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Propylene Carbonate as a Nonaqueous Solvent for Capillary Electrophoresis: Mobility and Ionization Constant of Aliphatic Amines

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The two properties of aliphatic amines were investigated in propylene carbonate as solvent that are decisive for capillary electrophoretic migration: the actual mobilities and the pK_a* values. Solutes were eight primary, secondary, and tertiary amines. Roughly, the actual ionic mobilities of the ammonium ions are inversely proportional to the solvent viscosity, fairly obeying Walden's rule. The pK_a* values of the cation acids, HB^+ (the corresponding acids of the amines, B), were related to the conventional pH* scale of the buffers. Determined from the effective mobilities as a function of the pH*, they are increased by ∼7 units compared to water. This increase was interpreted based on the concept of the standard free energy of transfer of the individual species in the acid−base equilibrium. The corresponding medium effect on the proton, log $_m\gamma_{H^+}$ (the logarithm of the transfer activity coefficient $_m\gamma_{H^+}$) is ∼+8. The medium effect on the free base, B, was obtained from solubility data; it is about −1 and smaller. Plausible values for the medium effect on the cation HB^+ (−1 to −2) lead to a sum of the increments, which corresponds with the overall effect, expressed by the change in pK_a*. Examination of the individual contributions shows that the drastically lower basicity of propylene carbonate compared to water is mainly responsible for the increase in pK_a upon transfer of the acid−base equilibrium of aliphatic ammonium/amine from the aqueous to the organic solvent.

A number of organic solvents are used in capillary electrophoresis as an alternative to water. In many cases, their application is simply motivated to better solubilize the analytes, because lipophilic solutes often cannot be dissolved in aqueous background electrolytes (BGEs) at concentrations high enough to enable their detection. Most common solvents are methanol and acetonitrile, due to their easy availability at high purity, low toxicity, compatibility with the UV absorbance detector, etc. Although having vast importance as solvent for the BGE, they might have some drawbacks, for example, that the electrophoretic mobility of the separands is influenced by ion association or ion pair formation, which could take place in these solvents although their dielectric constants are higher than 30. Although ion association might enhance selectivity in some cases, its unpredictable magnitude (connected to the lack on data about association constants) makes such organic solvent systems not easily suited for optimization.

In practice, many solvents of potential interest have the limitation that they possess a restricted compatibility with the most common detector in capillary zone electrophoresis (CZE), the UV absorbance detector, because they have an optical cutoff in the range of 230−260 nm. Thus, few organic solvents have been used in CZE (for a review, see, for example, ref 1). One interesting example is propylene carbonate (PC, 4-methyl-1,3-dioxolan-2-one), a medium for acid−base titrations used for a long time. We demonstrated in a previous paper that it is well suited for CZE of ionic solutes using conductivity detection.[2] Its optical properties (cutoff at 200−230 nm[3]) allow nevertheless the application of the UV absorbance detector at least for analytes with sufficiently high extinction coefficients at an appropriate wavelength. Tjørnelund and Hansen[4] applied it to microcolumn separations with UV detection for a kind of electrokinetic chromatography to resolve neutral solutes by the aid of "solvophobic" interactions with alkylammonium ions. The same detection was used in one of our previous papers for CZE.[5]

A remarkable property of PC[6] is its high relative permittivity ($\epsilon_r = 66.1$) compared to other organic solvents (*N*-methylamides are exceptions). PC enables working at normal or elevated temperature (freezing point −54.5 °C, boiling point 242 °C). Its density ($d = 1.198$ g cm^{-3}) is larger than that of many organic solvents, and its viscosity ($\eta = 2.513 \times 10^{-3}$ Pa·s) is comparably higher than water, the alcohols, and ACN but lower than DMSO. Its viscosity results in relatively low ionic mobilities, compared to water and many other organic solvents. Interestingly for CZE, it might selectively influence the acid−base properties of solutes; in this respect, it is similar to ACN. However, only few data on pK_a values are available for PC.

