Enthalpies of proton transfer of aminoalkylsulphonic acids in methanol–water mixtures by direct calorimetry

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Abstract

Enthalpies of proton transfer in methanol–water mixtures (0–90 wt% methanol) of 3-(*N*-morpholino)propanesulphonic acid (Mops), *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulphonic acid (Bes) and *N*-(2-hydroxyethyl)piperazine-*N'*-2-ethanesulphonic acid (Hepes) have been measured by direct calorimetry at 25°C. The results thereof are compared with the standard enthalpies for the protonation of the base tris(hydroxymethyl)aminomethane (Tris) and are discussed in terms of an adaptation of classical electrostatic formula and the three-dimensional structure in methanol–water mixtures as determined by molecular dynamic simulations. © 1999 Elsevier Science B.V. All rights reserved.
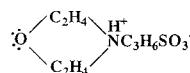
Keywords: Enthalpy of proton transfer; 3-(*N*-morpholino)propanesulphonic acid; *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulphonic acid; *N*-(2-hydroxyethyl)piperazine-*N'*-2-ethanesulphonic acid; Tris(hydroxymethyl)aminomethane; Methanol–water; Calorimetry; Born charging; Zwitterion; Three-dimensional structure; Ampholytes; Protonated amines; *N*-substituted amino acids
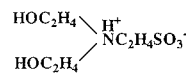
1. Introduction

This research work is a continuation of a series, which hopes to provide a better understanding of the microscopic structure of molecular liquids and solutions. The enthalpies of proton transfer of amines [1], hydroxy amines [2] in methanol–water mixtures by direct calorimetry, and the relation of solvent heats of mixing to the enthalpies of proton transfer [3] have been reported. We have now extended our study to include chemical systems of zwitterionic acids by examining the ampholytes 3-(*N*-morpholino)propane-sulphonic acid (Mops), *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulphonic acid (Bes) and *N*-(2-hydroxyethyl)piperazine-*N'*-2-ethanesulphonic acid (Hepes).

These compounds, primarily protonated amines or *N*-substituted amino acids, are compatible with many media of biochemical importance. Mops could be regarded as the closed ether ring, hydroxyl-free parent compound of the series:
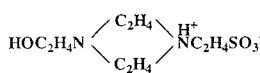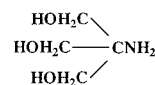

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The results reported here are direct measurements of the standard enthalpy change for the process:

$$B + H^+ = BH^+ \qquad (1)$$

in methanol–water mixtures of varying composition (0–90 wt% CH_3OH) where B represents Mops, Bes, Hepes and Tris in Eq. (1). The methanol–water solvent system was chosen because physicochemical data are available from several independent sources and because measurements have also been reported on the reaction $H^+(solv) + OH^-(solv)$ over the whole composition range [4] enabling data for Eq. (1) to be deduced from the experiment in which Mops, Bes and Hepes were titrated against an alkali.

It is proposed that the change of the measured standard enthalpy of reaction with mole fraction of methanol at infinite dilution provides information about the relative sizes of the solvent regions influenced by the charged species in the equilibrium.

2. Experimental

2.1. Materials

Deionized water was obtained from a Millipore system. The water had a specific conductance of less than $1 \times 10^{-6} \, S \, cm^{-1}$ and was stored in a closed polyethylene container equipped with a CO_2 trap and facilities for flushing with purified nitrogen. Methanol (BDH AristaR grade) was used without further purification.

Aqueous hydrochloric acid (BDH AristaR grade) was prepared by dilution to an initial concentration of approximately 1 molal and then standardized gravimetrically using AnalaR grade silver nitrate. Gravimetric analysis was conducted before and at the completion of the experiment to monitor any changes in the concentration of the stock solution. The standard deviation from both series of determinations was 0.03%. The change in concentration was 5×10^{-7} mol Cl^-/g HCl of stock solution which was negligible.

