] except that no minimum was observed for the g^-a form, which rather converged to the g^-g^+ form. In methoxymethoxide, the gauche form is considerably favored over the anti form (5.8 kcal/mol), due both to appreciable OC–H---O^- hydrogen bonding (the H---O distance is 2.46 Å) and to the double anomeric effect: strong O^-n–σ^*_{C-O} interactions in both conformers but an On_π–$\sigma^*_{C-O^-}$ interaction only in the gauche form. The corresponding difference ($ag^+ - g^-g^-$) in methoxymethanol is smaller (3.3 kcal/mol), and thus anti methoxymethoxide winds up with a higher proton affinity. The C–O bond lengths go along well with the described features (Figure 3): the C–O^- bond is shorter and the O–C bond is longer in the anti form (than in the gauche form) of methoxymethoxide

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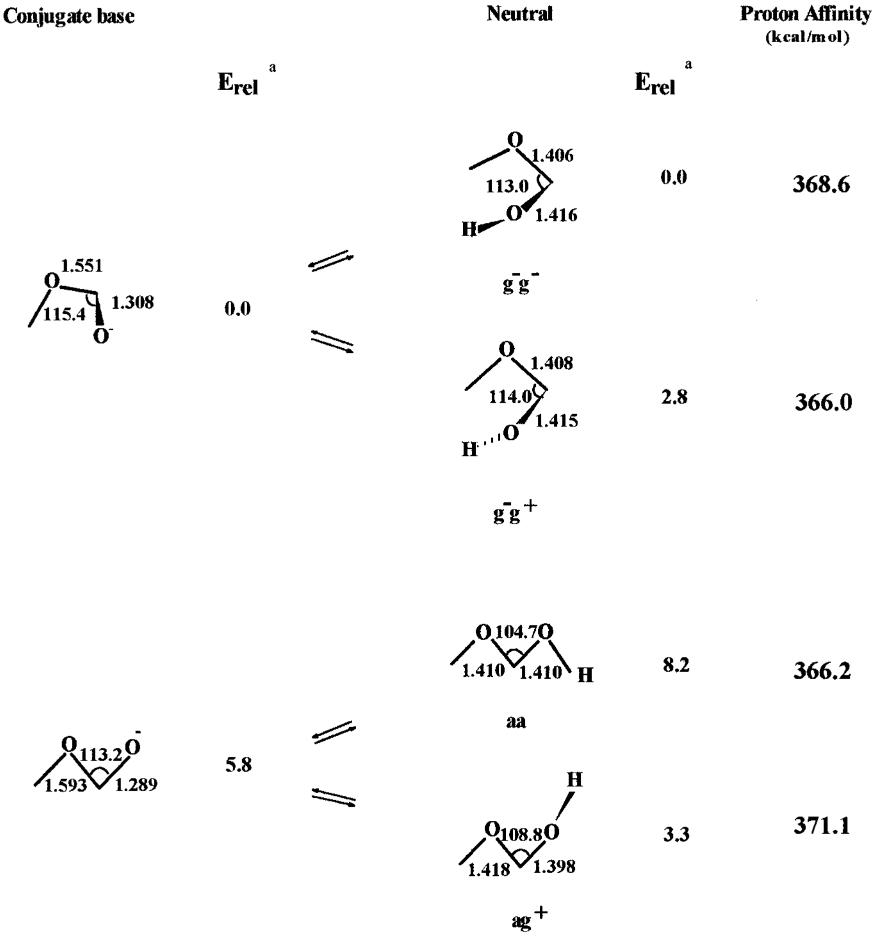

a) The energies of neutral and charged species are given in different columns and are relative only within each column (see also Table 5). b) *cf.* Table 2 for torsion angles.

Figure 3. Proton affinities (in kcal/mol) and selected geometrical parameters (bond lengths, Å, and angles, deg) of methoxymethoxide in its stable conformations.

because of a unidirectional $n_\pi-\sigma^*$ interaction, placing it halfway to the MeO$^-$---C=O pair, well-known reaction products of alkoxymethoxides. Finally, methoxymethoxide exhibits a lower proton affinity in any mode, i.e., it is a weaker base, than the simple alkoxides (Figure 2).