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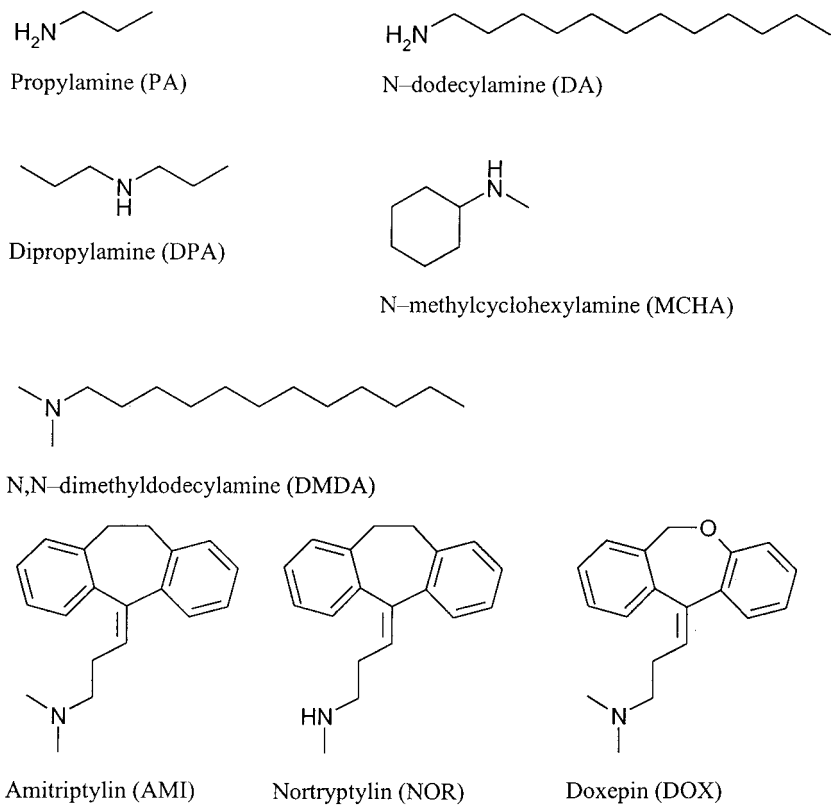

Figure 1. Structural formulas of the analytes. The abbreviations are given in parentheses.

There are several other potential advantages of PC as a solvent in CZE. Most remarkable are two: the high relative permittivity (see above), and the low dependence of the ratio μ/D on the ionic strength of the BGE (μ is the mobility, and D is the diffusion coefficient of the analyte). (i) The high relative permittivity suppresses ion association, which allows a more straightforward prediction of the optimal separation conditions, because in this case the separation parameters are better defined (the extent of ion pair formation is hard to predict, and corresponding association constants are nearly not available from the literature). In this respect, PC resembles water as solvent and is in contrast to acetonitrile and methanol (where surprisingly high ion pair formation was found[7,8]). (ii) The ratio μ/D is decisive for the maximum achievable plate number in CZE (when longitudinal diffusion is the only cause of peak broadening). Note that the mobility is always more strongly reduced by increasing ionic strength than the diffusion coefficient, and thus, the ratio μ/D decreases with ionic strength. Consequently the maximum plate number decreases as well.[9,10] The magnitude of this reduction depends on the relative permittivity and the viscosity of the solvent. In comparison with other organic solvents, PC seems to be as favorable as water in this respect and much more favorable than commonly used methanol and acetonitrile.[10]

In previous work, we observed changes in the migration sequence of amines in PC, compared to water and a number of other organic solvents.[2] To get insight into the cause of such effects, we systematically investigate in the present paper in PC the two parameters decisive for the electrophoretic migration: the actual ionic mobilities (that of the fully charged ions) and the pK_a values in comparison to water. The aliphatic amines shown in Figure 1 are selected as analytes. All compounds are strong bases in water, with pK_a values around 10. The pK_a* values in the organic solvent were determined by measurement of the effective mobilities in BGEs with different pH*. The pH* scale established here is based on the conventional pK_a* values[11] of certain acids and bases as pointed out in a previous publication.[7,8] Conventional pH* values of the BGEs are adjusted by mixing these acids or bases with their respective salts, according to the Henderson−Hasselbalch equation. In this way, systematic errors (due to liquid junction potentials and aqueous reference buffers) that take place in measuring the buffering pH* by the use of a glass electrode are excluded.