Aqueous sodium hydroxide (BDH AnalaR grade) was used to prepare the carbonate free stock solution described by Bates [5]. Standardized hydrochloric acid was used to standardize the sodium hydroxide solution by weight titration. The standard deviation for the five determinations was 0.06%. Tris-(hydroxymethyl)aminomethane (SigmaUltra >99.9%) was dried in a vacuum oven (50 mm Hg) at $100°C$ for 3 h. Mops (Sigma) was recrystallized twice from 80 wt% ethanol (BDH AnalaR grade) and dried under vacuum for 4 h at $80°C$. The purified compound was assayed by titration with the carbonate free NaOH solution. The results obtained for three samples averaged 99.9%. Bes (Sigma) was recrystallized twice from 80 wt% ethanol and assayed by formal titration with the carbonate free NaOH solution. The results obtained indicated an average purity of 99.9%. Hepes (SigmaUltra >99.9%) was used without further purification and assayed 99.9% when titrated with carbonate free NaOH solution. The chemicals used in this investigation were stored in a desiccator over drierite for at least 12 h before use.

All solutions were prepared by weight and deaerated with purified nitrogen. All weighings were corrected for buoyancy.

2.2. Measuring equipment

The enthalpies of the reaction were measured with a microcalorimeter (LKB 2277 Bioactivity Monitor) equipped with an external thermostatic water circulator (LKB 2219 Multi-temp II) and a pair of peristaltic pumps (Jublie Perpex 10046). Electrical calibrations were made prior to each reaction at $25°C$. Temperature control and precision; reproducibility and accuracy of results, etc.; and the use of Tris as a calorimetric standard for chemical calibration are described in [1]. The measurement technique used was the flow-mix mode [6].

2.3. Experimental procedure

The calorimeter was energized and equilibrated for 24 h before any measurements were made. The calibration of the peristaltic pumps, flow rate of reactants, stability of base-line and operation of the pumps during the measurement of the enthalpy of reaction are described in [1]. To ensure constancy of flow rates, the peristaltic pumps were subjected to a further electronic calibration by monitoring the built-in tachnogenerator frequency by means of a Philips PM 6612 counter/timer after a warm-up period of 2 h. A flow

rate of 9.8 ± 0.2 ml h^{-1} was finally achieved enabling the base-line stability to be better than $0.1\,\mu$W. The sequence employed during the measurement of the enthalpy of the reaction was similar to earlier studies [1]. Flow rates were checked at the beginning and at the end of the experiment and the results obtained usually differed by no more than $5\,\mu$W for the reaction.

Optimal working concentrations for Mops, Bes, Hepes and Tris were 0.04 and 0.01 mol dm^{-3} for hydrochloric acid and sodium hydroxide [1].

Calculations with these concentrations, after allowing a loss of 1.8 pK units for the dielectric constant effect in 90% (w/w) methanol [7] show that an extent of reaction exceeding 99% is reasonably assured for all bases having an aminium ion with a thermodynamic pK_a in aqueous solution greater than 5.8. This condition is met by all the ampholytes in this work. The experimental results are given in Tables 1 and 2 and are represented graphically in Fig. 1.

Table 2
Values of dΔH^0/dx and $[(r_{BH^+})^{-1} - (r_{H^+})^{-1}]$ calculated from the slope of $[(1-LT)/D]^a$ vs. methanol mole fraction and Eq. (2) in the water-rich domain (W) and methanol-rich domain (M) at 25°C

Compound	(dΔH^0/dx)[b]		$[(r_{BH^+})^{-1} - (r_{H^+})^{-1}]$[c]	
	(W)	(M)	(W)	(M)
Tris	−23.5	−34.0	1.691	2.447
Mops	−21.3	−0.66	1.530	0.056
Bes	−29.1	3.57	2.093	−0.234
Hepes	−35.8	6.24	2.579	−0.408

[a] Data from Ref. [8] was used to find the best fit for L and D in the Abegg expression: $D=D_0\exp(-LT)$.
[b] kJ.
[c] 10^{10} m^{-1}.

3. Results and discussion

Both the electrostatic and molecular-equilibrium concepts have been used by researchers to interpret

