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Influence of the distance between ionizable groups on the protonation behavior of various hexaamines

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A synthesis route for *N*,*N*,*N*′,*N*′-tetraaminoethyl-1,2-ethylenediamine, *N*,*N*,*N*′,*N*′-tetraaminopropyl-1,2-ethylenediamine, *N*,*N*,*N*′,*N*′-tetraaminopropyl-1,3-propylenediamine and *N*,*N*,*N*′,*N*′-tetraaminopropyl-1,4-butylenediamine is presented. These molecules differ from each other in the number of carbon atoms between the six amino groups. This results in different protonation behavior. Potentiometric titrations are performed in 0.1 M and 1.0 M KCl, and the six macroscopic protonation constants are obtained from these curves. An Ising model with a limited number of microscopic protonation constants and short-ranged pair interactions describes the protonation behavior quantitatively. The results are compared to those of other, similar molecules. The advantage of the Ising model over empirical relations such as the Taft equations is the more systematic approach with which the titration curves of more complex molecules can be described. The values for the Ising model parameters obtained here can be used to predict the protonation behavior of more complex, in particular larger, polyamines.

Introduction

In the past empirical relations have been developed to understand the protonation behavior of smaller molecules. These rest on the assumption that the individual pK (logarithm of dissociation constant) can be described with the pK' of the isolated group in question, and the sum of neighboring group contributions.[1] These latter corrections on the pK' have been derived empirically with Hammet and Taft equations.[2] The pK of an individual ionizable site is then calculated for a certain protonation state. To describe a potentiometric titration, the procedure must be repeated for all different protonation states of the molecule, and is therefore exclusively used for smaller molecules, typically with up to three acid–base sites. For the more complex polyelectrolytes the above approach becomes too difficult mainly because the number of pK calculations grows with $N2^{N-1}$ for N ionizable sites.

In parallel to these empirical Taft relations a different method has been developed to describe the ionization behavior of polyelectrolytes in terms of local charges.[3–7] An Ising model with pairwise interactions was used for this purpose. The Ising model also assigns to the individual groups in the system microscopic pK values (given that all other groups in the molecule are deprotonated) and extends it with interaction energies between pairs and triplets of protonated sites. The approach resembles the classical empirical method if only pair interactions between neighboring sites are taken into account. This assumption is justified if the interactions are sufficiently short-ranged.

The advantage of the Ising model is the more systematic parametrization of the problem; with a few parameters the macroscopic pK values can be calculated in a straightforward manner. Amongst the large variety of acid–base systems, the amines are the first candidate for a more thorough study with the Ising model, as there are only three different types of ionizable sites: primary (R–NH_2), secondary (R_2NH) and tertiary amines (R_3N). In the past the Ising model has already been successfully applied to small oligoamines,[8] poly(ethylene imines)[6,7] and poly(propylene imine) dendrimers.[9] From these previous studies a lot of information about pair and triplet interactions has already been obtained; only the microscopic protonation constants and their dependence on the chemical environment are still unresolved. These are however of great importance in future research in order to predict the protonation behavior for more complicated structures.

Therefore we present here the ionization behavior of a series of similar oligoamines and determine the microscopic or intrinsic protonation constants for the different chemical environments and ionic strengths. For that purpose three new molecules were synthesized with different spacer lengths between the ionizable sites, and titrations were performed at two ionic strengths. The macroscopic protonation constants are compared, and all differences in protonation behavior are directly related to the distance between the various amine groups. We believe that we demonstrate that the Ising model is a simpler approach to extract the same information on the intrinsic protonation constants than the empirical relations, which are more commonly used in the literature.

