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The effect of spacer chain length on ion binding to bidentate α,ω-diamines: Contrasting ordering for H^+ and Li^+ ion affinities†

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Electrospray ionisation mass spectrometry studies and quantum chemical calculations indicate that bidentate ligation of Li^+ ion to the diamines leads to symmetric bridging and exhibits contrasting relative affinity orderings compared to that of proton for α,ω-diamines.

Knowledge of accurate proton and metal ion binding interactions in polyfunctional macromolecules is an important step in understanding the biophysical processes.[1] Good correlations exist between the metal ion and proton binding affinity to the bases, albeit the proton affinities are much higher.[2,3] In biological system, especially in proteins, several basic motifs exist, separated by varying distances. Polyamines found to be present in the cells of microorganisms and animal organisms, contribute to the stabilization of the structure and activity of tRNA and DNA.[4] Protonation of α,ω-diamines has been extensively studied using mass spectrometric methods and computational techniques.[3,5,6] Intramolecular hydrogen bonding and the consequent chelating ring size were found to be the key factors controlling the stability of the protonated complexes.[3,5,6] In contrast, studies of the alkali metal ion affinities on the diamines are scarce, except on the simplest case of ethylene diamine.[3]

Here, we undertook a systematic experimental and computational study on the measurement of relative gas phase affinity of lithium ion and compared them with the proton affinities, on seven α,ω-diamines ($H_2N–(CH_2)_{2–8}–NH_2$, **1–7**). We would like to address the following questions: How are the variations in the relative binding affinities of proton and Li^+ ions in the given series? What is the nature of bridging interactions the Li^+ ion have? What are the structural differences between the proton and Li^+ ion complexes of diamines? The kinetic method[7] and quantum chemical calculations were employed to address the above questions. The kinetic method is widely applied to determine proton affinities, metal ion affinities, gas phase acidities, electron affinities, *etc.*[7,8] The method[7,8] is based on the collision induced dissociation (CID) of Li^+ bound heterodimers,[9] $[L_1{\cdot}Li^+{\cdot}L_2]$ where L_1 and L_2 are two different diamines, and the correlation of relative abundances of the Li^+ bound monomers ($Li^+{\cdot}L_1$ and $Li^+{\cdot}L_2$) formed during the dissociation with the relative Li^+ ion affinities of the two bases.

The natural logarithm of intensity ratio, $\ln(I_{(Li^+{\cdot}L2)}/I_{(Li^+{\cdot}L1)})$ values are calculated from the CID spectra of all possible heterodimers at similar experimental conditions, where the Li^+ ion affinity of L_2 is higher than L_1, and are used to obtain the Li^+ ion affinity ladder. In a similar way we have obtained relative proton affinity by replacing lithium by proton, and the order can be given as $\mathbf{1}H^+ < \mathbf{2}H^+ < \mathbf{7}H^+ \leqslant \mathbf{6}H^+ < \mathbf{5}H^+ < \mathbf{4}H^+ < \mathbf{3}H^+$, which is in good agreement with the literature values.[10] However, the relative Li^+ ion affinity order for α,ω-diamines obtained from Li^+ ion affinity ladder[11] (Fig. 1) is $\mathbf{1}Li^+ < \mathbf{3}Li^+ \leqslant \mathbf{2}Li^+ < \mathbf{4}Li^+ < \mathbf{6}Li^+ < \mathbf{5}Li^+ \leqslant \mathbf{7}Li^+$.

For chemically similar compounds, the natural logarithm of intensity (I) ratio values are directly proportional to the binding energy difference (ΔE) (eqn. (1)) between the used diamines with lithium ion, where the entropy term is close to zero.[8]

$$\ln(I_{(Li^+{\cdot}L2)}/I_{(Li^+{\cdot}L1)}) \approx \Delta E/RT_{\text{eff}} \qquad (1)$$

Attempts were made to convert $\ln(I_{(Li^+{\cdot}L2)}/I_{(Li^+{\cdot}L1)})$ order into relative lithium ion affinities by measuring the T_{eff} of the dissociating cluster ions.[8,12] However, due to the non availability of enough number of references among the studied diamines we could not obtain reliable T_{eff} values.[12] Hence, the present study is limited to the relative lithium ion affinity order. The cumulative natural logarithm ratios of all the diamines are used as a measure of relative affinity order. We seek to explain the observed contrasting ordering for H^+ and Li^+ ion affnities of α,ω-diamines through quantum chemical calculations.

The metal ion and proton affinities are estimated using eqns. (2) and (3), respectively.[6] B3LYP/6-31G* method is used for the geometry optimisations and obtaining the thermochemical data. All the structures considered are characterised as minima on the potential energy surface. This is followed by single point calculations at MP2/6-311++G** level. Counterpoise method

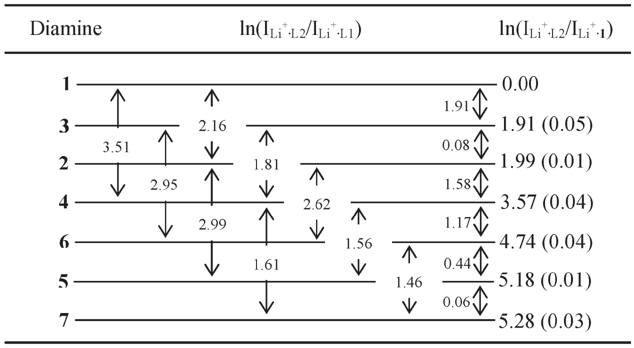

Fig. 1 Measured $\ln(I_{Li^+{\cdot}L2}/I_{Li^+{\cdot}L1})$ values for Li^+-bound hetero dimers of diamines (**1–7**). The data presented under the heading $\ln(I_{Li^+{\cdot}L2}/I_{Li^+{\cdot}\mathbf{1}})$ are average cumulative values expressed relative to ethylene diamine (**1**). The numbers given in parentheses are estimated errors resulting from the measurement of abundance ratios.