Table 1
Standard enthalpy of reaction (1) in methanol–water mixtures

Wt% MeOH	x MeOH	$-\Delta H^0$ (kJ mol^{-1} at 25°C)			
		Tris [1]	Mops[a]	Bes[a]	Hepes[a]
0	0	47.55	20.90	24.31	22.54
		±0.11	±0.17	±0.14	±0.30
10	0.0588	48.44	21.85	31.18	26.39
		±0.15	±0.25	±0.14	±0.13
20	0.1232	49.90	25.65	32.49	26.88
		±0.22	±0.20	±0.18	±0.12
30	0.1942	51.16	26.93	34.28	28.03
		±0.20	±0.23	±0.10	±0.19
40	0.2726	49.36	29.23	31.70	30.11
		±0.30	±0.15	±0.12	±0.14
45	0.3151	48.92	28.16	–	–
		±0.21	±0.14	–	–
50	0.3599	48.04	27.40	29.62	25.43
		±0.20	±0.13	±0.16	±0.19
55	0.4073	47.65	27.11	–	–
		±0.16	±0.11	–	–
60	0.4575	47.73	26.38	27.62	24.61
		±0.19	±0.11	±0.16	±0.10
70	0.5674	47.04	25.18	25.29	24.76
		±0.20	±0.13	±0.14	±0.22
80	0.6922	47.72	24.35	24.05	23.67
		±0.23	±0.15	±0.11	±0.11
90	0.8350	50.51	24.44	23.48	22.53
		±0.22	±0.23	±0.15	±0.15

[a] Data from Ref. [4] was used to calculate $-\Delta H^0$ for the protonation of Mops, Bes and Hepes.
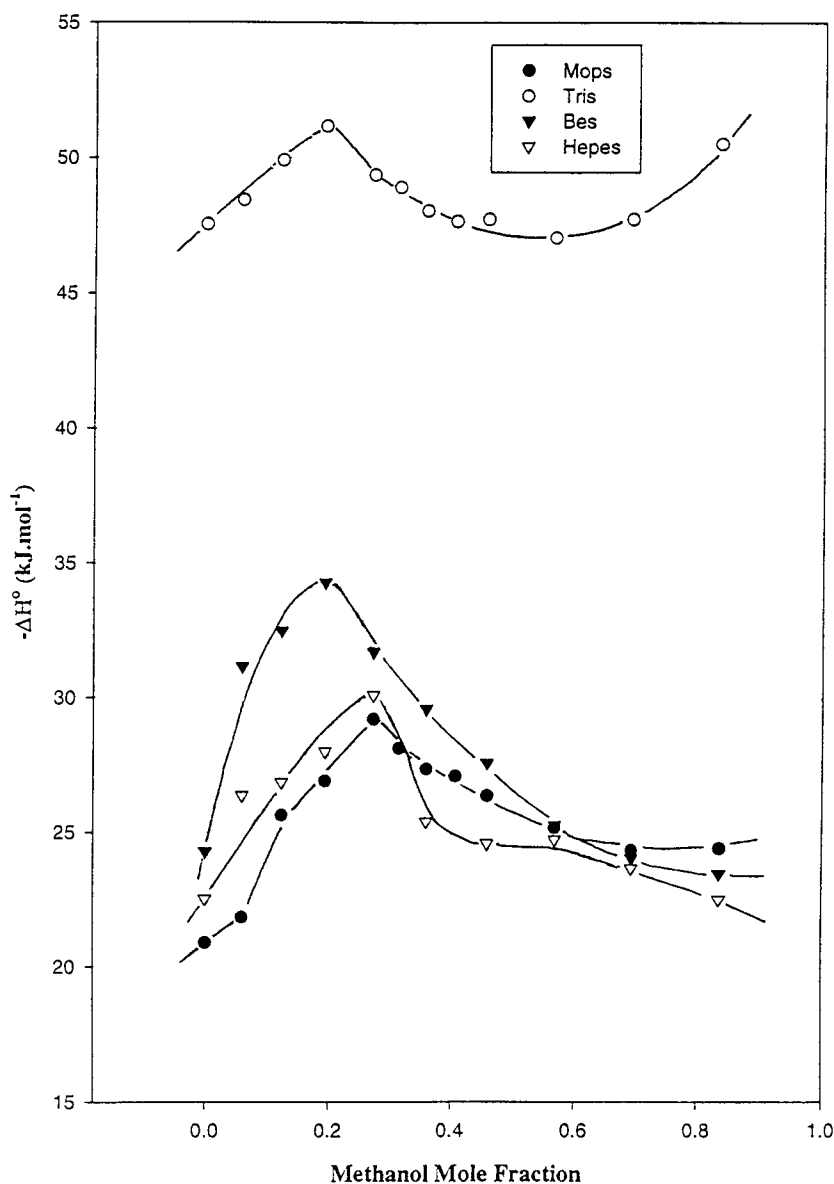
Fig. 1. $-\Delta H^0$ for the protonation reaction (Eq. (1)) in methanol–water mixtures at 25°C for the animoalkylsulphonic acids.

the thermodynamic data for amines studied in mixed solvents.

