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Solvent effects on relative acidities for a series of substituted organic acids

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Plots of relative acidities for a series of substituted benzoic acids as well as substituted phenols $\Delta pK_a = pK_a^{unsubst} - pK_a^{subst}$ in a number of solvents against ΔpK_a in the gas phase give for both series two linear sections, separately for electron withdrawing and releasing substituents (relatively to hydrogen in the unsubstituted acid). For benzoic acids slopes of the correlation lines for releasing substituents in all solvents and for the withdrawing substituents in protic solvents decrease with the solvent Lewis acidity indicating a dominant role of the anion solvation.

Introduction

Substituted benzoic acids and phenols have widely been used in organic reactions as relatively weak organic acids and their equilibrium acidities have been determined in water[1] as well as in a number of organic solvents.[2] Solvent effects on pK_a values are complex and difficult to describe because non-specific electrostatic interactions (ion–ion, ion–dipole, *etc.*) as well as a short-range specific solvation of both ions and a neutral molecule should be taken into account.[3] Moreover, specific solvent interactions can include not only the solvation of a reaction centre but also the acidic or basic centre of a substituent leading, for *para*-substituents, to the specific substituent solvation-assisted resonance effect (SSAR),[3–6] and to some attenuation of field/inductive effects for both the *para*- and *meta*-substituents.[3,5] These phenomena change the transmission of substituents' electrical effects and are thus fundamental for the understanding and practical use of linear free-energy relationships, like the Hammett equation;[3] more references and discussion of this subject can be found in a review.[7]

In order to compare solvent effects on the acidity of organic acids their pK_a values in a given solvent were plotted against pK_a in a reference solvent (water[8] or dimethyl sulfoxide, DMSO[9,10]) and then slopes and intercepts of linear correlations were discussed. As a result it was reported that acetonitrile (ACN) is the more discerning of the phenols acidity than propylene carbonate and benzonitrile[8] and that absolute acidities of organic acids in *N*,*N*-dimethylformamide (DMF) and 1-methyl-2-pyrrolidone (NMP) are very similar but a little higher than those in DMSO.[9,10] Kalinowski *et al.* recently reported[11] a good correlation of the Hammett reaction constants for pK_a values of a series of benzoic acids with the Kamlet and Taft[12] solvent basicity parameter β indicating a dominant role of the proton solvation, as discussed earlier[13] for the absolute pK_a values of phenols. However, separate lines for protic and "aprotic" solvents were observed,[11] but a one correlation line was obtained after the use of a planar regression with β and α parameters, *i.e.* taking into account Lewis basicity and acidity of solvents, respectively.

Some more detailed information on the solvation of anions can be obtained from relative acidities (related to acidity of unsubstituted acid), in which the contribution of proton solvation as well as the main part of the solvent contribution to ion–ion interactions are cancelled.[13,14] Relative acidities of organic acids *e.g.* in DMSO and NMP are similar, indicating similar anion solvation.[10,13] A comparison between the gas phase $\delta\Delta G^\circ_{(g)}$ and the aqueous $\delta\Delta G^\circ_{(aq)}$ acidity of phenols and benzoic acids showed[14] great attenuation of substituent effects from the gas phase to the aqueous solution. It was suggested[14] that the last effect is most probably caused by the hydrogen bonding of the anion with the solvent, whereas a similar attenuation in DMSO is quite small.[14,15] Further examination of the plots of $\delta\Delta G^\circ_{(g)}$ *vs.* $\delta\Delta G^\circ_{(aq)}$ and $\delta\Delta G^\circ_{(DMSO)}$ for an extended series of phenols[3,4] showed a substantial increase in their relative acidities in solution for electron withdrawing substituents and also allowed one to separate field/inductive and resonance effects.[3] (Electron withdrawing and releasing properties of substituents considered above and later in this paper are relative to hydrogen in the unsubstituted acid.) Then, it was shown[3,4] that solution acidities of π electron-donor (−R) and π electron-acceptor (+R) substituents should be considered separately but only phenols of the first group were examined in detail.[4] However, in a review[7] only one correlation line is shown in the plot of $\delta\Delta G^\circ_{(g)}$ *vs.* $\delta\Delta G^\circ_{(aq)}$ for a series of benzoic acids with points for conjugated *para* π electron-donor substituents not fitting the line. In this report, in order to elucidate solvent effects on relative acidities, both groups of substituents are treated separately and the pK_a values of benzoic acids in a variety of solvents are compared.

