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Relative solvation and strength of polycyano- and polynitromethanes in water: a study with molecular dynamics simulations[†]

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ABSTRACT: The long-known saturation effect in the acidity of polynitromethanes as the number of electron-withdrawing substituents is increased has no parallel in the polycyanomethane series, leading to a reversal in acidity when the two series are compared. A theoretical study based on molecular dynamics simulations was carried out, with a view to investigating the solvation patterns of all acidic polynitro- and polycyanomethanes and their conjugate bases in water. The results provide a qualitative interpretation of the causes of the saturation effect and the observed reversal in acidity. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: acidity; polynitromethanes; polycyanomethanes; molecular dynamics simulation

INTRODUCTION

Theoretical studies on the acid–base properties of organic molecules are a subject of continuing interest in the literature.[1–12] The task of theoretically explaining and comparing the acidities or basicities of families of compounds is simpler in the gas phase.[2,3,7,9,12] In solution, interactions with the solvent may change intrinsic acidities or basicities drastically, so that calculations must take into account not only the intrinsic properties of the studied molecules but also their environment. This may be obviated by considering the medium as a continuum, capable of introducing significant perturbations on the geometries and charge distributions of the solute.[4,6,8] Alternatively, specific solute–solvent interactions may be taken into account in the calculations, which may then treat the solvated substrate as a supramolecule.[11]

In spite of the importance of the medium in defining the acidity of compounds, the behavior of limited sets of acids in solution has sometimes been successfully described in terms of intrinsic descriptors, with the neglect of any solvent contributions.[1,13] This may be the result of the linear correlations which are sometimes obtained between gas-phase and solvent acidities of families of organic acids.[14] Thus, we have been successful in describing the acidity of carbon acids, and not only in the gas phase[15] but also in solution,[16] in terms of theoretical descriptors, without including solvent perturbations in the calculations. The same treatment has been successfully applied by us in describing the basicity of carbonyl compounds in CCl_4.[17] A simple model relying on two descriptors proved successful in a regression analysis of 32 carbon acids in water, spanning a range of nearly 31 pK_a units.[16] The first descriptor was the calculated heat of deprotonation of the acid and the second was the total charge variation on the hard centers of the substrate upon deprotonation. This charge descriptor was envisaged as a measure of the degree of interaction of the acid and its conjugate base with the solvent, since solvation in water should be predominantly a result of hydrogen-bond interactions of the hard centers of the molecule with the medium.

In this work, we undertook a different approach to the rationalization of the acidic behavior of carbon acids in water, based on molecular dynamics simulations. This theoretical tool has been only rarely employed for the study of inorganic acids and bases in solution.[18–20] We hoped to arrive at detailed pictures of the patterns of solvation of a set of acids and their conjugate bases in solution. We chose two sets of carbon acids, polynitro- and polycyanomethanes, that exhibit a reversal in their acidities in water as the number of electron-withdrawing substituents on the molecule increases. Our theoretical approach, if successful, should be able to rationalize this observed reversal in acidity, an expectation which was

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only partially fulfilled by our previous theoretical model.[16]

RESULTS AND DISCUSSION

It has long been known that the acidity of carbon acids of the form $CH_{4-m}X_m$ where X is an electron-withdrawing group such as NO_2, COR or SO_2R, does not increase linearly with the number of X groups. Pearson and Dillon[21] had already observed that 'it would be misleading to estimate the ionization constant of a di- or trisubstituted acid from those of the monosubstituted acids', drawing attention to the fact that this 'saturation effect ... sets in more strongly the greater the electron-withdrawing power of the substituting group'. This behavior is illustrated in Fig. 1, where the pK_a values[22] of two sets of carbon acids $CH_{4-m}X_m$ are plotted against the number m of substituents X, where $X = NO_2$ and CN. In contrast with the polynitromethanes, the acidity of polycyanomethanes does not exhibit a saturation effect as the number of CN substituents increases. As a result, when the two sets of substituted methanes are compared, a reversal of their acidity behavior is observed. Nitromethane is a much stronger acid ($pK_a = 10.24$) than acetonitrile ($pK_a = 25$), whereas trinitromethane ($pK_a = 0.06$) is a comparatively weaker acid than tricyanomethane ($pK_a = -5.1$).