As the majority of the analytes are non-UV absorbing (and because of the optical cutoff of PC at 230 nm), the electrical conductivity detector was used in connection with the UV absorbance detector. The conductivity detector has the further advantage that there is no restriction concerning the light absorbance of the buffering electrolytes used for the BGEs.

EXPERIMENTAL SECTION

Instrumentation. All experiments were carried out with a ^{3D}CE instrument (Agilent Technologies, Palo Alto, CA) with fused-silica capillaries of i.d. 50 μm, o.d. 375 μm, total length 30.5 cm,

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Table 1. Conventional pH* and Composition of the BGEs Used for the Determination of the Mobilities of the Analytes

conventional pH*	composition	water content (%)
1.6	25 mM perchloric acid	0.06 (v/v)
16.95	50 mM butylamine/25 mM perchloric acid	0.06 (v/v)
18.04	250 mM acetic acid/ 25 mM tetraethylammonium acetate	0.18 (w/v)
20.04	2.5 mM acetic acid/ 25 mM tetraethylammonium acetate	0.18 (w/v)

and length to the contactless conductivity detector (CCD) 16.5 cm (Composite Metal Services Ltd., Hallow, England). The high-frequency CCD was laboratory-made; its construction was described previously (see, for example, refs 2 and 12). The detector cell together with the electronics is built into the cassette of the ^{3D}CE instrument and has a compact construction. Output signal is processed by the HP3900E A/D converter (Agilent Technologies) and analyzed using ChemStation software. The capillary column passes through both the conductivity cell and the alignment of the UV diode-array detector. The distance between the two detector cells is 5.5 cm. The employed configuration easily enables one to use both detection techniques simultaneously.

Chemicals. Propylene carbonate (99%), tetraethylammonium acetate, tetrahydrate (99%), butylamine (99.5%), dipropylamine (99%), *N*-dodecylamine (98%), *N*-methylcyclohexylamine (98%), and tetraphenylphosphonium tetraphenylborate (p.a.) were obtained from Fluka (Buchs, Switzerland). Acetic acid, glacial (99.7%), *N*,*N*-dimethyldodecylamine (97%), and propylamine hydrochloride were obtained from Aldrich (Steinheim, Germany). Anthracene and perchloric acid (70−72%, both analytical grade) were obtained from Merck (Darmstadt, Germany). Amitriptyline hydrochloride, nortriptyline hydrochloride and doxepin hydrochloride were obtained from Sigma (Steinheim, Germany).

Procedures. The background electrolytes used are specified in Table 1. The pH* values of the buffers are those calculated according to the Henderson−Hasselbalch equation. The p*K** values of 19.04 [13] for acetate and of 16.95 for butylammonium[13] in PC are taken from the literature. According to the literature, perchloric acid is a strong acid in the nonaqueous solvent (pK_a* of $HClO_4$ is 1.3 [14]). However, a small amount of water leads to the presence of H_3OClO_4, which is fully dissociated in propylene carbonate.[14] Due to the presence of water traces in the BGEs (see Table 1), full dissociation of perchloric acid can be assumed under the present conditions.

The actual and the effective mobilities of the analytes were measured in duplicate by CZE in the usual way from their velocity and the electric field strength. The span was typically within 0.05 $\times$ 10^{-9} m^2 V^{-1} s^{-1}. We further use the term mobility units for 10^{-9} m^2 V^{-1} s^{-1}. The mobilities were corrected for the EOF.

The mobility of the EOF was determined with a pressure-mediated dual-ion technique as described in our previous paper.[15] The precision of the values measured in duplicate, expressed by the span, is typically 0.02 mobility unit.