Results and discussion

The difference in pK_a values for unsubstituted and substituted organic acids in a solution $\Delta pK_a^{solv} = pK_a(AH) - pK_a(XAH)$ is analysed in this paper in comparison with the same difference in the gas phase ΔpK_a^{gas}. It is evident that ΔpK_a values are equal to $\log K_1$ for the reaction (1), *i.e.* K_1 is the equilibrium constant for

$$XAH + A^- \rightleftharpoons XA^- + AH \qquad (1)$$

the proton exchange between a substituted and unsubstituted acid. Thus, positive values of ΔpK_a obtained for most substituents (for *meta*- and *para*-positions) that are accepting relative to hydrogen (positive Hammett substituent constants: $\sigma_{m,p} > 0$) indicate that the equilibrium (1) is shifted to the right-hand side, *i.e.*, the unsubstituted acid is more stable than the substituted one. On the other hand, for donor groups ($\sigma_{m,p} < 0$) the reaction (1) is shifted in the opposite direction because the substituted acid is more stable due to an electron shift from the substituent to the oxygen atom at the reaction centre and ΔpK_a values are negative. This simple situation characterizes gas

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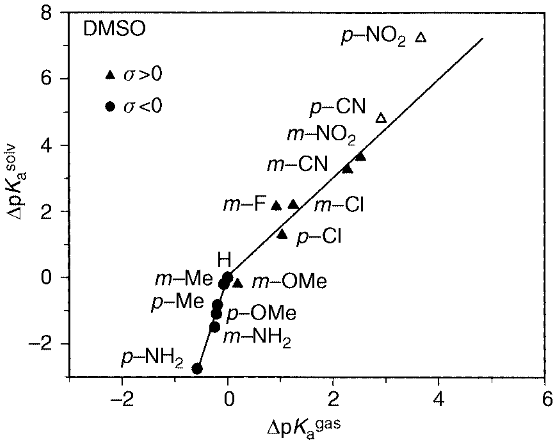

Fig. 1 Relative acidities of phenols ΔpK_a^{solv} in DMSO (from refs. 16, 17) against ΔpK_a^{gas} in the gas phase (from ref. 3). The open triangles indicate substituents deviating from the correlation line obtained for other +R substituents due to acidifying SSAR effect (see text).

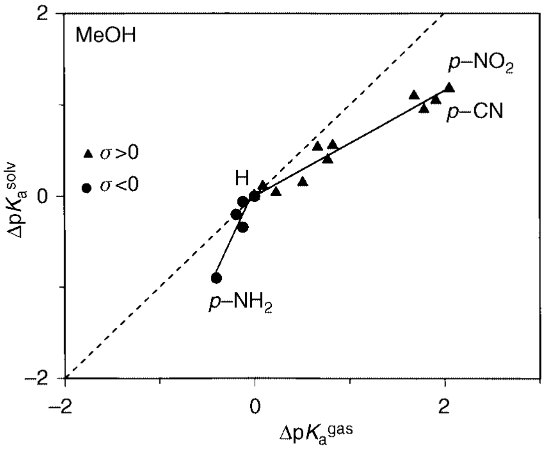

Fig. 2 Relative acidities of benzoic acids ΔpK_a^{solv} in methanol (from ref. 18) against ΔpK_a^{gas} in the gas phase (from ref. 14). Separate lines for electron withdrawing and releasing substituents (full lines) and the theoretical (dashed) line with a unit slope are shown.

phase behaviour, *e.g.* ΔpK_a^{gas} of phenols[3,14] and benzoic acids.[14] The plot of ΔpK_a^{solv} for a series of phenols in DMSO (all acidities obtained in the laboratory of Bordwell[16,17]) against ΔpK_a^{gas} values[3] is shown in Fig. 1. For π electron-acceptor substituents the correlation corresponds to the behaviour described previously,[4] *i.e.*, the conjugated *para* substituents (*p*-CN and *p*-NO_2, open triangles in Fig. 1) which are both π-electron and hydrogen bond acceptors deviate from the correlation line proper for other compounds due to the SSAR effect.[4] However, it is also evident that π electron-donor substituents (not considered by Mashima *et al.*[4]) form a separate line with a different slope. Similar behaviour was obtained for a series of benzoic acids in a variety of solvents, *e.g.* in methanol as is shown in Fig. 2. Both groups of substituents form separate lines, however the SSAR effect is relatively weak and all substituents with $\sigma > 0$ lie on one correlation line, as found previously[7] in the aqueous solution. For benzoic acids solvent acidities reported by Ludwig *et al.*[18] in 7 solvents, ACN, DMF, acetone (Ac), sulfolane (TMS), methanol, ethanol and water, as well as data in DMSO obtained earlier in the same laboratory[19] and the gas phase pK_a values of McMahon and Kebarle[14] are used because they include the largest series of substituted benzoic acids investigated in the same laboratory. It should be noted here that similar bilinear plots with smaller slopes for −R than +R *para* substituents were observed by Fujio *et al.*[3] for the Hammett plots of relative acidities against the inherent $\sigma^-_{(g)}$ substituent constants obtained from the gas phase acidities; it was observed for *N*,*N*-dimethylanilinium ions in nitromethane and thiophenols in 48% aqueous ethanol as well as for ^1H chemical shifts of OH groups for phenols in DMF. The different line for −R substituents was explained[3] by the specific solvation of hydrogen-bond acceptor substituents by water molecules influencing the field/inductive effect and by π-electron repulsions of a *para* −R substituent with the π charge at the *para* carbon influencing the resonance effect.