This reversal in acidity was previously rationalized by a reversal of the relative stabilities of the acids and their conjugate bases in the gas phase.[16] In polysubstituted acids, the nitro group is increasingly less effective than the cyano substituent in stabilizing the conjugate bases, because of steric and electronic repulsions that are present in the former but not in the latter series of compounds. A comparison of the heats of deprotonation of all polynitro- and polycyanomethanes should provide support to the above rationalization. This theoretical parameter was found to be a good measure of relative gas-phase acidities of carbon acids. A plot of the experimental ΔG° values versus the deprotonation energy ΔE of 13 acids CH_2ZY yielded a straight line with a correlation coefficient $r = 0.985$ and a standard deviation of $2.3\,\text{kcal mol}^{-1}$ ($1\,\text{kcal} = 4.184\,\text{kJ}$).[16]

Figure 2 is a plot of the calculated heats of deprotonation [16] of carbon acids $CH_{4-m}X_m$ against the number m of substituents X, where $X = NO_2$ and CN. An attenuation effect is observed in the gas-phase acidities of the polynitro- but not of the polycyanomethanes. When Fig. 2 is compared with Fig. 1, it becomes clear that the gas-phase behavior of the two series of acids may partially account for the observed behavior in water. However, an additional contribution in solution must be invoked in order to explain the reversal in acidity present in Fig. 1 but not in Fig. 2. Solvation by water molecules should modify the relative stabilities of all acids and their conjugate bases in aqueous solution. We therefore resorted to molecular dynamics simulations in trying to gain a more detailed insight into these solvation effects. Dissociation of a carbon acid in water leads to the formation of an anion, where the negative charge is shared among the carbon and the hard centers (oxygen and nitrogen atoms) conjugated with it, as shown for the tricyano and trinitromethyl anions (Scheme 1).

The spheres of solvation around each of these centers are different for the acid and its conjugate base. For a given center, a comparison of its solvation pattern upon deprotonation should provide us with a measure of its contribution to the relative stability of the acid and its conjugate base. We may assume that a significant increase in solvation of a given center upon deprotonation should reflect a large contribution to the anion stabilization and therefore to the acidity of the corresponding acid.

Figures 3–6 depict radial distribution functions (RDFs) of the water molecules around the carbon and oxygen or nitrogen centers of the polycyano and -nitro acids, comparing in each case the variations in solvation

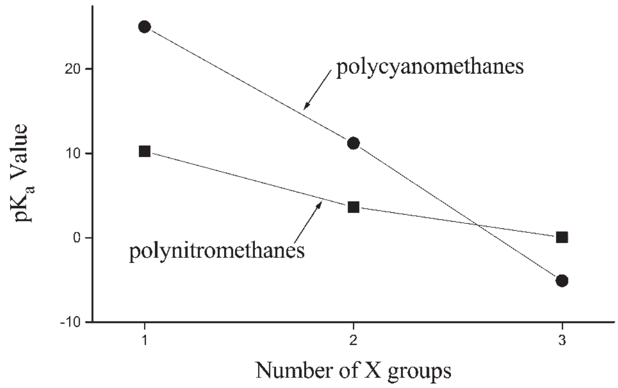


Figure 1. Variation of the pK_a values of polycyano- and polynitromethanes with the number of electron-withdrawing substituents X. The data were taken from Ref. 22