Tetrahydropyran 2-oxide (Figure 4) is a similar but more interesting case, and the anomeric effect is manifest in the stability of the axial relative to the equatorial form by 3.0 kcal/mol. The energy difference is small compared to the methoxymethoxide system (Figure 2) and is probably due to the fewer degrees of freedom in the relaxation process of the substituted tetrahydropyran ring. This rigidity also reduces the strength of the OC−H---O$^-$ hydrogen bond in the axial tetrahydropyran 2-oxide. Scrutiny of the structural parameters reveals (Figure 4) remarkable similarity of the two forms; clearly, a strong $O^-n-\sigma^*_{C-O}$ interaction operates in both conformers and the $On_\pi-\sigma^*_{C-O^-}$ interaction in the axial (gauche) form is very weak ($\sigma^*_{C-O^-}$ is a very poor acceptor). Under these circumstances, a compelling explanation of the higher relative stability of the axial tetrahydropyran 2-oxide is that while in the axial (gauche) a $O^-n_\pi-\sigma^*_{C-O}$ is operating, in the equatorial (anti) form a higher energy $O^-n_\sigma-\sigma^*_{C-O}$ obtains. This interesting phenomenon has not been reported to date and deserves further probing.

The relative energies of the axial and equatorial conformers of tetrahydropyran-2-ol show that the g^-g^- form is the most stable one, in accord with experiment,[21,22] and the rotational energy differences are similar to those of Salzner and Schleyer's computed results at the HF/6-31G* level[4d] with the exception of the *aa* form, which was not obtained, but instead converged on MP2 correction to ag^- (Figure 4). The calculated proton affinity of the equatorial tetrahydropyran 2-oxide is, hence, higher than that of the axial one. This can now readily explain the experimental observation that 1-O-alkylation (glycosidation) of D-glucopyranose 1-oxide yields preferentially β-glucosides.[23] At the same time, 2-THP−O$^-$ is also, generally, a weaker base than are simple alkoxides (Figures 1 and 4).

To probe the proton affinity of neutral 1,3-dioxa systems, as affected by the anomeric effect, we studied methoxymethanol (Figure 5), dimethoxymethane (Figure 6), and 1,3-dioxane (Figure 7). Two possible (gauche and anti) directions of protonation on each oxygen were examined, and in the asymmetric conformations two selective protonation modes were emulated: on the oxygen lone pair involved in anomeric effect and on the oxygen with undelocalized lone pairs.

The computed conjugate acids of methoxymethanol are shown in Figure 5, and the interpretation is not straight-

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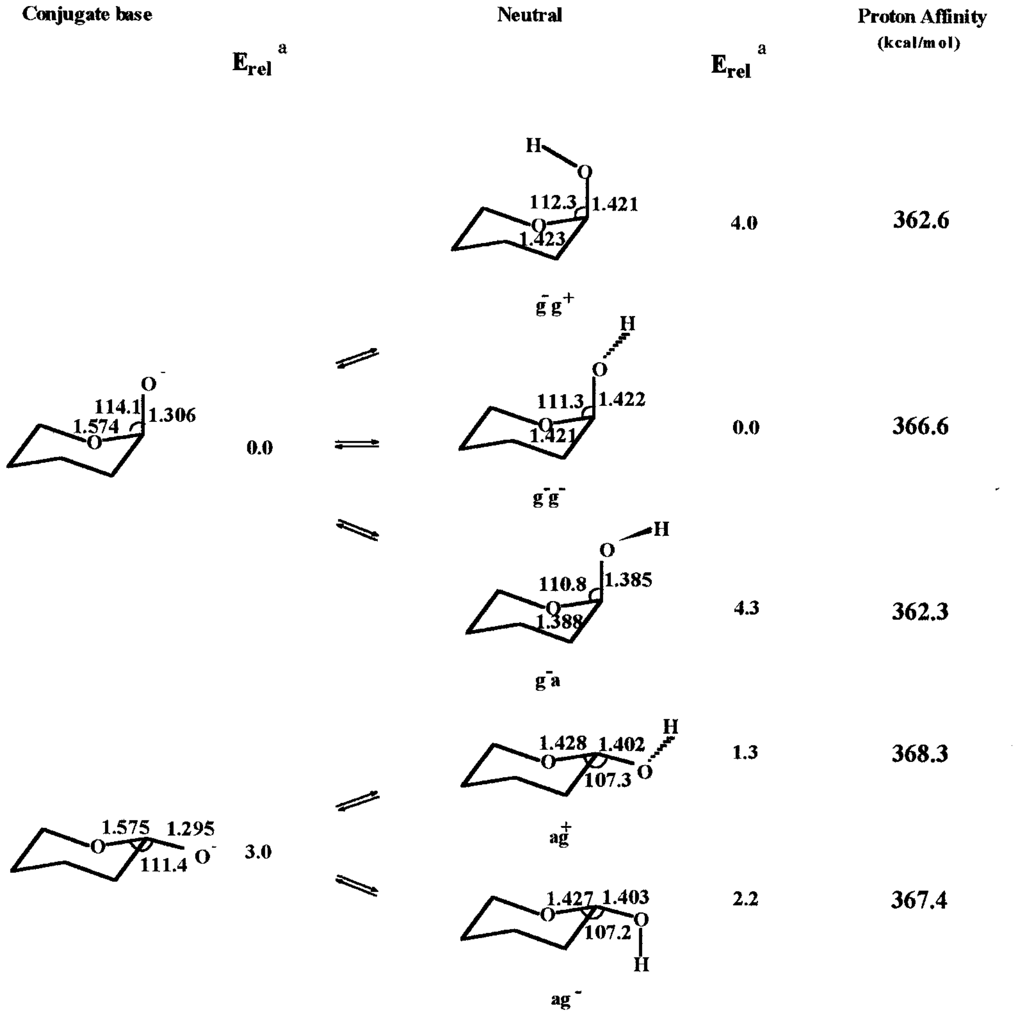

