range of the experimental estimate.

Calculational Details

All of the calculations described in this work were performed using the Gaussian suite of programs[22] running on a Multiflow Trace-14/300 and a Silicon Graphics 4D/320 workstation. Geometry optimizations were greatly facilitated by its ability to calculate analytic first derivatives for the HF, MP2, and QCISD methods as well as analytic second derivatives for the HF[23] and MP2[24] methods. The AIM charges were calculated using PROAIM.[25]

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Supplementary Material Available: Full lists of geometric parameters for all optimizations performed (9 pages). Ordering information is given on any current masthead page.

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Theoretical Study of the Inversion of the Alcohol Acidity Scale in Aqueous Solution. Toward an Interpretation of the Acid–Base Behavior of Organic Compounds in Solution

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Abstract: Some homologous series of organic compounds present an acid–base behavior in solution very different from that in the gas phase. The series formed by MeOH to *t*-BuOH is a representative example of these series with a gas-phase acidity order (*t*-BuOH > *i*-PrOH > EtOH > MeOH) following the greater ability of the methyl group relative to hydrogen to stabilize the charged centers while in solution the final ordering is just the opposite. In this paper, the change in the alcohol's acidity scale when passing from the gas phase to solution is studied. Gas-phase energies are calculated at the MP4 level with the 6-31G* basis set and an sp diffuse function added on the oxygen atom. Calculated deprotonation free energies are in very good agreement with the experimental values. Solvation energies are obtained in the framework of the continuum model using a quantum description of the solute charge distribution. The main contribution to the change in the acidity scale in solution is the electrostatic component of the solvation energy of the basic forms, and the charge delocalization produced by the progressive substitution of hydrogen atoms by methyl groups can be used to understand the order in solution. Our results, which reproduce quite well experimental ordering and magnitude, seem to indicate that a simple electrostatic argument could explain the origin of this inversion and can be employed to rationalize the acid–base behavior of some homologous series.

Introduction

The development of several techniques such as high-pressure mass spectrometry[1] and flowing afterglow[2] and ion cyclotron resonance (ICR) spectrometry[3] has provided an accurate set of thermochemical data for acidities and basicities of organic compounds in the gas phase.[4] From the acidity–basicity order of some homologous series in the gas phase (NH_3 to Me_3N and MeOH to *t*-BuOH) it became clear that simple charge-induced dipole interaction models could explain the effect of increased charge-releasing ability of the methyl group compared with hydrogen.[5,6] However, in solution these same series present an irregular order or just the opposite[6] order from that in the gas phase. This different behavior is a good test for theories and models to estimate the solvation free energies and molecular properties in solution. Calculation and understanding of acidity–basicity free energies in solution are some of the most important challenges for theoretical methods because they are the key to interpreting several reaction mechanisms in solution.[7] In a recent work[8] we have dealt with the irregular ordering of methylamines' basicities by using the polarizable continuum model of the solvent,[9] obtaining a good agreement with experimental data. Moreover it was shown that the methyl substitution, while stabilizing charged species in vacuo, diminishes the energies of interaction with the solvent. These two opposite trends result in an irregular basicity ordering in solution for methylamines.

The alcohols present a homologous series for which a total inversion in the acidity scale is produced when going from the gas phase to solution. This series is formed by MeOH to *t*-BuOH. The gas-phase acidity ordering is *t*-BuOH > *i*-PrOH > EtOH > MeOH, following the greater ability of the methyl group relative

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to hydrogen to stabilize the charged centers by a charge-induced dipole interaction.[5] The acidity ordering of the alcohols has been the object of numerous experimental studies both in the gas phase[4,10,11] and in several solvents: water,[12-14] dimethyl sulfoxide,[13,15] and others.[13,16] Many theoretical studies[17-20] are dedicated to the irregular basicity ordering of methylamines in solution, but in spite of the interesting aspects of the acid-base problem in solution that these systems present, to our knowledge none treat the inversion of the alcohols' acidities.