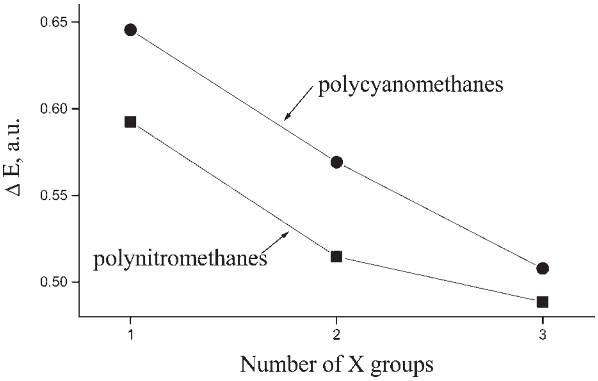
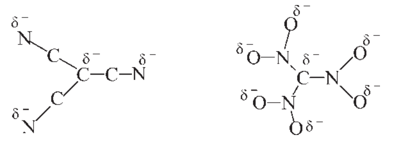


Figure 2. Variation of the calculated heats of deprotonation, ΔE, of polycyano- and polynitromethanes with the number of electron-withdrawing substituents X. The ΔE values, calculated with the B3LYP/HF/6–31G(d)//HF/3–21G method, were taken from Ref. 16



Scheme 1

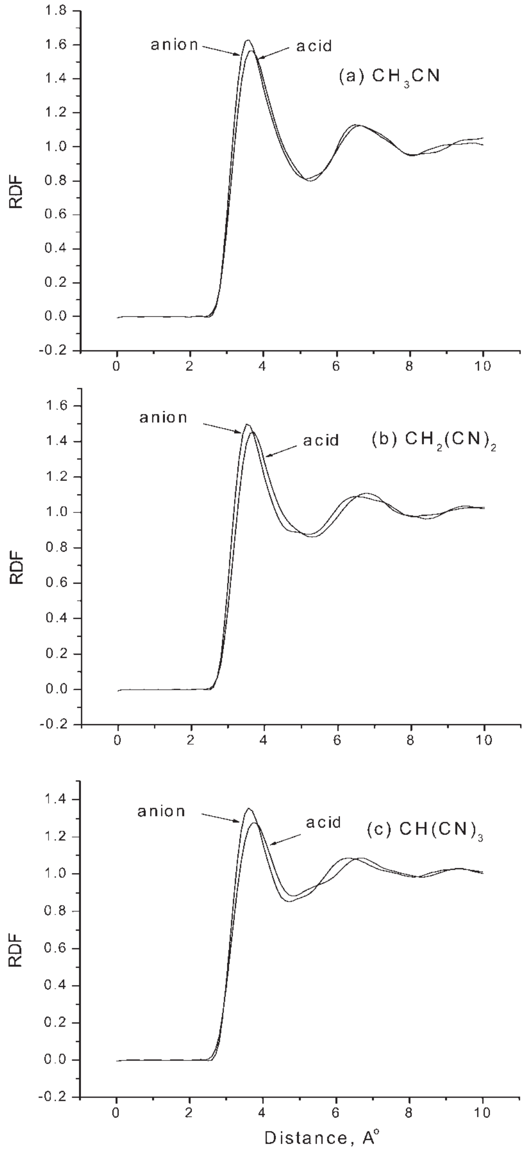


Figure 3. Radial distribution functions (RDFs) for the solvating water molecules around the carbon atoms of the neutral acid and the corresponding anion for (a) CH_3CN, (b) $CH_2(CN)_2$ and (c) $CH(CN)_3$

brought about by deprotonation. A solvation sphere is easily recognized as a peak, reflecting a sharp increase in the number of water molecules at a given distance from the center under investigation. In most cases, one or more solvation spheres are apparent from the plots. The first sphere corresponds to the water molecules that are actually solvating the reference atom. The second, and sometimes third, spheres comprise water molecules that accumulate further away from the reference center, and that may also belong to solvation spheres of other atoms in the molecule.