a) The energies of neutral and charged species are given in different columns and are relative only within each column (see also Table 5). b) *cf.* Table 2 for torsion angles.

Figure 4. Proton affinities (in kcal/mol) and selected geometrical parameters (bond lengths, Å, and angles, deg) of tetrahydropyran 2-oxide in its stable conformations.

forward. The protonation process is often allosteric; in particular the *aa* form does not preserve its conformation in the process. The results are, therefore, characteristic of open chain systems of this kind. Protonation of the hydroxy oxygen in the g^-g^- and ag^+ conformers leads to a charge-dipole complex, halfway toward methylmethoxonium ion and water): $CH_3O{=}CH_2^+\cdots OH_2$, similar to the results reported by Grein et al.[10a] (in their studies on the so-called reverse anomeric effect) for the protonation of hydroxy oxygen of aminomethanol, due to a strong $Nn_\pi{-}\sigma^*_{C-O}$ interaction. Both forms, but in particular the ag^+ one, exhibit an analogous interaction between the donor HO lone pair and C$-$O(σ*) acceptor, which leads to another, albeit weaker, distorted species $CH_3OH\cdots CH_2{=}OH^+$. Notably, all protonated forms have similar energies (within 0.5 kcal/mol), which implies that the differences in proton affinity stem mainly from the relative stabilities of the base conformations. This assigns a greater proton affinity to the higher methoxymethanol form, ag^+, and more affinity to the most unstable one, *aa*; for the latter, the value is evidently artifactual. The proton affinity of the hydroxy oxygen is, hence, comparable or slightly higher than that of the alcohols (Figures 1 and 5). The conjugate acids of the methoxy oxygen result from protonation of either the free oxygen lone pair or of the lone pair involved in the n$-\sigma$* interaction. The calculated proton affinities of g^-g^- and ag^+ are slightly lower than that of dimethyl ether (Figure 5). The structural parameters of these conjugate acids show the expected bond shortening of the C$-$O bond to give protonated formaldehyde and O$-$C bond lengthening to give MeOH (Figure 5). Similar to that of the oxides and in accord with Deslongchamps' postulate[1c] and Fraser-Reid's lower level result,[8] an acetal oxygen which is not engaged in an n$-\sigma$* interaction has a higher electron density and, hence, proton affinity than one which is not involved. This has been exemplified by the proton affinities of the g^-g^- and ag^+ forms (Figure 5), with 3.3 kcal/mol in favor of the latter. Altogether, the anomeric species is a somewhat weaker base than the corresonding isolated (ether or alcohol) species.