It is evident from Figs. 1 and 2 that for electron releasing substituents ($\sigma < 0$) all ΔpK_a^{solv} values are negative as in the gas phase. For the second group of substituents most of the ΔpK_a^{solv} values are positive, indicating a stronger acidity for the substituted acid, as was found in the gas phase. Only for weak withdrawing substituents (*m*-OMe, *m*-OH) in some solvents are the values of ΔpK_a^{solv} negative, but deviations of these points from the correlation lines of other benzoic acids are small and were neglected. The most important result shown in Figs. 1 and 2, the separate correlation lines with different slopes, shows different solvent effects for both groups of substituents. This behaviour can be explained for a series of benzoic acids by analysing the consistent set of pK_a values in different solvents.[18,19] The behaviour of phenols is more complex because of the additional SSAR effect (Fig. 1) and will not be analysed here.

In all solvents acceptable correlations of ΔpK_a^{solv} *vs.* ΔpK_a^{gas} were obtained, separately for both groups of substituents, as indicated by the values of correlation coefficients *r* and Snedecor *F* test which are collected in Table 1. Let us discuss first the group of substituents with $\sigma > 0$, where the accuracy is better because of a greater number of substituted acids (6 in DMSO and 10 in all other solvents). The slopes of correlation lines, which are determined with a reasonable accuracy (standard deviations are given in Table 1) for dipolar non-hydroxylic solvents, are close to unity indicating that the relative solvation of neutral acids and anions is negligibly small. That result is in accordance with the behaviour found for other organic acids[10,13,16] and the conclusion[16] that DMSO is a good model solvent for other non-hydrogen-bond donor solvents. However, for protic solvents the slope decreases from ethanol to water and ΔpK_a^{solv} is lower than ΔpK_a^{gas}, indicating that the equilibrium (1) becomes less shifted to the right-hand side in comparison with the gas phase. This behaviour can be explained by a stronger solvation of the unsubstituted anion A^- in those protic solvents, probably due to the formation of hydrogen bonds, as suggested previously.[14] It can be added that the slopes obtained decrease linearly with the solvent Lewis acidity, described by the Dimroth and Reichardt E_T^N parameter,[20] as shown in Fig. 3 (line 2 for $n = 3$, $r = 0.998$) or by the Kamlet and Taft *a* parameter ($r = 0.996$). The observed dependence is fully conceivable taking into account that a stronger solvation of the unsubstituted anion A^- decreases the shift of the equilibrium (1) to the right-hand side as compared with the shift in the gas phase.

The situation found for the group of substituents with $\sigma < 0$ is more difficult to explain. All ΔpK_a^{solv} values are negative, as found in the gas phase, due to the higher acidity of unsubstituted acid. However, ΔpK_a^{solv} values are more negative than ΔpK_a^{gas}, indicating an additional shift of the equilibrium (1) to the left-hand side. This shift cannot be explained by the solvation of anions (the solvation of a substituted anion is stronger), by the formation of hydrogen bonds between an acid and a solvent molecule (acids with substituents of $\sigma < 0$ are weaker donors for hydrogen bonding, as established *e.g.* for phenols[21]), nor by the homoconjugation effect[13] which also acts in the opposite direction. Thus, the only explanation of greater stabilization of a neutral acid with π-donating substituents in a solution is given by the formation of resonance transquinoidal structures with a separated charge which are more favourably solvated but are not important in the gas phase, as discussed in the literature.[7,14] In particular, those structures are important for *para*-substituents like *p*-NH_2 but they were also proposed[14] for the

Table 1 Statistical parameters of correlations of pK_a^{solv} against pK_a^{gas} for a series of benzoic acids in different solvents