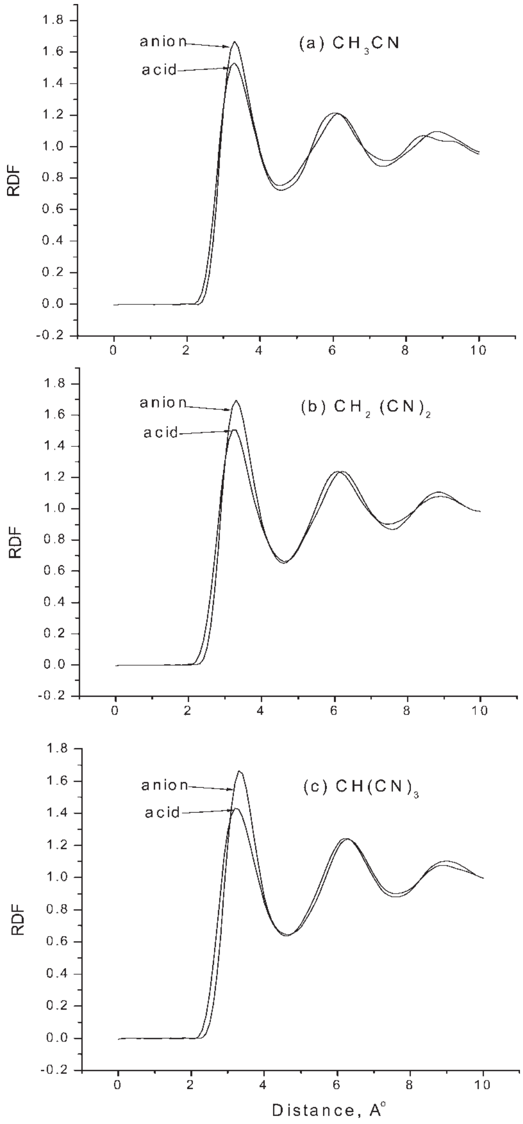


Figure 4. Radial distribution functions (RDFs) for the solvating water molecules around the nitrogen atoms of the neutral acid and the corresponding anion for (a) CH_3CN, (b) $CH_2(CN)_2$ and (c) $CH(CN)_3$

Figure 3 shows that, for all three members of the series, the polycyano acids exhibit little qualitative difference in the patterns of solvation of their carbon centers between the acid and its conjugate base. The anionic carbon atom is slightly more solvated than the corresponding protonated C atom, with a first solvation sphere around 3.5 Å. The second, more diffuse, solvation sphere reflects contributions from the nitrogen atom(s) of the molecule. These localized contributions, further away from the central carbon atom, appear small because of the greater distance from the reference atom. The same observation applies to the distribution plots around the nitrogen atoms