Dimethoxymethane is one of the most often and arduously studied prototypical anomeric systems, much of it ab initio;[24] the most recent computational contributions[24c−f] provide much insight in its stereoelectronic features. Our computed relative stabilities of the dimethoxymethane g^-g^+, g^+g^+, ag^+, and *aa* conformers

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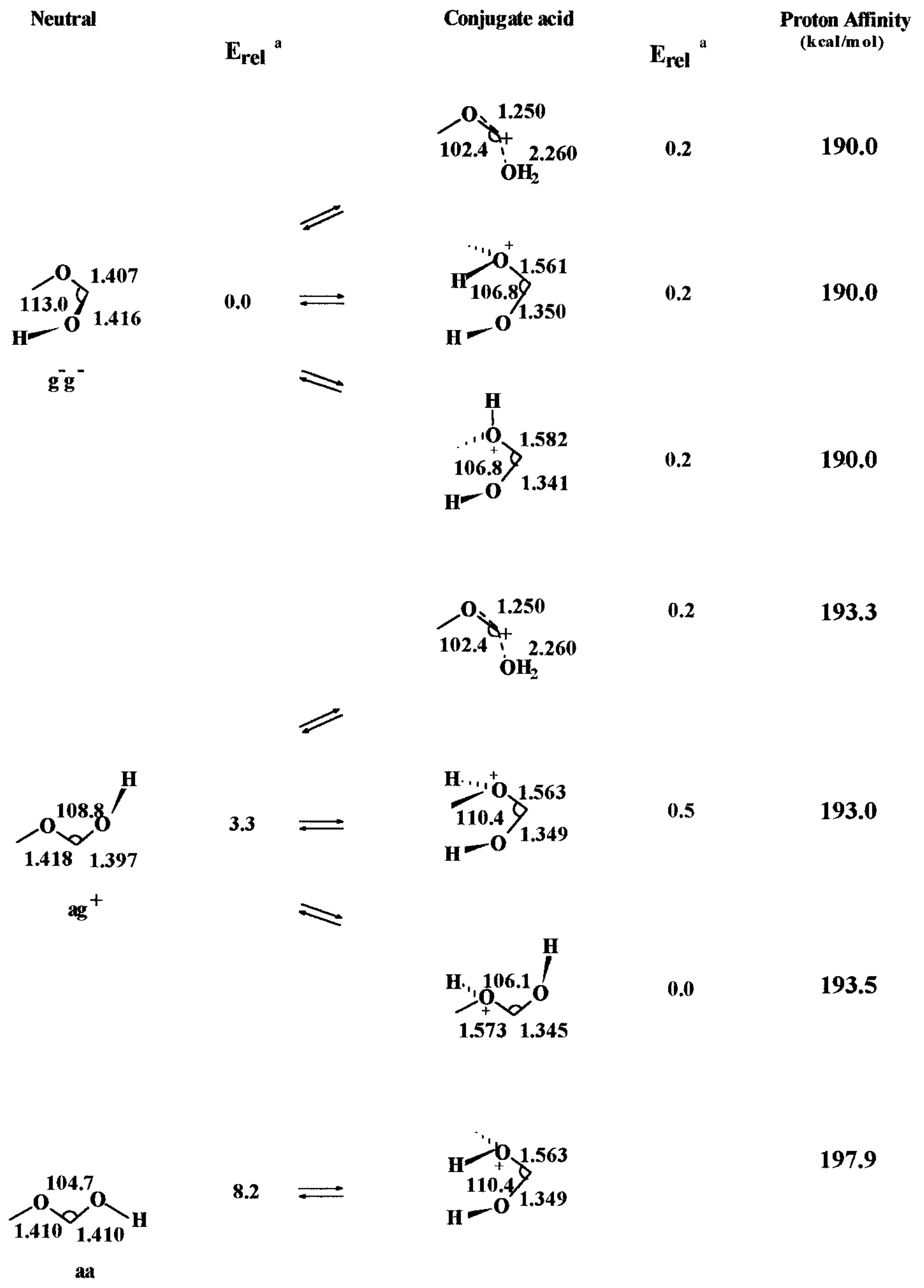
(23) (a) Schmidt, R. R.; Michel, J.. *Tetrahedron Lett.* **1984**, *25*, 67. (b) Schmidt, R. R.; Reicharth, M.; Moering, U. *J. Carbohydr. Chem.* **1984**, *3*, 821.



a) The energies of neutral and charged species are given in different columns and are relative only within each column (see also Table 5). b) *cf.* Tables 2&3 for torsion angles.