Ising model

The Ising model has been used quite extensively throughout the literature to describe the acid–base properties of various polyamines.[4,6–9] The model weighs all possible positions at which a proton can adsorb onto the molecule in terms of energy costs. All these so called protonation microstates are characterized with a set of site variables $\{s_1, \ldots, s_N\}$ where $s_i = 0$ if deprotonated and $s_i = 1$ if protonated. N is the total

number of ionizable sites. Under rather general conditions, the free energy F of formation of a given protonation state $\{s_1, \ldots, s_N\}$ can be expanded as

$$\frac{F(s_1, \ldots, s_N)}{kT \ln 10} = \sum_i (\mathrm{pH} - \mathrm{p}\hat{K}_i)s_i + \frac{1}{2}\sum_{i \neq j} \varepsilon_{ij}\, s_i\, s_j + \cdots \quad (1)$$

where kT denotes the thermal energy, pH is the common negative logarithm of the proton activity, $\mathrm{p}\hat{K}_i$ is the logarithm of the dissociation constant for site i, and ε_{ij} is the pair interaction parameter.

$\mathrm{p}\hat{K}_i$ reflects the energy needed to protonate site i considering all other groups are deprotonated. In the case of the hexaamines this would be the same as the intrinsic pK in the empirical Taft equations,[2] which covers the energy needed to protonate a particular site while other groups are deionized.

Higher order terms in the free energy of formation consist mainly of electrostatic interactions with other ionizable groups. Assuming short-range interactions the Taylor expansion reduces to pair interactions ε_{ij} only. It can be further simplified taking only pair interactions between neighboring sites into account. These nearest neighbor pair interactions (NNI) resemble Taft corrections for the polarity of substituents in these empirical relations.[10–12]

The potentiometric titration curve gives the mean average of all thermal expectations of the state variables corresponding to a certain degree of protonation θ, which can be determined with a partition function Ξ,

$$\theta = \frac{z}{N}\frac{\partial \ln \Xi}{\partial z} \quad (2)$$

where z is the activity of the protons ($\mathrm{pH} = -\log_{10} z$).

The more classical way of analysis of the titration curve in terms of macroscopic protonation steps is recovered by writing the partition function as a polynomial in the activity:[13]

$$\Xi = \sum_{i=0} \bar{K}_i z^i \quad (3)$$

with $\bar{K}_i$ the so called formation constants. The macroscopic pK_i values (logarithm of acidity constants) are given by $\mathrm{p}K_i = \log_{10} K_i$ where $K_i = \bar{K}_i/\bar{K}_{i-1}$ contains the average over all possible microstates, belonging to a certain protonation state.

Experimental

Synthesis

A schematic picture of the structure and the synthesis route for the different compounds studied (see Table 1 for nomenclature) is provided in Fig. 1. The notation (n,m), which is used to distinguish the different molecules, is correlated to the number of carbon atoms in between the sites: n stands for the spacer length between the two inner tertiary amines, and m relates to the number of carbon atoms between a tertiary and primary amine.

Table 1 Explanation of the abbreviations for the various hexaamines studied in the present article

Nomenclature	(n, m)
N,N,N',N'-tetraaminoethyl-1,2-ethylenediamine (PENTEN)	(2,2)
N,N,N',N'-tetraaminoethyl-1,3-propylenediamine) (PTETRAEN)	(3,2)
N,N,N',N'-tetraaminopropyl-1,2-ethylenediamine (TAPEN)	(2,3)
N,N,N',N'-tetraaminopropyl-1,3-propylenediamine	(3,3)
N,N,N',N'-tetraaminopropyl-1,4-butylenediamine	(4,3)

(n,m) stands for the hexaamine with n carbon atoms in the core unit, and m carbon atoms between the primary and tertiary amines (see also Fig. 1). The abbreviations PENTEN, PTETRAEN and TAPEN originate from ref. 17.