In order to calculate the free energy of deprotonation of alcohols in solution, the following thermodynamic cycle can be considered:

$$\begin{tikzcd}
ROH_g \arrow[r, "\Delta G_{ag}"] \arrow[d, "\Delta G_s(ROH)"'] & RO^-_g \arrow[d, "\Delta G_s(RO^-)"'] & + & H^+_g \arrow[d, "\Delta G_s(H^+)"'] \\
ROH_s \arrow[r, "\Delta G_{as}"] & RO^-_s & + & H^+_s
\end{tikzcd}$$

from which ΔG_{as}, that is the thermodynamic property related to the concept of acidity in solution, is

$$\Delta G_{as} = \Delta G_{ag} + \Delta G_s(RO^-) - \Delta G_s(ROH) + \Delta G_s(H^+) \quad (1)$$

The first term on the right-hand side is the deprotonation free energy in the gas phase, and it can be divided into an enthalpic part and an entropic part. The entropic part is mainly due to the proton contribution.[7] In fact, from MeOH to *t*-BuOH, the remaining entropic part ($S(RO^-) - S(ROH)$) can be considered equal for these alcohols.[4] The enthalpic part can be calculated as the sum of the difference in the internal energy of the products and reactants in the minimum of its potential well (ΔE_{ag}), the differences in the vibrational energies (due to differences in the zero-point energies, ΔZPE, and in the population of the vibrational levels, ΔE_{vib}), the balance of the changes in the rotational and translational degrees of freedom ($^3/_2RT$), and the PV work (RT):

$$\Delta H_{ag} = \Delta E_{ag} + \Delta \mathrm{ZPE} + \Delta E_{vib} + {}^5/_2RT \quad (2)$$

As we are dealing with the breaking of an O-H bond, the sum of the last three terms is very similar in all the alcohols studied here. In our calculations the maximum difference obtained for these three terms between MeOH and *t*-BuOH equilibria is less than 0.3 kcal/mol. Thus, differences in the deprotonation free energies in the gas phase among the alcohols studied here are almost completely due to differences in the internal energies.

The last three terms of eq 1 are related to the solvation process. The solvation free energy of the proton is a constant term appearing in all the alcohols, and then the difference between in vacuo and in solution equilibria is determined by the difference between solvation free energies of neutral and charged forms. Considering that the differences in the solvation energies of the neutral alcohols studied here are only slight (i.e. a maximum difference of 0.6 kcal/mol[21]), the solvation energies of the charged species must play the crucial role in the equlibria in solution, determining the inversion of the acidity scale.

Thus, the decisive factors in the acidity ordering of alcohols in solution are ΔE_{ag} and $\Delta G_s(RO^-)$. The purpose of this paper is to show the influence of each of them in the calculation of acidity and the relative importance of both solvent and charge-induced dipole effects. A number of workers have employed several computational techniques to enable the calculation of these quantities, and a revision has been recently made by Karplus et al.[7] The continuum dielectric method has the advantage of taking into account the polarization of the solvent, and the quantum continuum model puts this polarization into the calculation of the electronic distribution of the solute. This makes it an adequate model for our study in spite of the lack of information about the solvent structure around the solute. Moreover the recent development of a semiempirical continuum model[22] makes this approach suited to dealing with solvation processes of larger molecules, opening up the continuum model to a great variety of problems.

Computational Aspects

Calculations have been carried out with the 6-31G* basis set[23] and an sp diffuse function[24] added on the oxygen atom because it supports a large electronic charge. All geometries were fully optimized at the Hartree-Fock level with Berny's algorithm[25] by means of the GAUSSIAN88 package of programs.[26] In order to compute deprotonation enthalpies, zero-point corrections have been obtained from unscaled frequency calculations on minima at the HF level and contributions from degrees of freedom have been considered. Internal energy has been recalculated at the MP4(full) level (considering singles, doubles, triples, and quadruples excitations) to take into account electron correlation effects. We have also carried out MP2 calculations with larger basis sets (6-31+G*,[23,24] 6-311+G*,[27] and 6-31+G**[23,24]), but they do not introduce any significant improvement over the level of calculation we have chosen. The entropic contributions to the gas-phase free energies have also been obtained at the HF level and range between 22.0 and 24.3 eu. These values compare well with that of Bartmess et al.,[4] which gives a constant factor of 22.0 eu.