Figure 5. Proton affinities (in kcal/mol) and selected geometrical parameters (bond lengths, Å, and angles, deg) of methoxymethanol in its stable conformations.

are shown in Figure 6 and are in good agreement with the high-level literature data,[24c−f] and again, their high proton affinities are misleading due to the allosterism involved. An interesting point concerns the relatively high energy g^-g^+ form: while it might enjoy high anomeric stabilization, it suffers from strong steric strain, which is relaxed by strong molecular deformation brought about by considerable torsion angle opening (Table 2). Hence, the only realistic way to probe the g^-g^+ geometry is to impose rigidity on the molecule (vide infra). The general variation (O−C bond shortening, C−O bond lengthening, etc.) in structural parameters fits the On−σ^*_{C-O} interactions involved in gauche conformers. Here too, the trend of proton affinities shows that the free lone pairs are much easier to protonate than those involved in n−σ^* interactions[8] (Figure 6) but the calculated proton affinity of the most stable g^+g^+ form is comparable to or lower than the proton affinity of dimethyl ether or its higher homologues.[16,17] This general behavior observed also (vide supra) in methoxymethanol is in line with very early experimental work[25] in which acetals were shown to be weaker bases than ethers.

Another repeatedly studied system, 2-methoxytetrahydropyran, is the archetypical glycoside model. All fea-

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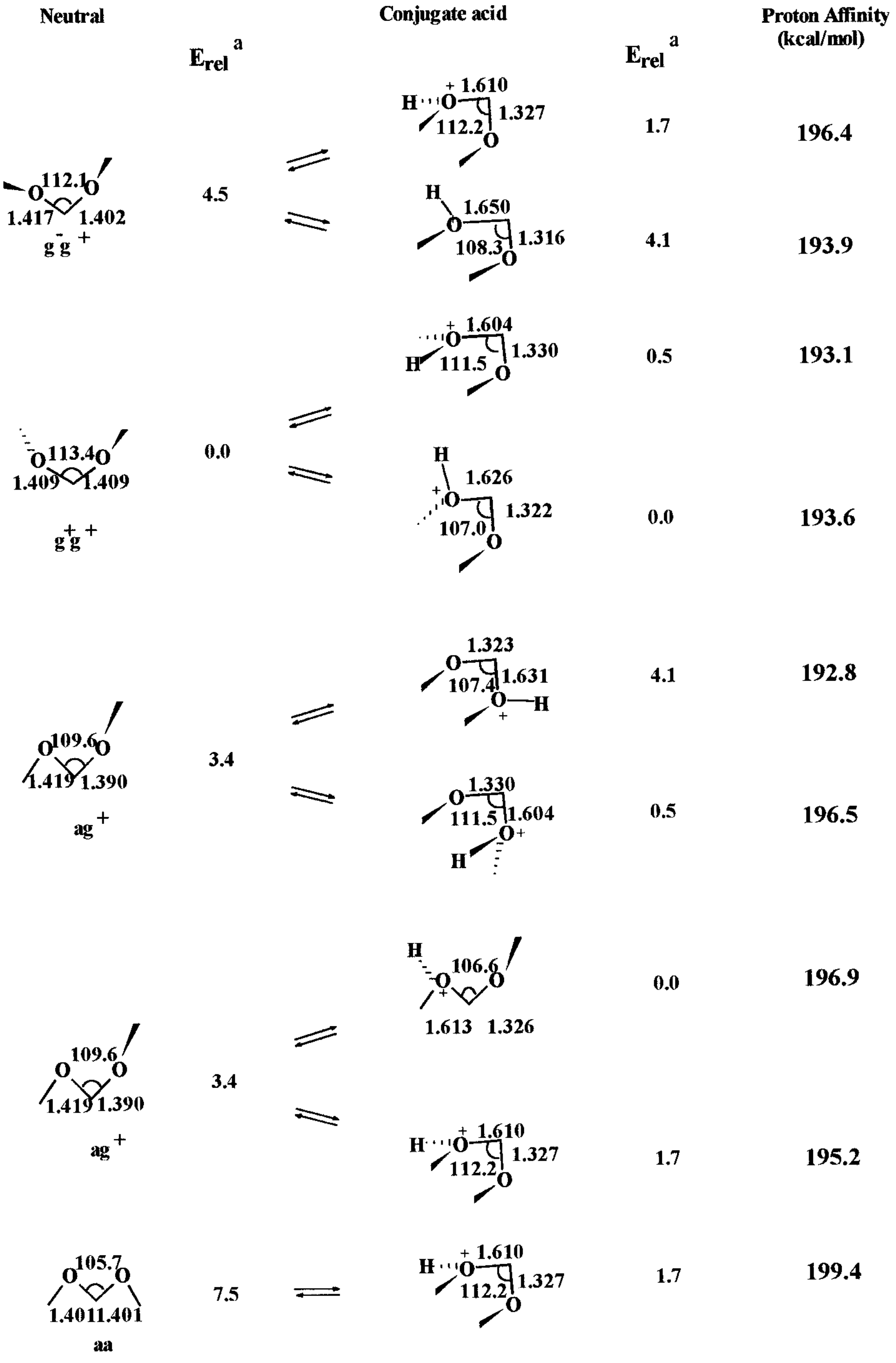
(24) (a) Jeffrey, G. A.; Pople, J. A.; Binkley, S.; Vishveshwara, S. *J. Am. Chem. Soc.* **1978**, *100*, 373. (b) Van Alsenoy, C.; Schafer, L.; Scarsdale, J. N.; Williams, J. O.; Geise, H. J. *J. Mol. Struct. (THEOCHEM)* **1982**, *86*, 111. (c) Wiberg, K. B.; Murcko, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4821. (d) Krol, M. C.; Huige, C. J. M.; Altona, C. *J. Comput. Chem.* **1990**, *11*, 765. (e) Werstiuk, N. H.; Laidig, K. E.; Ma, J., in ref 1d, p 176. (f) Smith, G. D.; Jaffe, R. L.; Yoon, D. Y. *J. Phys. Chem.* **1994**, *98*, 9072. (g) Kneisler, J. R.; Allinger, N. L. *J. Comput. Chem.* **1996**, *17*, 757.