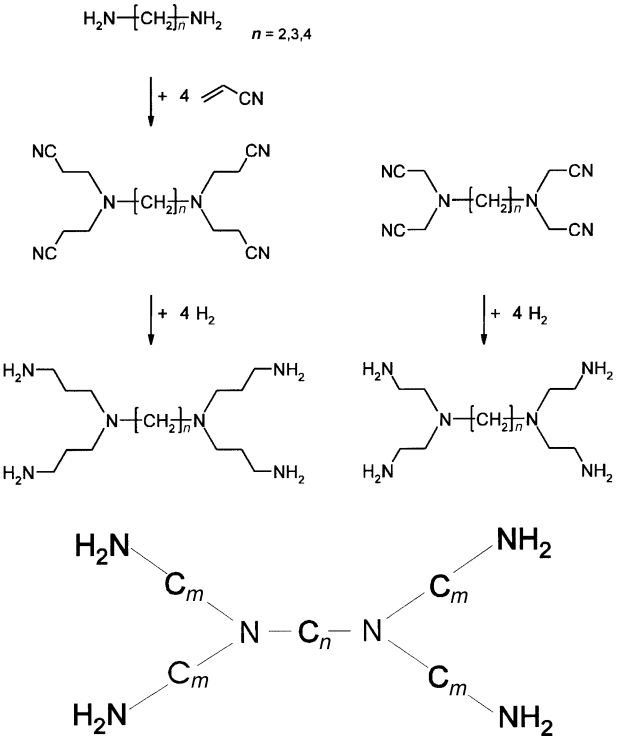

Fig. 1 The synthesis route is drawn for both the case of $m = 3$ (left hand side) and $m = 2$ (right hand side). The first step in the latter case has already been described in ref. 15. In this article the various molecules will be addressed with (n,m) and therefore a schematic overall picture of the hexaamines is shown below. n corresponds to the number of carbon atoms in the core unit between the tertiary amines, and m relates to the number of carbon atoms in the outer shell, between the tertiary and primary amines. The different combinations compared in the present article are listed in Table 1.

***m* = 3: *N*,*N*,*N*′,*N*′-tetraaminopropyl-1,2-ethylenediamine [compound (2,3)].** First, 1175 ml of water and 100 g of ethylenediamine (1.67 mol) are intensively mixed at 40 °C and within 90 min 443 g acrylonitrile (8.35 mol) is added. The reaction mixture is kept constant at 40 °C for 1 h and then heated for 2 h at 80 °C. Afterwards half of the water and the excess of acrylonitrile were evaporated under reduced pressure, and after cooling the precipitate was isolated by filtration. The residue was recrystallized from methanol–water mixture to yield 478 g of *N*,*N*,*N*′,*N*′-tetracyanoethyl-1,2-ethylenediamine (1.58 mol).

Yield: 94%. M.p.: 66 °C. ^{1}H-NMR: 2.53 ppm, t, 8H, –C$\underline{\mathrm{H}}_2$–CN; 2.72 ppm, s, 4H, N–C$\underline{\mathrm{H}}_2$–C$\underline{\mathrm{H}}_2$–N; (CDCl_3) 2.92 ppm, t, 8H, N–C$\underline{\mathrm{H}}_2$–CH$_2$–CN.

Then 400 ml h^{-1} of a mixture of 20 wt.% *N*,*N*,*N*′,*N*′-tetracyanoethyl-1,2-ethylenediamine and 80 wt.% *N*-methylpyrrolidone and 3500 ml h^{-1} ammonia were passed at 130 °C under 200 bar of hydrogen over 4 liters of a fixed bed catalyst of composition 90 wt.% CoO, 5 wt.% MnO and 5 wt.% P_2O_5 in a 5 liter fixed bed reactor.[14] Removal of the solvent under reduced pressure and fractional distillation resulted in *N*,*N*,*N*′,*N*′-tetraaminopropyl-1,2-ethylenediamine.