The solubility of free bases in water and PC, respectively, at saturation was measured by CZE as follows: to 100 μL of solvent in an Eppendorf vial, an excess of amine (sufficient to ensure formation of two phases) was added. The closed vial was placed in an ultrasonic bath for 10 min at 25.0 °C. After phase separation, the solvent phase was diluted (10 or 100 times for water or PC, respectively) and an aliquot injected into the CZE column with conductivity detection. The BGE for determination of the concentration of the amine in the solvent at saturation contained 0.02 mol L^{-1} perchloric acid in *N*,*N*-dimethylacetamide as nonaqueous solvent. Separation voltage was 10 kV, with typical current ~9 μA. All samples were run in duplicate, and the solubility was calculated from the sample peak area by the aid of a calibration curve in the usual way.

Curve fitting was carried out by Origin 6.1 software (OriginLab Corp., Northampton, MA).

RESULTS AND DISCUSSION

Mobilities. In Table 2, the actual mobilities of the analytes in solutions of perchloric acid in PC as solvent at the ionic strength of 25 mmol L^{-1} are presented. It can be assumed that all analytes are present as fully protonated ammonium ions in this acidic solution. In the same table, the absolute ionic mobilities (at zero ionic strength) in water are given (for the drugs Amitriptylin, Nortryptylin, and Doxepin, no such values were found in the literature). For a comparison of the mobilities in both solvents, one must take into account that the presence of the counterions lowers the mobilities. The dependence of the mobility of ion, *i*, on ionic strength is expressed by the limiting equation according to Debye, Hückel, and Onsager (see, for example ref 16) extended by Falkenhagen and Pitts,[17−19] which is for uni-univalent electrolytes given by

$$\mu_i = \mu_{0,i} - \left[\frac{8.204 \times 10^5}{(\epsilon_r T)^{3/2}}\mu_{0,i} + \frac{4.275}{\eta(\epsilon_r T)^{1/2}}\right]\frac{\sqrt{I}}{1 + 50.29a(\epsilon_r T)^{-1/2}\sqrt{I}} \quad (1)$$

where the suffix 0 indicates zero ionic strength; the mobility is in units of 10^{-9} m^2 V^{-1} s^{-1}; ϵ_r and η are dielectric constant (the relative permittivity) and the viscosity (in Pa.s), of the solvent, respectively; T is the absolute temperature; and I is the ionic strength in mol L^{-1}. a (in Å) is the distance of closest approach between ion and counterion. When the ions are considered as point charges ($a = 0$), the denominator of the term outside the brackets in eq 1 is unit, and the mobility decreases linearly with the square root of I by the so-called Onsager limiting slope of the

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Table 2. Actual Mobilities, μ_{act}, at 25 mmol L^{-1} Ionic Strength, and Their Products with Solvent Viscosity, η, in PC and Water. Temperature 25 °C[a]

	PC		H_2O		
analytes	μ_{act}	$\mu_{act}\eta_{PC}$	μ_0	μ_{act}	$\mu_{act}\eta_{H_2O}$
propylammonium	11.25	28.3	43.0	38.3	34.1
dipropylammonium	11.03	27.7	33.1	28.6	25.5
methylcyclohexylammonium	10.66	26.8	33.5	29.0	25.8
dodecylammonium	7.46	18.8	24.7	20.5	18.2
dimethyldodecylammonium	8.39	21.1	24.2	20.0	17.8

[a] Mobilities are given in 10^{-9} m^2 V^{-1} s^{-1}, and products are in 10^{-12} nV^{-1}. In PC, the actual mobilities, μ_{act}, were measured by CZE. The absolute mobilities, μ_0, in water were taken from the literature.[34] The actual mobilities in water at ionic strength of 0.025 mol/L were calculated according to ref 22 (see text for details). Viscosity of water is 0.8904×10^{-3} Pa·s and of PC 2.513×10^{-3} Pa·s.[35]

line (see. for example, the discussion given in refs 7, 8, 20, and 21).

Insertion of the appropriate physical constants of water at $T = 298$ K enables the calculation of the mobilities of the analytes at 0.025 mol L^{-1} ionic strength from the absolute mobilities (which are known from the literature). The resulting actual mobilities are given in Table 2, also. They were obtained taking a factor of 2.4 as the value for $50.29a(\epsilon_r T)^{-1/2}$ in the denominator of eq 2, as described by Li and co-workers[22] for similar ammonium ions.