Grunwald et al. [9] showed that the thermodynamics of solvation of ions may be separated into a term characteristic of an identical uncharged ion plus an electrostatic part. Experimental data showed that the electrostatic part becomes negligible for large ions.

The Gibbs function for the transfer of the solvated proton and ions from water to methanol–water has been treated successfully as an electrostatic process followed by solvent-exchange at the solvated proton [10–12]. This applies to low mole fractions of methanol. At high mole fractions of methanol, multiple substitution of water molecules in $H^+(H_2O)_4$ by

CH$_3$OH molecules occur and the simple treatment is no longer applicable. The basic underlying structural patterns appear to be largely determined by that preferred by the dominant species in these binary mixtures; in particular, it has been found that the number of nearest neighbours for both water and methanol decrease by one in going from water-rich to methanol-rich solutions [13]. The competition for H-bond sites can be seen to play an important role in affecting the nature of the short-range order around molecules of both species.

There have been very successful non-electrostatic approaches to the problem of ion solvation in aqueous, non-aqueous and mixed solvents as well [14–25]. However, Lilley [26] has shown recently that major contributions to solvation properties of zwitterionic amino acids arise from electrostatic sources and have nothing to do with "structural" properties per se.

3.1. Aminoalkylsulphonic acids

The standard enthalpy change for reaction (1) is due to the production of a solvated aminium ion and the disappearance of a solvated proton and an uncharged amine molecule. We assume that part of the amine structure remote from the charge centre in the ion does not contribute to the enthalpy of the reaction since it is conserved when the reaction takes place. The measurements are effectively at infinite dilution. Changes in solvent composition are accompanied by changes in dielectric constant and so enable the electrostatic part ΔH_{el}^0 of the enthalpy change to be investigated. For this purpose we may assign to each ion a radius r which defines a conducting sphere, outside of which there may be an insulating annular shell and the solvent which is assumed to behave as a continuum having its bulk dielectric properties. This type of model has provided successful interpretations of a number of experimental studies, notably those of Grunwald et al. [9,14]. Over the whole composition range of methanol–water solvent it is clear from the experimental results (Fig. 1) that complex changes occur in these radii. Under conditions of limiting dilution of one solvent in the other, changes in these radii with solvent composition will be at their minimum and it may be acceptable to assume that, in the limit, they remain constant. Adapting the simple Born charging expression [9–12,19,27,28] to this situation,

we may write

$$
\lim_{x \to 0} (\mathrm{d}\Delta H_{el}^0 / \mathrm{d}x)
$$
$$
= \frac{Ne^2}{8\pi\epsilon_0} [(r_{BH^+})^{-1} - (r_{H^+})^{-1}] \frac{\mathrm{d}}{\mathrm{d}x} [(1 - LT)/D], \tag{2}
$$

where L and D are constants.

3.2. Water-rich mixtures

Using published data [8] and finding the best fit for L and D in the Abegg expression [28] $D = D_0 \exp(-LT)$, the function $(1 - LT)/D$ (Eq. (2)) at 25°C is a very good approximation of a linear function of methanol mole fraction from 0 to 0.45 with a slope of -0.020. It does not display the reversals of sign of $\mathrm{d}\Delta H^0 / \mathrm{d}x$ seen in the experimental results for this group of ampholytes in Fig. 1. Consequently, the structures of the solvated ions (aminium and/or proton) must undergo important structural changes as the solvent is changed in the intermediate range of compositions. The experimental limiting slopes of ΔH^0 vs. x for Mops, Bes, Hepes and Tris in water-rich mixtures are listed in Table 2 together with the values for $(r_{BH^+})^{-1} - (r_{H^+})^{-1}$.

The limiting slopes for Tris and the ampholytes are negative, hence $(r_{BH^+})^{-1} - (r_{H^+})^{-1}$ have positive values, which range from 1.530×10^{10} to 2.579×10^{10} m^{-1}. The positive values imply that the solvated proton is the larger ion, and influences more of the solvent than the aminium ion. Closer observation of the data indicates that the solvated proton is much larger in the zwitterions viz. Bes and Hepes than in Tris. In methanol–water mixtures the competition for H-bond sites play an important role in affecting the nature of the short-range order around molecules of both components of the mixture i.e. the value of r_{H^+}. The zwitterionic nature [26] of the compounds studied plays a key role in influencing the r_{H^+} value.