Yield: 95%. B.p.: 218 °C (6 mbar). ^{1}H-NMR: 1.46 ppm, m (broad), 16H, N–CH$_2$–C$\underline{\mathrm{H}}_2$–CH$_2$–N (8H) and –N$\underline{\mathrm{H}}_2$(8H); (d-DMSO) 2.38 ppm, m, 8H, –C$\underline{\mathrm{H}}_2$–NH$_2$; 2.42 ppm, s, 4H, N–C$\underline{\mathrm{H}}_2$–C$\underline{\mathrm{H}}_2$–N; 2.55 ppm, t, 8H, N–C$\underline{\mathrm{H}}_2$–CH$_2$–CH$_2$–NH$_2$. ^{13}C-NMR: 31.1 ppm, N–CH$_2$–C$\underline{\mathrm{H}}_2$–CH$_2$–N; 41.6 ppm, –C$\underline{\mathrm{H}}_2$–NH$_2$; ($\mathrm{D_2O}$) 52.4 ppm, N–C$\underline{\mathrm{H}}_2$–C$\underline{\mathrm{H}}_2$–N; 53.8 ppm, N–C$\underline{\mathrm{H}}_2$–CH$_2$–CH$_2$–NH$_2$. ESI-MS: Peak at 289.2 $(\mathrm{M} + \mathrm{H})^+$

(theoretical MW: 288). Amine number: 1134 mg KOH g^{-1}. Nitrile number: <1 mg KOH g^{-1}.

The synthesis routes for the other compounds with $m = 3$ [(3,3) and (4,3)] are analogous to the recipe described above.

***m* = 2: *N*,*N*,*N*′,*N*′-tetraaminoethyl-1,2-ethylenediamine [compound (2,2)].** The synthesis of the precursor *N*,*N*,*N*′,*N*′-tetracyanomethyl-1,2-ethylenediamine is described in ref. 15. The compound was recrystallized from methanol–water to eliminate traces of HCN. The hydrogenation step is again similar to the description above and described in ref. 14.

Potentiometric titrations

Conventional acid–base titrations of the hexaamines with different spacer lengths were carried out with a VIT90 Video Titrator and a combined electrode (Radiometer, Copenhagen). The electrode was calibrated with buffer solutions of pH 4 and 7 (titrisol, Merck). All titrations were performed with HCl and KOH (titrisol, Merck) at (22 ± 1) °C, with KCl as the supporting electrolyte (p.a., Merck). The contribution of the hexaamines to the ionic strength was negligible; the initial concentration of ionizable groups was lower than 10^{-2} M. All titrations were reproduced with an error of ±1% in the degree of protonation between pH 2.5 and 11. Backward base titrations showed no hysteresis. The nitrogen content needed to normalize the titration curves to the protonated fraction of ionizable groups was determined with a CHN analyzer.

The ionization constants were obtained from the titration curves as successive dissociation constants (p*K* values) by means of a non-linear least squares fit procedure, with the hexaamine concentration as an additional fit variable. The difference between the additional fit variable and the total number of sites determined with the CHN analyzer was within 1%. The accuracy of the obtained macroscopic protonation constants was 0.1 pH units.

For more detailed information about both the method and the analysis the reader is referred to ref. 9.

Results and discussion

The protonation curves of (2,3), and (3,3) hexaamines in 1.0 M KCl, together with data for (4,3) from the literature,[9] are presented in Fig. 2. Protonation involves two steps for the case $n = 3$, and $n = 4$ and $n = 2$ even show a third step. In all cases the titration curves at 0.1 M and 1.0 M KCl are of similar quality, albeit with a shift in pH, due to screening effects.