In order to calculate solvation energies of neutral and charged species, we have not considered contributions of motion (vibrations and librations). As we are interested in the difference between the neutral and charged forms, this must be a good approximation. The solute-solvent interaction term has been broken down into the electrostatic and non-electrostatic (cavitation and dispersion) contributions. Thus

$$\Delta G_s(M) = \Delta G_{el} + \Delta G_{nel} \quad (3)$$

We have obtained the electrostatic term using the polarizable continuum model,[9] where the solute is inscribed in a cavity surrounded by a continuous dielectric that represents the solvent. Electrostatic contributions were obtained at the HF level with the same basis sets as in the gas-phase calculations with a modified version of the MONSTERGAUSS program.[28] For the dielectric constant, a value of 78.39 was used, corresponding to water at 298.15 K. The molecular surface as defined by Richards[29] has been used for the cavity model and computed by means of the GEPOL92 program.[30] This kind of surface seems to be more appropriate in the study of solute behavior.[31] As usual in the

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Table I. Total Energies of the Neutral and Basic Forms (in hartrees) and Absolute and Relative Deprotonation Internal Energies (in kcal/mol) of the Alcohols in the Gas Phase Obtained at the MP4(SDTQ) Level

	E(ROH)	E(RO$^-$)	ΔE_{ag}	Rel ΔE_{ag}
MeOH	−115.390 007	−114.771 526	388.10	0.0
EtOH	−154.581 482	−153.967 799	385.09	−3.01
i-PrOH	−193.774 403	−193.163 860	383.12	−4.98
t-BuOH	−232.967 741	−232.359 168	381.89	−6.21

Table II. Absolute and Relative Deprotonation Free Energies of Alcohols Obtained with MP4(SDTQ) Internal Energies and Experimental Values (in kcal/mol)

	ΔG_{ag}-(MP4)	Rel ΔG_{ag}(MP4)	ΔG_{ag}-(exp)[12]	Rel ΔG_{ag}(exp)
MeOH	372.70	0.0	372.6	0.0
EtOH	369.13	−3.57	369.5	−3.1
i-PrOH	367.21	−5.49	367.5	−5.1
t-BuOH	366.60	−6.10	366.7	−5.9

polarizable continuum model,[9] the sphere radii used for atoms have been 20% larger than van der Waals radii (hydrogen 1.44 Å, carbon 1.96 Å. oxygen 1.68 Å). However in the case of the basic form, the presence of a large localized charge on the oxygen atom makes this choice questionable, as was previously pointed out by Bonaccorsi et al.[32] Thus, in a way similar to that proposed by these workers, we have performed a set of intermolecular distance optimizations of CH_3O^-–H_2O complexes for several possible conformations and compared them with those for CH_2O–H_2O complexes. Then, using the value of 1.68 Å for the oxygen radius in CH_2O and comparing the mean optimal distances of CH_2O–H_2O (2.323 Å) and CH_3O^-–H_2O (1.936 Å), we obtained a value of 1.4 Å for the oxygen radius of the basic form, assuming that the dielectric radii are proportional to the solute–solvent intermolecular distance. It must be pointed out that this value coincides with Pauling's radii for O^- and is close to that given by Karplus et al.[7] for the oxygen atom in methoxide (1.5 Å in comparison with 1.6 Å in methanol). This adjustment of the oxygen radius is also consistent with the cavity radii of Rashin and Honig,[33] defined as the radius of a sphere which contains a negligible electron density contribution from the surrounding solvent. It must be pointed out that geometry optimization in solution has not been considered, and thus in vacuo geometries were used. Previous work on methylamines and other systems[8,34] supports this decision because of the modest changes both in geometric parameters and in energy contributions. Moreover, conformational changes are not expected for these systems, as was shown by Jorgensen et al. in an MC study of methanol in water[35] and in pure methanol.[36] Solvent effects on conformational equilibria are not expected unless there are significant changes in polarity between conformers. Geometry optimizations in solution should be considered when intermolecular interactions are studied, as recently shown in several studies of water–water[37] or water–cation[38] complexes.