The actual mobilities in PC are significantly lower than in water. For a particular ion, they differ by a factor of ~3. In a first approach, this reduction can be interpreted by the different frictional resistance acting on the moving ions. This extension of Walden's rule leads to a surprisingly good accordance of the normalized mobility (that corrected by the solvent viscosity) in water and PC (see Table 2). The extended Walden products for a particular ion vary only between 3 and 17% (note for comparison that the mobilities vary by up to 330%). This accordance is not obvious, because Walden's rule is based on the oversimplification of hydrodynamic friction acting on the ion moving as a spherical, rigid particle in a continuum with a viscosity equal to its macroscopic viscosity. The change of the structure of the solvent in the vicinity of the ion (so-called structure-making and -breaking effects), changes in ionic radii due to solvation in the different solvents, or the microdynamics of motion (causing, for example, dielectric friction[23]) are not regarded in this model.

According to the Henderson−Hasselbalch relation the effective mobility depends on the actual mobility and the pK_a of the analyte, and the pH of the BGE by

$$\mu_{\mathrm{eff},i} = \frac{\mu_{\mathrm{act},i}}{1 + 10^{\mathrm{pH}^* - \mathrm{p}K_{a,i}^*}} \qquad (2)$$

The typical titration curves for mobility versus pH* are indeed followed by the experimental data, as shown for two examples in Figure 2. It allows derivation of the pK_a value: it is the pH at the inflection point of the curve. The resulting pK_a* values of the solutes are given in Table 3.

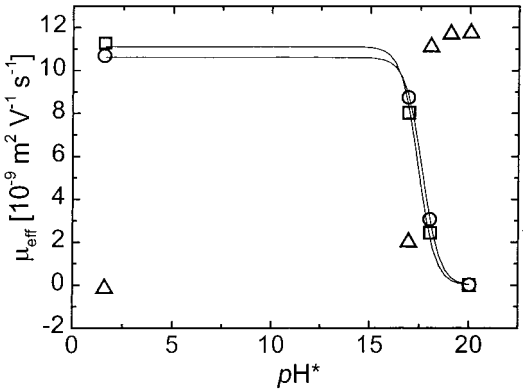

Figure 2. Typical plot of mobility as a function of the conventional pH* of the BGE. The BGE composition is given in Table 1. The curves are fitted according to the Henderson−Hasselbalch relation (see, for example, eq 2): □, propylamine; ○, methylcyclohexylamine; Δ, EOF.

Table 3. pK_a* Values of the Analytes (as Cation Acid) in PC Obtained by Fitting the Measured Mobilities to Eq 2[a]

analyte	pK_a*	analyte	pK_a*
PA	17, 42	DA	17, 51
DPA	17, 65	AMI	17, 67
MCHA	17, 64	NOR	17, 58
DMDA	17, 71	DOX	17, 62

[a] The pK_a* values are based on the conventional pH* scale (for details, see text). The abbreviations are according to Figure 1.

pK_a Values. The change of the pK_a values when transferring the protolysis equilibrium of a cation acid and its conjugated base according to

$$HB^+ = H^+ + B \qquad (3)$$

from water to an organic solvent reflects the particular stabilization of all three particles involved in the reaction: the proton, the cation acid HB^+, and the uncharged particle, the molecular base, B. This change can be interpreted by the concept of the transfer activity coefficient and the medium effect (see, for example, refs 24−28).