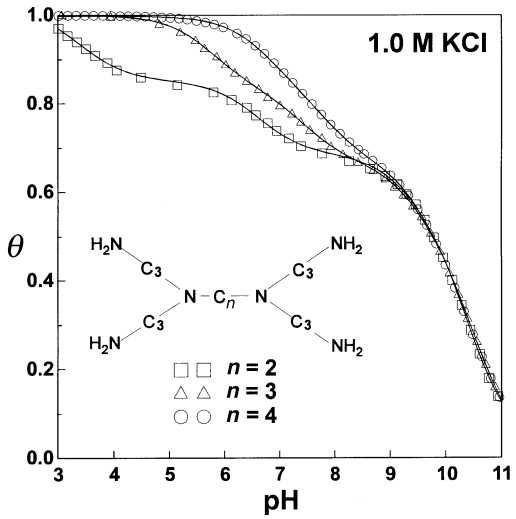

Fig. 2 Degree of protonation θ as a function of pH for (*n*,3) hexaamines at 1.0 M KCl, with $n = 2$ (□), 3 (△) and 4 (○). The results for low ionic strength are of similar quality. The titration curve for (4,3) is taken from ref. 9. The lines through the points are the macroscopic fits of the protonation constants; results are presented in Table 3.

Fig. 2 clearly shows the influence of the inner spacer *n*, the number of carbon atoms between the two tertiary amines in the core. All three hexaamines exhibit exactly the same protonation behavior starting from the deprotonated state, up to pH 8, when the (first) plateau is reached. The most favored microstate at that pH is that one with the four outermost, primary amines protonated. In the next protonation step a tertiary amine is involved, and the different length scales (*n*) among the three hexaamines result in different magnitudes of the electrostatic interactions. The last step is even more pronounced for the smallest molecule (2,3); electrostatic effects between the two tertiary amines make it impossible to reach full protonation even at pH 2.

Fit results of the macroscopic protonation constants for the three hexaamines at both 0.1 M and 1.0 M KCl are presented in Tables 2 and 3 respectively, together with data from the literature for (2,2) and (3,2) at 0.1 M KNO_3 (refs. 16, 17) and (4,3) (refs. 9). Literature data for (3,2) at 1.0 M are not available. The macroscopic fit results are shown together with the experimental data in Fig. 2 for the case of $m = 3$. The fit method does not provide enough accuracy to obtain information about the last step in the protonation scheme in the case of (2,2).

For the hexaamines with $m = 3$ the protonation of the primary amines in the first four steps should be identical (see Fig. 2); the short-range interactions are negligible. The pK_1–pK_4 show fluctuations around a mean average of about 0.1 pH units, an indication of the accuracy with which the macroscopic constants are obtained. The same holds for the data sets (2,2) and (3,2). A macroscopic fitting of pK_4 with the fugacity expression [eqn. (3)] appears to be slightly influenced by the input value for pK_5. This could explain the (minor) difference of 0.2 pH units for the two compounds with outer spacer $m = 2$.

Table 2 Successive macroscopic protonation constants pK_i in 0.1 M KCl are presented for hexaamines with inner and outer spacer length *n* and *m*, respectively (for structure see Fig. 1)

pK_i	(2,2)		(3,2)	(2,3)	(3,3)	(4,3)
1	10.30	*10.08*	*10.31*	10.81	10.94	*10.83*
2	9.63	*9.58*	*9.63*	10.12	10.11	*10.22*
3	9.26	*8.99*	*9.26*	9.71	9.87	*9.72*
4	8.31	*8.42*	*8.52*	9.06	8.91	*9.13*
5	3.1–3.5	*1.33*	*2.5*	6.03	6.65	*7.16*
6	–	–	–	2.75	4.97	*6.01*

Literature values for (2,2), (3,2) and (4,3) hexaamines are indicated in italic.[9,16,17] Literature p*K* values for (3,2) are interpolations to 22 °C, based on two different data sets at 20 °C and 25 °C. All experimental pK_i values are obtained with fluctuations of ±0.1 pH units.

Table 3 Successive macroscopic protonation constants pK_i at 1.0 M KCl are presented for (*n*,*m*) hexaamines. (*n*,*m*) stand for the inner and outer spacer length between the six ionizable sites (Fig. 1)

pK_i	(2, 2)	(2, 3)	(3, 3)	(4, 3)
1	10.70	11.04	10.92	*10.93*
2	9.94	10.47	10.63	*10.58*
3	9.71	10.14	10.15	*10.06*
4	8.83	9.51	9.48	*9.56*
5	3.6–4.0	6.73	7.46	*7.91*
6	–	3.40	5.77	*6.77*

Literature values for (4,3) are indicated in italic.[9] All experimental pK_i values are presented with a standard deviation of ±0.1 pH units.