Dispersion energies have been computed within the continuum approximation with the method proposed by Floris et al.[39,40] Only the first term in the r^{-n} expansion (n = 6) has been considered because it is expected to represent the major part of this energy term.[40] The atom–atom parameters used are those called set 1 in ref 39. The cavitation term is calculated from the total area of the cavity using the model of Pierotti.[41] All solvent effects calculations have been carried out at 298.15 K.

For the proton we have used a solvation free energy of −260.5 kcal/mol, given by Noyes.[42] More recently a mean value of −259.5 kcal/mol has been calculated[7] as the average of five measurements of the standard hydrogen potential,[43] but because of the similarity of both values and in order to be consistent with our previous work,[8] we have used the first.

Table III. Electrostatic, Nonelectrostatic, Total, and Experimental Solvation Energies of the Neutral Forms of the Alcohols (in kcal/mol)

	ΔG_{el}	ΔG_{nel}	ΔG_s	ΔG_s(exp)[21]
MeOH	−6.10	0.77	−5.33	−5.11
EtOH	−5.95	0.94	−5.01	−5.01
i-PrOH	−6.20	1.29	−4.91	−4.76
t-BuOH	−6.51	1.83	−4.68	−4.51

Table IV. Electrostatic, Nonelectrostatic, and Total Solvation Energies of the Basic Forms of the Alcohols (in kcal/mol)

	ΔG_{el}	ΔG_{nel}	ΔG_s
MeO$^-$	−96.69	−0.12	−96.81
EtO$^-$	−92.08	0.07	−92.01
i-PrO$^-$	−90.00	0.50	−89.50
t-BuO$^-$	−88.27	0.99	−87.28

Table V. Calculated Deprotonation Free Energies in Solution and the Experimental Values (in kcal/mol)

	ΔG_{as}	ΔG_{as}(exp)[12]
MeOH	20.72	20.7
EtOH	21.63	21.8
i-PrOH	22.12	23.4
t-BuOH	23.50	26.3

Results

In Table I are shown the total energies of the basic and neutral forms and the absolute and relative internal energies of deprotonation of the alcohols in the gas phase obtained at the MP4(SDTQ) level. According to experiments,[4,10] progressive substitution of hydrogen atoms by methyl groups reduces the energy needed to break the O–H bond. As will be discussed below, the stabilization of the basic form is the reason for this tendency. In Table II calculated absolute and relative free energies together with the experimental values of Bartmess et al.[12] are given. Zero-point corrections and thermal contributions have been calculated at the HF level and can be sent upon request together with the optimized geometries. Our results are in very good agreement with the experimental free energies both in absolute and relative values. The experimental relative values are believed to be accurate to ±0.2 kcal/mol and the experimental absolute values to ±2.0 kcal/mol.[12] Comparing the relative values of this table with those of the preceding shows, as discussed in the previous section, that the differences in the gas-phase deprotonation free energies of the alcohols studied here are mainly due to differences in internal energies, with the other contributions to the relative energies being of very modest magnitude. It can be concluded that the present level of calculation, basis set, and order of perturbation theory are good enough to deal accurately with the gas-phase energies. This fact is very important in the final ordering of our results in solution because of the little differences in the deprotonation energies of the alcohols in aqueous solution.