a) The energies of neutral and charged species are given in different columns and are relative only within each column (see also Table 5). b) *cf.* Table 4 for torsion angles.

Figure 6. Proton affinities (in kcal/mol) and selected geometrical parameters (bond lengths, Å, and angles, deg) of dimethoxymethane in its stable conformations.

tures and conclusions bearing on 2-hydroxytetrahydropyran and dimethoxymethane are bound to apply also to this system, and it was not included due to the heavy computational burden implied but mainly because it recently received a thorough and competent treatment, both computationally[4d,8b,26] and experimentally.[26c]

A rigorous probe of the proton affinity of a free lonepair vs one which is involved in an n-σ^* interaction on the same oxygen is best achieved on conformationally fixed systems. This need, the mentioned COCOC g^-g^+ problem (vide supra), and our involvement with the 1,3,5,7-tetraoxadecalin systems[27] led us to choose 1,3-dioxane for this study. The fixed g^-g^+ geometry of the C−O−C−O−C part enables the operation of a double anomeric effect "of the second kind" in the O−C−O moiety, namely, involving the equatorial lone pairs in On_σ−$\sigma^*_{\mathrm{C-O}}$ interactions and leaving the axial lone pair free. This is bound

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(25) (a) Kagya, T.; Sumida, Y.; Inoue, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 767. (b) Kankaanperä, A. *Acta Chem. Scand.* **1969**, *23*, 1723. (c) Kankaanperä, A. *Acta Chem. Scand.* **1969**, *23*, 1728. (d) Kankaanperä, A.; Lahti, M. *Acta Chem. Scand.* **1969**, *23*, 2465.

(26) (a) Tvaroska, I.; Carver, J. P. *J. Phys. Chem.* **1994**, *98*, 9477. (b) Wiberg, K. B.; Murcko, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4821. (c) Wiberg, K. B.; Marquez, M. *J. Am. Chem. Soc.* **1994**, *116*, 2197.