A fit of the Ising model to the titration data involved microscopic pK_i values and nearest neighbor pair interactions ε_{ij} only (see Fig. 3). The nearest neighbor pair interactions are taken to be independent of the chemical environment, but only dependent on the spacer length. ε_2, ε_3 and ε_4 represent the repulsive interaction between two amines with two, three and four carbons in between, respectively.

Previously it was shown that the pair interactions are largely independent of ionic strength.[7–9] The values are based on results obtained there. The only real fitting parameters are the intrinsic protonation constants for the primary and tertiary amines. Based on the different empirical relations for the various types of aliphatic amines[10–12] these constants are split up for amines with a different chemical environment and different ionic strength. $p\hat{K}^{(1)}_{m=3}$ is used for the primary amines in hexaamines with outer spacer $m = 3$, and $p\hat{K}^{(1)}_{m=2}$ for spacer $m = 2$. $p\hat{K}^{(3)}$ is different for all hexaamines because of the variable inner spacer n. Due to the fact that pK_5 and pK_6 could not be obtained sufficiently accurately for the hexaamines with $m = 2$ (Table 2), $p\hat{K}^{(3)}$ was not determined for these cases. The resulting parameter values for the hexaamines for both ionic strengths are given in Table 4, and the calculated macroscopic pK values based on these Ising parameters in Table 5 for the case of $m = 3$. Because of the incomplete fit results for the case of $m = 2$ the calculated macroscopic pK values are left out, although the first three experimentally obtained pK values were again reproduced within 0.2 pH units.

Protonation constants for similar compounds with only four amine groups are also available in the literature[18] for various spacer lengths at 0.1 M. These molecules differ in that the two tertiary amines are replaced by secondary amines. Using the same Ising model with the same pair interaction parameters (only $p\hat{K}^{(2)}$ instead of $p\hat{K}^{(3)}$ on literature data for molecules with $m = 3$ and $n = 2$, 3 and 4 gave $p\hat{K}^{(1)}_{m=3} = 10.10$ and $p\hat{K}^{(2)} = 9.09$, 9.48 and 9.99 in 0.1 M KCl, respectively.

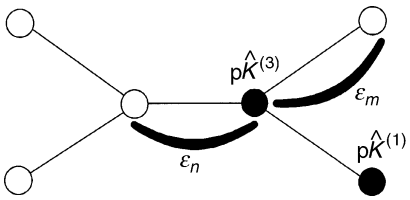

Fig. 3 Schematic representation of the hexaamine showing the various parameters used to fit the Ising model to the macroscopic protonation constants. All hexaamines are treated with a fixed nearest neighbor pair interaction parameter ε_n and ε_m based on previous work.[8,9] At one ionic strength $p\hat{K}^{(1)}$ is kept constant for a series of hexaamines with $m = 3$ and $m = 2$, but $p\hat{K}^{(3)}$ is variable. The idea behind this approach is that the microscopic protonation constants are strongly dependent on the chemical environment.

Table 4 Values of the Ising parameters needed to fit the macroscopic pK values of (n,3) hexaamines at 0.1 M and 1.0 M KCl are presented

Ising model parameters	0.1 M KCl	1.0 M KCl
$p\hat{K}^{(1)}_{m=2}$	9.40	9.79
$p\hat{K}^{(1)}_{m=3}$	9.95	10.28
$p\hat{K}^{(3)}$ (n,m) = (2,3)	7.50	8.17
$p\hat{K}^{(3)}$ (n,m) = (3,3)	8.32	9.13
$p\hat{K}^{(3)}$ (n,m) = (4,3)	8.90	9.67
ε_2	*2.20*	*2.20*
ε_3	*1.00*	*1.00*
ε_4	*0.60*	*0.60*

An explanation of the parameters is given in Fig. 3. Fixed values in the fitting routine are indicated in italic.