Table III gives the electrostatic and nonelectrostatic components of the solvation energies of neutral species. The total solvation free energy compares very well with the experimental values.[21] At the level of calculation we are dealing with, such good agreement (i.e. a maximum error of 0.4 kcal/mol) must be considered as taking benefit from some compensation of errors, i.e. having ignored such specific effects as contribution of motions, repulsion, and other contributions. Moreover as it has been recently pointed out, experimental solvation energies should be revised to take into account size differences between solute and solvent.[44] The irregular order in the electrostatic contributions

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Table VI. Solvation Free Energies of the Basic Forms of the Alcohols Studied with an Oxygen Radius of 1.68 Å and the Corresponding Deprotonation Free Energies in Solution (in kcal/mol)

	$\Delta G_s(RO^-)$	ΔG_{as}
MeOH	−87.68	29.85
EtOH	−82.71	30.93
i-PrOH	−80.84	30.78
t-BuOH	−79.01	31.77

to the solvation energy can be rationalized considering that the dipole moments decrease from MeOH to *t*-BuOH but the polarizabilities and quadrupole moments increase.[45] The final experimental ordering is reached when the nonelectrostatic contributions are added. Table IV gives the solvation energies of the charged species. The nonelectrostatic contributions are similar to those of the neutral species, increasing from the smaller to the larger members of the series in an interval of 1 or 2 kcal/mol. This supports the idea of disregarding variations of nonelectrostatic contributions in the study of reactions involving charges when there are not very important changes in size.[46] The behavior of the electrostatic component of the solvation energy differs completely from that of the neutral species. It diminishes in a regular sequence and more quickly from MeO^- to $t\text{-}BuO^-$ than in the neutral alcohols, this fact being the decisive factor in the inversion of deprotonation energies from the gas phase to solution.

Thus, by using eq 1 and with the value $\Delta G_s(H^+) = -260.5$, we are able to calculate deprotonation free energies in solution. The values obtained are presented in Table V together with the experimental free energies in solution.[12] Our results reproduce the acidity ordering in solution, just the opposite of that in the gas phase, and have a very good quantitative agreement with the experimental values. The differences in the solvation energies of the basic forms of the alcohols produce the inversion in the acidity scale. These results confirm the suitability of the size and shape of the cavity used in the continuum model and of the level of quantum calculations.

Influence of Cavity Size. Determination of the cavity radii to be used in the Born model of ion solvation, or more generally in the continuum model, has been the object of several papers and of the interest of many workers.[33,47,48] In our case, as it has been said, the critical radius is that of the oxygen atom in the basic form. As it has been previously explained, we have calculated the oxygen radius to be used in every basic form from a set of optimizations of the methoxide–water complex. This must be a good approximation, since the ethoxide–water distances only differ from the previous one by +0.01 Å. However, it could be partially responsible for the increasing errors in the calculated ΔG_{as} as we move forward into the series of the alcohols.

We have carried out a set of calculations to test the effect of varying the oxygen radius of the basic forms on the final results. The solvation energies of the basic forms of the alcohols have been recalculated by using the same radii as those in the neutral forms, i.e. $R_0 = 1.68$ Å. These new results appear in Table VI together with the deprotonation free energies in solution obtained with these solvation free energies. In fact, for methoxide we have studied the dependence of ΔG_s on the cavity radius, obtaining a sensitivity parameter of about 30 kcal/(mol Å). In addition to the expected result that the solvation energies diminish quickly when the oxygen radius grows, it is important to notice that the deprotonation free energies in solution present a larger error and an irregular ordering in the acidity scale. This example shows the importance of making a good choice of cavity radii, above all of those zones of the molecules with large localized charges. The procedure adopted here, which is similar to that proposed by Rashin and Honig,[33] seems to be a plausible way to select some cavity radii.

Table VII. Mulliken Charges (in au) for the C–O Group of the Basic Forms of the Alcohols in the Gas Phase

MeO^-	−0.957
EtO^-	−0.801
$i\text{-}PrO^-$	−0.664
$t\text{-}BuO^-$	−0.548

Discussion

The results presented here and that of our previous work about methylamines' basicities in solution[8] demonstrate the applicability of the continuum representation of the solvent together with a quantum description of the solute for a quantitative treatment of acid–base behavior of organic compounds in solution. As it has been shown, the method needs an accurate molecular wave function and a correct estimation of cavity radii to lead to correct results. In the case of methylamines, it was pointed out that an equilibrium between the methyl substitution effect in the gas-phase energies and solvation energies was responsible for the final irregular ordering of the methylamines' basicities in solution. In the case of the alcohols, a total inversion is obtained but the mechanism of the change in the acidity ordering is the same.