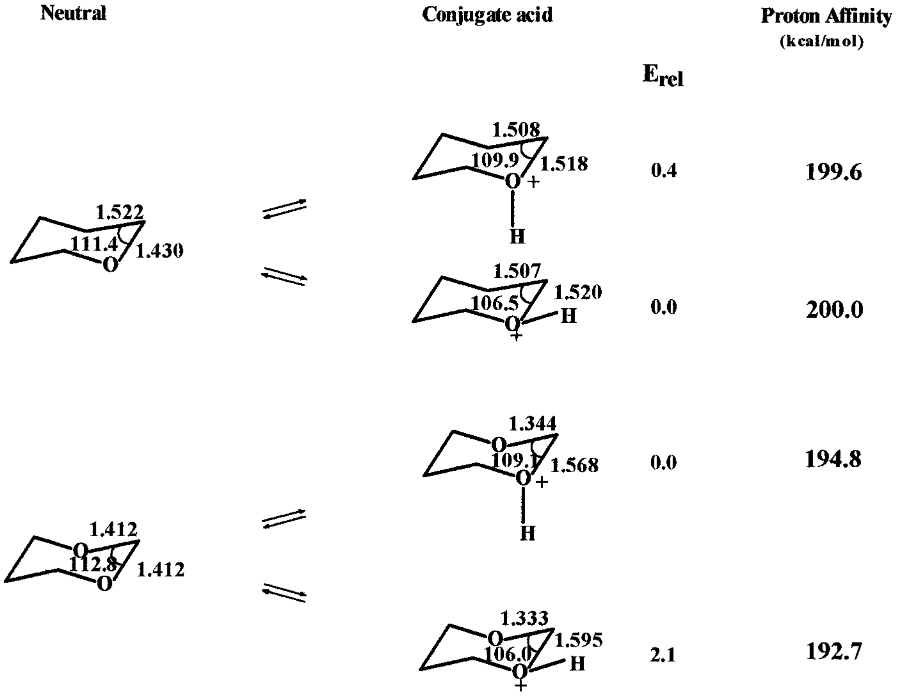


Figure 7. Proton affinities (in kcal/mol) and selected geometrical parameters (bond lengths, Å, and angles, deg) of tetrahydropyran and 1,3-dioxane in their stable conformations.

Table 3. Torsion Angles (deg) in Protonated Methoxymethanol Conformers (Figure 5), As Calculated ab Initio (MP2/6-31+G*)

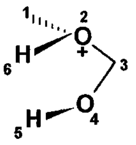
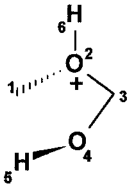
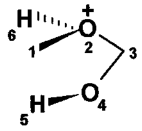
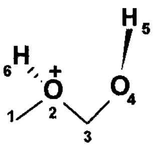
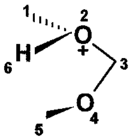
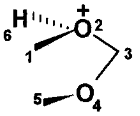
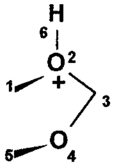
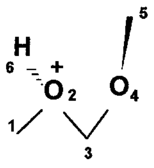
	1234	5432	6234
	-56.1	-97.8	70.0
	-60.2	-86.0	172.6
	61.9	-99.1	-63.3
	196.7	-88.5	-37.1

Table 4. Torsion Angles (deg) in Protonated Dimethoxymethane Conformers (Figure 6), As Calculated ab Initio (MP2/6-31+G*)

	1234	5432	6234
	-86.0	-50.6	76.7
	-94.7	67.1	-59.9
	105.2	-50.9	178.6
	196.7	-88.5	-37.1

to be a less stabilizing effect than the classic anomeric effect (due to the lower n_σ level and the consequently larger n_σ–C–O energy gap). Indeed, in the calculated neutral 1,3-dioxane (Figure 7), the symmetrical C–O bonds underwent less shortening than in, say, dimethoxymethane-g^+g^+ (Figure 6). The computed proton affinity for axial protonation is 2.1 kcal/mol more than that of the equatorial one, reflecting the fact that the axial lone pair is more available for protonation than the equatorial one. The structural parameters provide further evidence for such effects (Figure 7): comparing the

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(27) (a) Senderowitz, H.; Linden, A.; Golender, L.; Abramson, S.; Fuchs, B. *Tetrahedron* **1994**, *50*, 9691. (b) Senderowitz, H.; Golender, L.; Fuchs, B.; *Tetrahedron* **1994**, *50*, 9707. (c) Abramson, S.; Ashkenazi, E.; Goldberg, I.; Greenwald, M.; Jatzke, H.; Vardi, M.; Weinman, S.; Fuchs, B. *J. Chem. Soc., Chem. Commun.* **1994**, 1611. (d) Frische, K.; Greenwald, M.; Ashkenasi, E.; G. Lemcoff, N.; Abramson, S.; Golender, L.; Fuchs, B. *Tetrahedron Lett.* **1995**, *36*, 9193.