Table 5 The calculated macroscopic protonation constants pK_i at 0.1 M and 1.0 M KCl for (n,3) hexaamines are shown

	(2,3)		(3,3)		(4,3)	
pK_i	0.1 M	1.0 M	0.1 M	1.0 M	0.1 M	1.0 M
	10.55	10.89	10.55	10.90	10.57	10.93
2	10.12	10.46	10.13	10.47	10.13	10.48
3	9.77	10.11	9.77	10.11	9.77	10.10
4	9.34	9.68	9.34	9.67	9.34	9.66
5	5.80	6.47	6.61	7.42	7.18	7.93
6	3.00	3.67	5.02	5.83	5.99	6.76

The calculations are based on the Ising model with parameters presented in Table 4.

Trends are similar to the fit results obtained in Table 4. The obtained microscopic protonation constants together with the already determined pair interaction parameters can be used in future research to predict the protonation behavior for polyamines built up from these monomers.

Conclusion

In conclusion, we have shown that intrinsic pK values can be obtained from well-chosen model oligoamines. More extended study on the protonation behavior of amines may yield a more structural relation than the Taft equations for the intrinsic protonation constants. With the already established pair interaction parameters the Ising model has the advantage over these empirical relations that the protonation constants of an individual group can simply be calculated at any protonation state of the molecule. This brings the prediction of the titration curve for a given structure within reach, even for systems with a very large number of sites.

References

1 D. D. Perrin, B. Dempsey and E. P. Serjeant, *pK_a Prediction for Organic Acids and Bases*, Chapman and Hall, London, 1981.
2 R. W. Taft Jr, in *Steric Effects in Organic Chemistry*, ed. M. S. Newman, John Wiley and Sons, Inc., New York, 1956, p. 556ff.
3 R. A. Marcus, *J. Phys. Chem.*, 1954, **58**, 621.
4 A. Katchalsky, J. Mazur and P. Spitnik, *J. Polym. Sci.*, 1957, **23**, 513.
5 T. Kitano, S. Kawaguchi, K. Ito and A. Minakata, *Macromolecules*, 1987, **20**, 1598.
6 R. Smits, G. J. M. Koper and M. Mandel, *J. Phys. Chem.*, 1993, **97**, 5745.
7 M. Borkovec and G. J. M. Koper, *Prog. Colloid Polym. Sci.*, 1998, **109**, 142.
8 M. Borkovec and G. J. M. Koper, *J. Phys. Chem.*, 1994, **98**, 6038.
9 R. C. van Duijvenbode, M. Borkovec and G. J. M. Koper, *Polymer*, 1998, **39**, 2657.
10 F. E. Condon, *J. Am. Chem. Soc.*, 1965, **87**, 4481.
11 F. E. Condon, *J. Am. Chem. Soc.*, 1965, **87**, 4485.
12 H. K. Hall Jr, *J. Am. Chem. Soc.*, 1957, **79**, 5441.
13 T. L. Hill, *An Introduction to Statistical Thermodynamics*, Dover, New York, 1986.
14 L. Häußling and W. Paulus, EP 790 976, BASF AG, 09.11.1995.
15 H. Distler and K. L. Hock, EP 045386, BASF AG, 08.07.81.
16 P. Paoletti, R. Walser, A. Vacca and G. Schwarzenbach, *Helv. Chim. Acta*, 1971, **54**, 243.
17 E. Garcia-España, M. Micheloni, P. Paoletti and A. Bianchi, *Inorg. Chem.*, 1986, **25**, 1435.
18 R. M. Smith and A. E. Martell, *Critical Stability Constants*, Plenum Press, New York, 1989.

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