The concept is based on the standard free energy, ΔG_t^0, of transferring 1 mol of individual species, *k*, from water, W, to

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solvent, S. It is negative when the particle is more stable in S, and positive when it is better stabilized in W. The total standard free energy of transfer is composed from the contributions of the individual species involved in equilibrium. The equilibrium constant is connected to ΔG_t^0 in the usual way as

$$\Delta G_t^0 = -RT \ln K_a \quad (4)$$

Based on this concept, the change of the pK_a values of the cation acid can be related to the transfer activity coefficients, ${}_m\gamma_k$ or the medium effects (the logarithm, log ${}_m\gamma_k$) of the individual species according to

$$\Delta pK_a = pK_a^S - pK_a^W = \log\left[\frac{{}_m\gamma_{H^+}\,{}_m\gamma_B}{{}_m\gamma_{HB^+}}\right] = \log {}_m\gamma_{H^+} + \log {}_m\gamma_B - \log {}_m\gamma_{HB^+} \quad (5)$$

It can be seen that the change in pK_a depends on (i) the basicity of the solvent compared to water, reflected by log ${}_m\gamma_{H+;}$ (ii) the stabilization of the protonated base, the cation HB^+, expressed by log ${}_m\gamma_{HB+;}$ (iii) the stabilization of the free, molecular base, expressed by log ${}_m\gamma_B$.

(1) The Total Medium Effect. The pK_a* values (Table 3) are derived from the mobilities measured in the BGEs at different pH* by a curve fit to eq 2. The error for the determination of the pK_a* values was in the range of 0.04 pK unit (expressed as $\sqrt{C_{ii}\chi^2}$, where C_{ii} is the diagonal element of the variance−covariance matrix). All analytes have similar pK_a* values, between 17.4 and 17.7, irrespective of their degree of substitution on the nitrogen group. This is in some contrast to water, where the tertiary aliphatic amines with dimethyl substitution are slightly less basic than primary and secondary amines (see below). It should be noted that the range of pK_a's even in water is quite narrow; it lays within 1.5 pK units only. However, PC seemingly levels this small difference in basicity between amines (see also ref 29).

Comparison of the pK_a* values in Table 3 with the pK_a values in water shows that the cation acids are significantly less acidic in PC. For primary and secondary amines (pK_a in water for DA is 10.63,[30] for PA 10.69,[31] for DPA 11.0 [31]) the corresponding ΔpK_a values for DA, PA, and DPA are 6.9, 6.7, and 6.7 pK units, respectively. For the tertiary DMDA, ΔpK_a is ∼8 units, taking a value of 9.5 for a tertiary, aliphatic, dimethyl-substituted amine in water.[30] These ΔpK_a values are in good accordance with values found for cation acids derived from ring-substituted pyridines[29] and pyridine *N*-oxides.[32]

Table 4. Solubilities, **Φ**, at Saturation of Free Bases in Water (W) and PC, Respectively[a]

analyte	Φ^W	Φ^{PC}	log Φ^W/Φ^{PC}
DPA	3.47×10^{-1} [b]	3.26×10^{0}	∼−1
MCHA	1.65×10^{-1}	1.10×10^{1}	<−2[c]
DA	2.22×10^{-4} [b]	1.62×10^{-3}	∼−0.9
DMDA	7.40×10^{-3}	8.86×10^{-2}	∼−1

[a] The solubilities are given in mol L^{-1}. The differences of log Φ^W/Φ^{PC} for determinations in duplicate was <0.1. [b] From ref 36. [c] Full miscibility was observed at a 100-fold excess of the analyte over PC. Due to practical reasons, a possible miscibility gap was not determined.

According to eq 5, the ΔpK_a for the amines is composed from the individual contributions of the medium effect on the proton, the molecular base, and the ammonium ion. These contributions are discussed in the following.

(2) Medium Effect on the Proton, log ${}_m\gamma_{H^+}$. We found two values for the standard free energy of transfer, ΔG_t^0, for the proton (50 kJ mol^{-1},[6] 45.7 kJ mol^{-1} [14]) from water to PC in the literature. Accordingly, PC is a much less basic solvent than water. The corresponding medium effect, log ${}_m\gamma_{H+}$, has the high value of +8.8 and +8, respectively (the value was calculated according to eq 4). It reflects the much lower stabilization of the proton in PC. It is in the same order as the pK_a shift of the cation acids under consideration; however, it is not the only effect that determines the position of the acid−base equilibrium.