Table 5. Total Energies (in hartrees) of the Most Stable Forms of the Neutral and Charged Species, As Calculated ab Initio (MP2/6-31+G*)

propanol[a,b]	propoxide[b]	propanol-H$^+$ [a]
−193.69742	−193.09282	−193.99950
methoxymethanol[c,e]	methoxymethoxide[c]	methoxymethanol-H$^+$ [e]
−229.56224	−228.97482	−229.86545
2-hydroxy-THP[d]	THP 2-oxide[d]	
−345.91026	−345.32608	
dimethoxymethane[f]	dimethoxymethaneH$^+$ [f]	1,3 dioxane-H$^+$ [g]
−268.71788	−269.02633	−307.03335

[a] Cf. Figure 1. [b] Cf. Figure 2. [c] Cf. Figure 3. [d] Cf. Figure 4. [e] Cf. Figure 5. [f] Cf. Figure 6. [g] Cf. Figure 7.

bond lengths of axial and equatorial protonated forms, one can see, as previously analyzed,[1d] that the cross hyperconjugative effect operates only in the axial case, viz., the C−O bond (1.344 Å) is longer in the axial protonated form than in the equatorial one (1.333 Å), but the other C−O bond is shorter (1.568 vs 1.595 Å) in the axial case. As a reference case, we have used tetrahydropyran, which exhibits a higher proton affinity relative to either 1,3-dioxane (due to the absence of the inductive electron-withdrawing effect) or ethers (due also to minimal reorganization in the product) and only a small difference between the axial and equatorial protonation modes, in favor of the latter. 1,3-Dioxane, too, is a weaker base than comparable ethers.

Conclusions

The geometries and energies of negatively and positively charged species related to methanol, propanol, dimethyl ether, and tetrahydropyran, i.e., methoxymethoxide, tetrahydropyran 2-oxide, methoxymethanol, 2-hydroxytetrahydropyran, dimethoxymethane, and 1,3-dioxane have been computed ab initio at the MP2/6-31+G* level. A strong influence of the anomeric effect (On$_\pi$ and $\sigma^*_{\mathrm{C-O}}$ interactions) on the conformational behavior of negatively and positively (protonated) charged 1,3-dioxa species has been demonstrated.

The proton affinities of methoxymethoxide and tetrahydropyran 2-oxide are lower than those of methoxide and propoxide due to On$_\pi$−$\sigma^*_{\mathrm{C-O}}$ delocalization. In methoxymethanol, protonation of the hydroxy group leads to a charge-dipole complex due to strong On$_\pi$−$\sigma^*_{\mathrm{C-O}}$ interactions, while differential protonation of the methoxy lone pairs shows that the one engaged in a $n-\sigma^*$ interaction has a lower proton affinity than the “free” one. Similar behavior was observed for dimethoxymethane. The preferred site of protonation of 1,3-dioxane is axial, since the equatorial lone pair is hyperconjugatively delocalized. The geometrical parameters are diagnostic for this stereoelectronic behavior. As a rule, the anomeric O−C−O-containing molecular systems are weaker bases than the corresponding simple ethers or alcohols. These results are in line with experimental observations concerning hydrolytic processes of acetal systems and nucleophilic reactivities of anomeric oxides.

Finally, we have made available a large amount of data, viz., energies and geometrical parameters, the full discussion of which is too space demanding but which we believe will be of value to many research efforts to come, both in our[28] and other groups.

Acknowledgment. This work was supported in part by a research grant from the Israel Science Foundation of the National Academy of Sciences, by a postdoctoral fellowship from the National Council for Higher Education (to B.G.), and by generous Supercomputer CPU allocation by the Inter-University Computation Center.

JO9717503

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[28] Linden, A.; Ruechardt, Chr.; Beckhaus, H.-D.; Ganguly, B.; Fuchs, B. *trans*- *vs*. *cis*-1,3,5,7-Tetraoxadecalin and their Protonated Forms: Structure and Relative Stability. Submitted.