Table VII gives the Mulliken charges[49] for the C–O group of the basic forms of the alcohols in the gas phase. The C–O group is the structure kept along the series, so its Mulliken charge informs us about the delocalization effect produced by the progressive substitution of hydrogen atoms by methyl groups. It can be seen how the inclusion of the methyl groups diminishes the excess negative charge on the C–O group. This effect produces a more stable structure, making the deeprotonation process in the gas phase easier as we go from methanol to *tert*-butanol. The first substitution of a hydrogen atom by a methyl group diminishes the deprotonation free energy by about 3 kcal/mol, the second by about 2 kcal/mol, and the third by about 1 kcal/mol. This same behavior is observed in the decreasing negative charge on the C–O group, indicating how the presence of the methyl groups affects the deprotonation process. Thus, charge delocalization seems to be an important contribution for the progressive reduction in the deprotonation free energies in the gas phase. This explanation is in agreement with the electron-withdrawing character of methyl groups that has been invoked to explain dipolar moments[50] and NMR shifts[51] and that has been previously studied theoretically.[52,53] However, it must be pointed out that, since both gas-phase acidities[4,10] and gas-phase basicities[54] are enhanced with methyl substitution, some authors[10,55] have suggested that the extra stability is more likely due to the greater polarizability of the methyl group relative to the hydrogen atom rather than delocalization effects.

In solution, the situation is just the opposite. The solute–solvent electrostatic interaction energy for the basic forms is lower as the number of methyl groups increases, as could be deduced from the Mulliken charges given in the preceding table. With regard to this, in order to analyze how the delocalization of molecular negative charge affects electrostatic free energies, we present in Figure 1 the solvent reaction potential for methoxide and ethoxide. In both cases this potential is dominated by the presence of a large localized charge on the oxygen atom that produces a positive reaction potential of the solvent in the whole of the molecule. Both in methoxide and in ethoxide, the reaction potential on the oxygen is very similar, around 205 kcal/mol. However for the carbon atom closer to the oxygen, the reaction potential is 10 kcal/mol greater in methoxide than in ethoxide. The methyl group has a screening effect over the reaction potential of the solvent that extends also to the hydrogens of the first carbon atom. It can be seen how in this part of each molecule the isopotential lines are closer in ethoxide than in methoxide. This effect, related to

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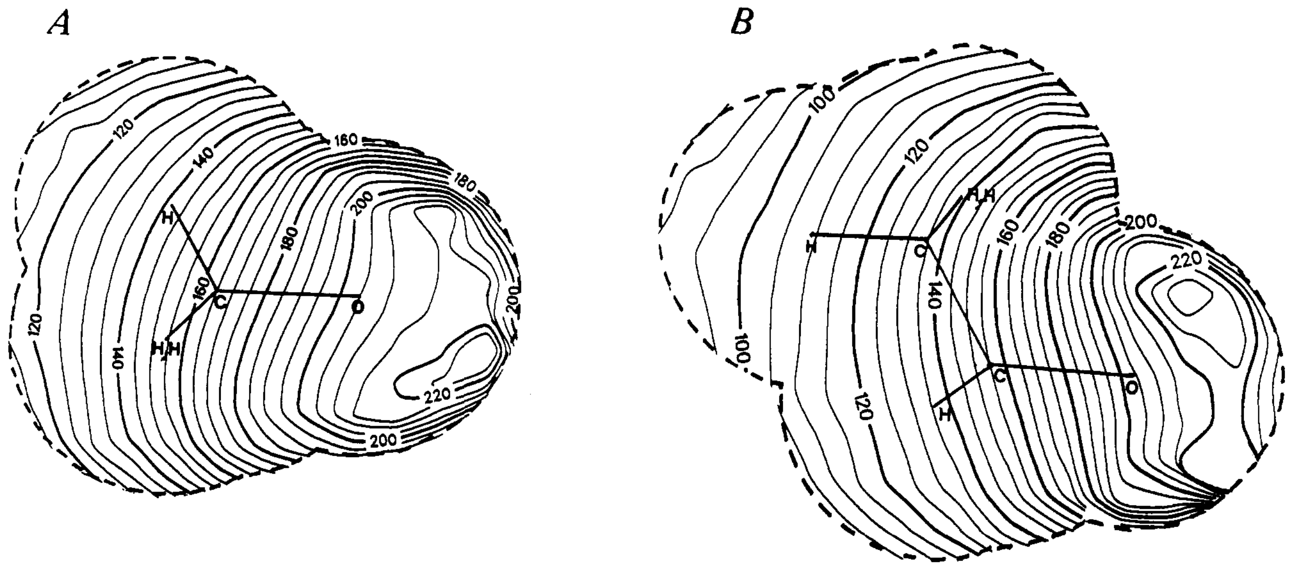