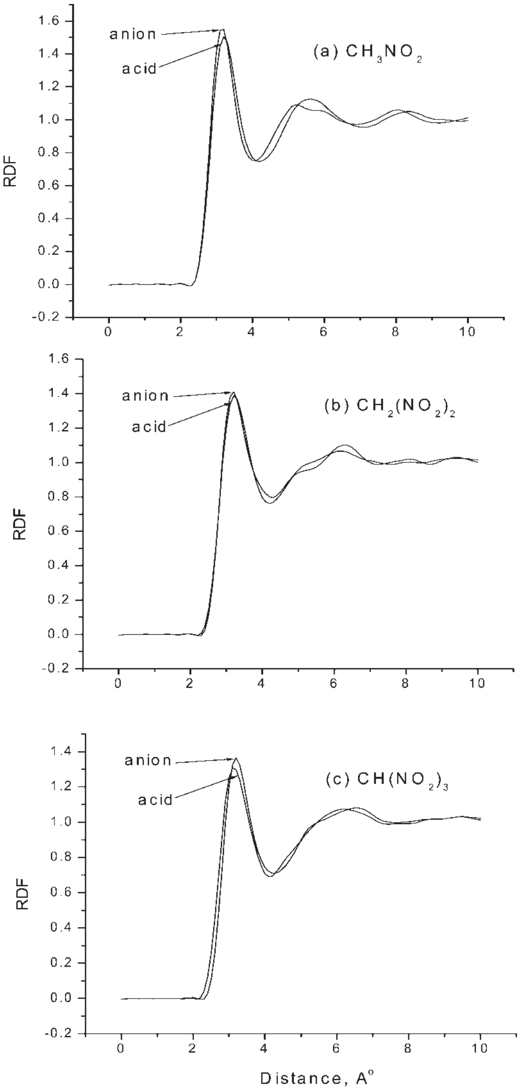


Figure 5. Radial distribution functions (RDFs) for the solvating water molecules around the oxygen atoms of the NO_2 groups in the neutral acid and the corresponding anion for (a) CH_3NO_2, (b) $CH_2(NO_2)_2$ and (c) $CH(NO_2)_3$. Curves (b) and (c) were constructed with average values for the non-equivalent oxygen centers

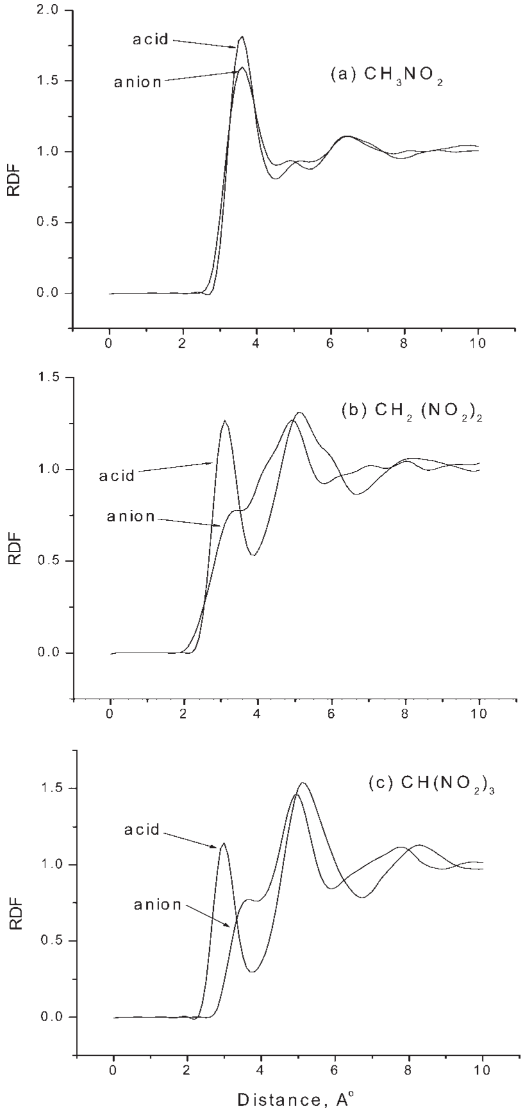


Figure 6. Radial distribution functions (RDFs) for the solvating water molecules around the carbon atom in the neutral acid and the corresponding anion for (a) CH_3NO_2, (b) $CH_2(NO_2)_2$ and (c) $CH(NO_2)_3$

(Fig. 4). The first sphere is apparent around 3.5 Å, followed by a second, smaller sphere around 6 Å, originating from contributions from the solvated carbon atom. Upon deprotonation, there is a steady increase in solvation by the water molecules of the carbon and the nitrogen atoms, with a resulting increased stabilization of the anionic form in solution. This leads to a regular increase in the acidity of polycyanomethanes with the number of cyano substituents.

The polynitromethanes behave differently. Although the nitro groups in these compounds were non-equivalent, with different partial charges on the oxygen atoms, the corresponding RDFs of these oxygen centers did not differ significantly. We therefore employed average values in the analysis of their solvation pattern.