The number of H-bond sites for Hepes and Bes is 4 and 5, respectively (see structures). Even though Hepes has a lower number of H-bond sites available, its structure lends itself to the formation of a large cavity. Cavity formation [25] leads to restructuring of the solvent molecules, hence a lower $-\Delta H^0$ value compared to that of Bes. The restructuring in turn

enhances structure around the proton leading to a larger r_{H^+} value for Hepes.

In the case of Mops, the number of H-bond sites is even lower than that of Hepes (see structure). The size of the molecule is smaller in comparison with Hepes, hence its influence in terms of cavity formation would be of a lesser order.

The hydroxyl groups in Bes can be seen to play an even greater role in solute–solvent interaction than cavity formation as indicated by comparing r_{H^+} and corresponding $-\Delta H^0$ values of Mops and Bes. This can be expected while considering the relative sizes of Mops and Bes which can be seen to be similar. The large r_{H^+} values in water-rich mixtures could also be accounted for by considering the fact that methanol takes on the H-bond character of water [13], i.e. methanol molecules in water-rich solutions tend to be double H-bond acceptors hence promoting "structuring" [29].

The protonation of Tris is about 20 kJ more exothermic when compared to Bes, Hepes and Mops. Results obtained in this investigation display similar trends to that obtained earlier [1,2] with the reaction becoming more endothermic from Tris to Mops with variation in the number of hydroxyl groups in the order Tris< Bes<Hepes<Mops.

3.3. Maxima at 0.2 methanol mole fraction

Maximum exothermicity shown by Tris and Bes at approximately 0.2 methanol mole fraction are similar to earlier investigations [1,2]. This maxima is a result of the associated OH groups which maintain the water structure to higher concentrations.

3.4. Maxima at 0.3 methanol mole fraction

The maxima can also be interpreted as the point at which water is the most structured, i.e. 30 wt% MeOH. At this point, methanol is essentially completely hydrated. However, molecular dynamic studies [13] have shown that these strongly hydrated methanol molecules adopt specific positions that most readily accommodate ordering within their hydration cages. This in conjunction with the cavity formation [25] and zwitterionic nature of the ampholytes [26] influence the resulting shift in maxima, i.e. 0.3 methanol mole fraction of both Mops and Hepes.

3.5. Methanol-rich mixtures

Between 0.55 and 0.80 methanol mole fraction, the function $(1-LT)/D$ at 25°C deviates slightly from linearity. An estimate of the slope gives a value of -0.017 in the methanol-rich domain of 0.55–1.0 mole fraction. In the methanol-rich mixtures, the limiting slopes of $-\Delta H^0$ vs. x for Tris and Mops are negative. This requires $(r_{BH^+})^{-1} - (r_{H^+})^{-1}$ to have positive values implying that the solvated proton is the larger ion even in the methanol-rich mixtures and therefore would influence a similarly large region of the solvent as in water-rich mixtures. However, in the case of Mops, the size of the solvated proton is smaller implying that the extent of solvation of the proton occurs to a lesser degree in methanol-rich mixtures than in water-rich mixtures. Therefore, the solvation of the aminium ion and the proton is similar as indicated by the value of r_{H^+}. For Bes and Hepes, there is a complete reversal in trend with the limiting slopes being 3.57 and 6.24 kJ, and the quantity $(r_{BH^+})^{-1} - (r_{H^+})^{-1}$ having values of -0.234×10^{10} and -0.408×10^{10} ml^{-1}, respectively. Hence aminium ions influence more of the solvent than the proton.

Our results show that a maximum r_{H^+} value in water-rich mixtures usually results in a minimum r_{H^+} value in methanol for Mops, Bes and Hepes. This is consistent with our earlier studies [2].

In methanol-rich solutions [13], the water–water correlations are very pronounced even at longer range but methanol retains most of its pure liquid structure. This would suggest that the structural patterns of the mixture is dominated by methanol. This could explain the maximum and minimum r_{H^+} values obtained.

In the case of Tris the opposite holds true. This difference could be ascribed to the amphoteric nature of Mops, Bes and Hepes when compared to Tris.

4. Conclusion

We extended our study to include the acid–base properties of ampholytes so that a better insight could be gained into methanol–water interactions, solvent structure and its interaction with solutes in the complex process of solvation including preferential solvation.

Acknowledgements

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