Figure 1. Solvent (ϵ = 78.39) reaction potential for MeO^- (A) and EtO^- (B) in kcal/mol.

the charge delocalization shown in the preceding table, reduces the solute–solvent electrostatic interaction and, consequently, the stabilization of the basic forms.

From this analysis it can be concluded that the substitution of hydrogen atoms by methyl groups plays two roles in the deprotonation free energy in solution. In the first place, methyl groups stabilize the internal distribution of charges of the basic form and thus they act in favor of the deprotonation of the alcohols. This is the only effect present in vacuo, so the deprotonation free energies in the gas phase decrease as the number of methyl groups increase. However, in solution, the stabilization of the charge distribution leads to a decrease in the electrostatic solute–solvent interaction energies. These two opposite effects are more pronounced in the case of the protonation of methylamines because the methyl groups are directly attached to the nitrogen atom that is the proton acceptor center.[8] Although the effect on the solute–solvent interaction is predominant for the larger members of both series, the final ordering of acidity or basicity in solution results from the equilibrium of the two effects: an irregular ordering in the case of methylamines and a total inversion for the alcohols studied here.

Conclusions

This paper is concerned with both quantitative and qualitative aspects of solvent effects on the acidity scale of alcohols as models of the acid–base behavior of organic compounds. Deprotonation free energies of MeOH to *t*-BuOH have been calculated in the gas phase and in solution. Gas-phase calculations have been carried out at the MP4 level with the 6-31G* basis set and an sp diffuse function added on the oxygen atom. The polarizable continuum model together with other methods of estimating cavitation and dispersion contributions has been used to calculate solvation free energies. It has been shown that, in this case, the polarizable continuum model gives solvation energies which are good enough to predict correctly the final acidity ordering of alcohols in solution and the magnitude of the deprotonation free energies in solution. The use of a quantum model of the solute charge distribution leads to a better understanding of the acidity ordering of the alcohols both in solution and in the gas phase. The quantum continuum model can tell us about changes produced in the electronic distribution of the solute and thus provides a complementary method to statistical methodologies more focused on the solvent structure.[56] Thus, simple electrostatic arguments, based on the charge delocalization concept, have been used to rationalize the progressive acidity of the alcohols when hydrogen atoms are substituted by methyl groups in the gas phase, with the effect on the solution energies being just the opposite.

As has been seen so far, it can be deduced that both the methyl-stabilizing effect and the electrostatic interaction with the solvent can explain the acid scale in solution. As both terms are related to molecular size, this explanation could be generalized. We can consider the next equilibrium:

$$AH \rightarrow A^- + H^+$$

In vacuo, as the size becomes greater by adding methyl groups, displacement of the equilibrium to the right is favored. In solution, the electrostatic stabilization is lower when the size increases, favoring the displacement of the equilibrium to the left. The balance between these two tendencies gives the final acidity (or basicity) ordering in solution.

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