Although solvation of the hard oxygen centers (Fig. 5) follows a pattern similar to that of the nitrogen atoms in the polycyano acids, there is a marked difference between the solvation patterns of the carbon atom of nitromethane [Fig. 6(a)] and the di-/trinitromethane pair [Fig. 6(b) and (c)]. For the latter compounds, deprotonation leads to a significant desolvation of the carbon center. In its first sphere, the solvating water molecules of the carbon atom of di- and trinitromethane practically disappear in the anionic form, merging with the second sphere of solvation, which becomes increasingly important with increase in symmetry of the molecule. Solvating molecules are pushed away from the anionic carbon center into the peripheral spheres of the oxygen atoms.

A second characteristic feature of the polynitromethanes is the significant contributions of the peripheral oxygen atoms to the second sphere of solvation of the carbon center. This observation [Fig. 6(b) and (c)] is in contrast with what happens with the di- and tricyanomethanes [Fig. 3(b) and (c)]. As discussed above, this reflects the larger number of strongly solvated oxygen atoms, symmetrically distributed around the central carbon atom in the di- and trinitromethanes.

Carbon desolvation has a destabilizing effect on the conjugate base of di- and trinitromethane that partly neutralizes the stabilizing effect due to oxygen solvation of the nitro groups. As a result, incorporation of one cyano group to cyanomethane increases the methane acidity more than the analogous incorporation of one nitro group to nitromethane. This pattern of behavior, repeated once more when a third electron-withdrawing group is added, has the result of inverting the relative acidities of these compounds and tricyanomethane becomes a stronger acid than trinitromethane.

This difference in behavior between the two sets of compounds may be assigned to steric effects. Access to the carbon center of polycyano anions by the solvating water molecules is not hindered by the increased number of substituents. In the case of the polynitro analogs, a different picture emerges. The optimized geometry of the trinitromethyl anion showed that the nitro groups are not coplanar. The central carbon atom lies in a plane shielded from above and below by three of the oxygen atoms of the surrounding nitro groups. This has the effect of blocking access of the water molecules from both sides of the plane to the carbanionic center.

In conclusion, the attenuation effect observed in the pK_a values of polynitromethanes is predicted by calculations of gas-phase acidities of these compounds, as a result of steric and electronic repulsions among an increasing number of substituents around the carbon atom. Calculations also show that the intrinsic acidities of polycyanomethanes do not follow this pattern, because of the smaller size of the linear CN group. Such trends in the gas-phase acidities of the two series of compounds are only partially responsible for the observed reversal in acidity depicted in Fig. 1. Molecular dynamics simulations show that solvation effects also contribute to the observed behavior in aqueous solution. Desolvation of the carbon atom of di- and trinitromethane upon deprotonation has a destabilizing effect on the corresponding conjugate bases. Such desolvation is a result of steric hindrance in these anions, and is not observed with di- and tricyanomethane. Thus, solvation effects add to the reduced intrinsic acidities of polynitromethanes when compared with their cyano analogs, leading to the observed reversal of their pK_a values in aqueous solution.

EXPERIMENTAL

The optimized molecular geometries and the partial atomic charges for each acid and the corresponding conjugate base were calculated with the Gaussian 98 w package[23] using the B3LYP/6–31G* method. Three-dimensional models of all structures in a water box of dimensions $20 \times 20 \times 20\,\text{Å}$ were built under periodic boundary conditions, using TIP3 water molecules. All molecular dynamics calculations were carried out with the program TINKER,[24] using MM3 force-field parameters.[25–27] Some specific parameters were taken from analogous functional groups, whenever they were not available in the literature, with the object of preserving the optimized molecular geometry, as obtained from the *ab initio* calculations.

The initial systems under periodic boundary conditions were relaxed using energy minimization and short molecular dynamics cycles until appropriate energy gradients were attained. Then a 100 ps dynamics was performed for system equilibration, followed by a 500 ps dynamics of data collection, employing a time step of 1 fs. During data collection, all systems showed potential energy fluctuations $<10\%$. Simulations were carried out without any restraints on the initial geometries. All calculations were done using a cutoff of 9 Å for coulombic and van der Waals interactions. The radial distribution functions were calculated using the gOpenMol program (v. 2.10).[28]

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