(3) Medium Effect on the Molecular Species, log ${}_m\gamma_B$. A value for the medium effect on the molecular species, B, can be derived from its solubility, Φ_B, at saturation in the different solvents,[33] according to

$$\log {}_m\gamma_B = \log(\Phi_B^W/\Phi_B^S) \quad (6)$$

Intuitively one accepts the assumption that the molecular species is better stabilized in the organic solvent, which would result in a larger solubility of the organic amines in PC. Unfortunately, only few quantitative data about solubilities of the present analytes in water are available, and for PC, the situation is even worse. Thus, we determined the solubilities experimentally by CZE for those analytes that are available as free bases (Table 4). As the ΔG_t^0 values were given on the molar scale, we express the solubility on this scale as well.

In PC, the solubility is larger by 1 order of magnitude or more, compared to water. Thus, the medium effect on B is <−1; the molecular species contributes to the pK_a with a decrease by the same values (see eq 5). The medium effect on the molecular base (taking a value ∼−2 for log ${}_m\gamma_B$) together with that on the proton (log ${}_m\gamma_{H+}$ ∼+8) reaches ∼+6. The difference to the total medium effect (ΔpK_a is ∼7−8) is thus about 1 to 2. This difference should stem from the remaining contribution brought by the cationic species, HB^+.

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(4) Medium Effect on the Ammonium Cation, log $_m\gamma_{HB^+}$. No direct values are available from the literature for the medium effect on the present ammonium cations. However, we can get an estimate for the magnitude of the effect by comparison with tetraalkylammonium ions, for which data are known. ΔG_t^0 from water to PC for tetramethylammonium, tetraethylammonium, tetrapropylammonium, and tetrabutylammonium is −11, −13, −22, and −31 kJ mol^{-1}, respectively.[6] The negative sign of all values indicates that these ions are more stable in PC than in water, a finding that is in contrast to the proton. It follows that the common assumption that a solvent stabilizing the proton stabilizes the cation acid as well (often taken to explain the lower shift of the pK_a values of cation acids compared to neutral acids) is too simplifying. However, the negative value of ΔG_t^0 on HB^+ contributes to a reduction of the acidity of the cation acids.

We assume that the analytes behave similar to tetraalkylammonium with short alkyl chains, because for both types of ions the positive charge is not such strongly shielded as it is in long-chained symmetrical quaternary ammonium ions. Due to the larger charge density on N^+ for the present protonated analytes, ΔG_t^0 could be expected in the lower range of the values given above. Thus, we take a value of ∼−10 kJ mol^{-1} and a medium effect of ∼−2 or lower for the HB^+ species of the analytes. Indeed, it can be seen that this value reasonably completes the sum of the contributions of the single species to the pK_a shift of 7−8 units.

CONCLUSIONS

(i) The actual ionic mobilities of the ammonium ions in PC are strongly reduced compared to water. This reduction correlates fairly with the viscosity of the solvents. This is not usual, because especially ionic migration in water is often determined by structural effects of the solvent in the vicinity of the ion (solvation, microviscosity, orientation of the solvent molecules in the field of the ion, etc.) rather than by bulk phase properties (e.g., macroviscosity).

(ii) The pK_a values of the analytes increase in PC by about 7−8 units compared to water. This increase can be assessed to the contributions stemming from (a) the destabilization of the proton in PC. The corresponding contribution to ΔpK_a is ∼+8 units. (b) The stabilization of the cation acid HB^+ in PC, contributing with ∼−2 pK_a units or less. (c) The stabilization of the molecular base, B, in PC, reflected by the better solubility in the organic solvent, contributing with ∼−2 pK_a units and more. These individual effects together result in a ΔpK_a of ∼8 units, which is close to the experimentally determined shift. The difference of these two values might be caused by the overestimated high literature value for the medium effect on the proton.

(iii) The most pronounced contribution to the shift of the pK_a* values of the cation acids is caused by the significantly lower basicity of PC compared to water. The effects on the pK_a* shift due to the higher solubility of B in the organic solvent and the better stabilization of HB^+ seem to compensate each other.

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