	$\sigma > 0^a$			$\sigma < 0^b$		
Solvent	Slope	r^c	F^d	Slope	r^c	F^d
DMF	0.9 ± 0.1	0.944	74.1	4 ± 1	0.932	19.9
ACN	0.88 ± 0.08	0.966	125.3	3 ± 1	0.890	11.4
Ac	0.9 ± 0.1	0.935	62.1	4 ± 1	0.890	11.5
TMS	0.7 ± 0.1	0.901	38.8	5.3 ± 0.3	0.997	352.9
DMSO[e]	1.0 ± 0.1	0.960	71.8	3.4 ± 0.9	0.917	15.9
EtOH	0.68 ± 0.06	0.971	147.0	2.6 ± 0.6	0.925	16.6
MeOH	0.58 ± 0.04	0.977	190.9	2.3 ± 0.5	0.926	18.1
H_2O	0.38 ± 0.03	0.971	150.0	1.4 ± 0.4	0.904	13.4

[a] Substituents: H, *m*-OMe, *m*-OH, *m*-F, *p*-F, *m*-Cl, *p*-Cl, *m*-CN, *p*-CN, *m*-NO_2, *p*-NO_2. [b] Substituents: H, *m*-Me, *p*-Me, *p*-OMe, *p*-NH_2. [c] Correlation coefficient of linear regression. [d] Value of Snedecor test. [e] Substituents: H, *m*-Me, *p*-Me, *m*-NH_2, *p*-NH_2, and H, *m*-OH, *m*-Cl, *p*-Cl, *m*-CN, *p*-CN, *m*-NO_2, *p*-NO_2, for $\sigma < 0$ and $\sigma > 0$, respectively.

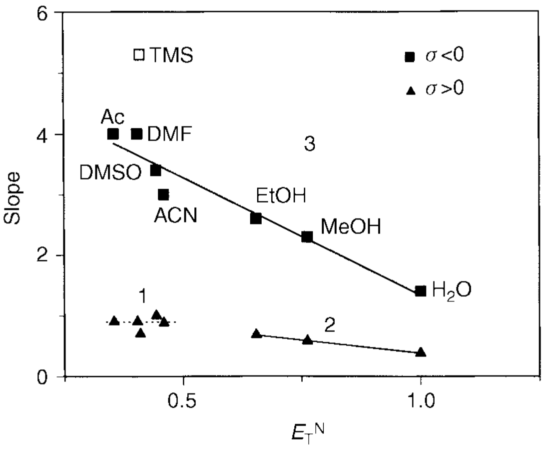

Fig. 3 Relationships between slopes of ΔpK_a^{solv} *vs.* ΔpK_a^{gas} plots for the series of benzoic acids and the Dimroth and Reichardt E_T^N solvent parameter: for electron withdrawing substituents in non-hydroxylic (1) and in protic (2) solvents and for electron releasing substituents (3).

unsubstituted benzoic acid in order to explain the differences in acidities of benzoic and acetic acids in aqueous solutions and the gas phase. In my opinion, the solvation of those resonance structures is important in all solvents, not only in water, as discussed previously.[7,14]

For the group of acids with electron releasing substituents ($\sigma < 0$) there are only 5 acids (4 in TMS and DMSO, without a pK_a value for *p*-OMe) and the range of ΔpK_a changes is much lower than for the previous group of acids. Thus, correlations of ΔpK_a^{solv} *vs.* ΔpK_a^{gas} are worse as indicated by the r and F values given in Table 1. The slopes of the obtained regressions have only an approximate character, nevertheless the resulting slopes in all solvents are higher than unity and they also decrease with the solvent acidity as shown in Fig. 3 (solid squares). The dependence shown (line 3) has the correlation coefficient of $r = -0.965$ for $n = 7$, excluding the most deviating point for TMS (for $n = 8$, $r = -0.880$). The relationship obtained means that the solvation of a substituted anion, not a neutral acid, is dominant in the observed solvent effect, diminishing the shift in equilibrium (1) caused by the solvation of resonance structures of a neutral acid. Moreover, the slope of the correlation 3 shown in Fig. 3 is much steeper than for the previous group of substituents (line 2), as expected for higher electron density on the oxygen atom of anions with electron releasing substituents.

In conclusion, the presented analysis supports the view that the relative pK_a values for a series of substituted organic acids depend on the anion solvation but separate correlation lines are observed for electron withdrawing and releasing substituents. This means that the linear dependencies of pK_a values in two solvents, described in the literature[8–10,13] and used to predict unknown acidities, should be restricted to only one group of substituents. Moreover, only for the acids with electron withdrawing substituents does the relative acidity not change in a number of non-hydrogen-bond-donor solvents.

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