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was used to calculate the basis-set super position error (BSSE). In our studies all the calculations were done using the Gaussian 98[13] suite of program.

$$\text{Metal ion affinity } (\Delta H_{298}) = \Delta E_{\text{ele}} + \Delta E_{\text{thermal}} + T\Delta S\text{-BSSE} \quad (2)$$

$$\text{Proton affinity } (\Delta H_{298}) = \Delta E_{\text{ele}} + \Delta E_{\text{thermal}} + 5RT/2 \quad (3)$$

The relative binding affinity orderings of the computed results are in excellent agreement with the experimental observations for both proton and Li$^+$ ion affinities, except the change of proton affinity order between **4** and **5**. Theoretically obtained proton and lithium ion affinity orders can be given as **1**H$^+$ < **2**H$^+$ < **7**H$^+$ < **6**H$^+$ ⩽ **4**H$^+$ < **5**H$^+$ < **3**H$^+$ and **1**Li$^+$ < **3**Li$^+$ ⩽ **2**Li$^+$ < **4**Li$^+$ < **6**Li$^+$ < **5**Li$^+$ ≈ **7**Li$^+$. Fig. 2 depicts the optimised geometries of the Li$^+$ and protonated complexes. All the Li$^+$ complexes are virtually symmetrically bridging, and as the length of the spacer chain increases Li$^+$ is going into the cavity of the molecule. In agreement with the previous studies,[2] computations reveal that the Li$^+$ ion affinities are less than one third of the proton affinities to the diamines. The non-linearity of the relative binding affinities of Li$^+$ ions can be clearly traced to the subtle and intricate conformational changes in the Li$^+$ complexed cyclic structures. In addition, higher energy monodentate minimum energy structures where the cation is bound to the acyclic isomers are obtained. Systematic conformational analysis of neutral diamines reveal that the open chain linear structures are global minima besides several other local minima with warped on cyclic structures. The energy difference between the acyclic and cyclic neutral conformation (ΔE_1), the conformation reorganization energy upon complexing with the cation (ΔE_2), and the relative energy differences for the mono- and bidentate complexation of the cations (ΔE_3) are given (Table 1). The latter two quantities (ΔE_2 and ΔE_3) aid in dispersing exact differences in the ion bridging to the diamines, while ΔE_1 granges the conformational flexibility of the diamines. One salient feature is that while the complexation energy going from acyclic to cyclic structures increase by about 5–11% for proton, it is more than 80% for Li$^+$ ion. Therefore, although metal ions have much smaller magnitudes of affinity to diamines, their gain in going to bidentate ligation is substantial as reflected in the corresponding higher ΔE_3 for Li$^+$. In contrast, the fact that ΔE_2 is consistently higher for H$^+$ shows that the proton induces higher strain in the diamine skeleton upon complexation. Thus, although Li$^+$ ion gains substantially due to the coordination of the second amine group, the corresponding Li$^+$ ion cyclic complex has a less strained diamine motif compared to that of proton complex. The larger size of Li$^+$ ion as well as its non-covalent nature of interaction are responsible for a highly flexible complexation, as reflected in smaller ΔE_2.

Table 1 Calculated energy (kcal mol^{-1}) difference between various conformations at MP2/6-311++G**//B3LYP/6-31G* level of theory

		Li$^+$		H$^+$		Affinity	
Structure	ΔE_1	ΔE_2	ΔE_3	ΔE_2	ΔE_3	Li^{+a}	H^{+b}
1	0.1	4.8	27.9	12.0	12.6	62.7	228.7
2	2.6	4.0	29.5	12.1	18.1	66.3	236.6
3	2.4	6.0	28.1	14.8	21.2	65.0	240.8
4	4.7	1.4	31.6	13.6	19.4	69.6	239.1
5	2.7	1.8	35.2	15.7	19.5	73.8	239.5
6	5.3	1.9	34.6	13.1	19.0	73.4	239.0
7	5.4	2.2	34.4	15.7	17.7	73.8	238.3

[a] Proton affinities (kcal mol^{-1}) at MP2/6-311++G**//B3LYP/6-31G* level of theory. [b] Lithium ion affinities (kcal mol^{-1}) at MP2 (full)/6-311++G**//B3LYP/6-31G* level of theory.

While the lithium bridging is virtually symmetrical in all cases, the proton bridge is highly unsymmetrical. The contrasts in the trends of the relative stability orderings are due to an interplay of intricate conformational energetics during the formation of metal ion chelate ring. Thus, the combined experimental and computational study on the binding affinities of Li$^+$ and H$^+$ ions to α,ω-diamines highlights the disparities between the complexation energetics and structures. It is worth mentioning that the kinetic method amplifies even small differences between similar compounds in the measurement of important thermodynamic parameters. Thus, while both proton and metal ion α,ω-diamine

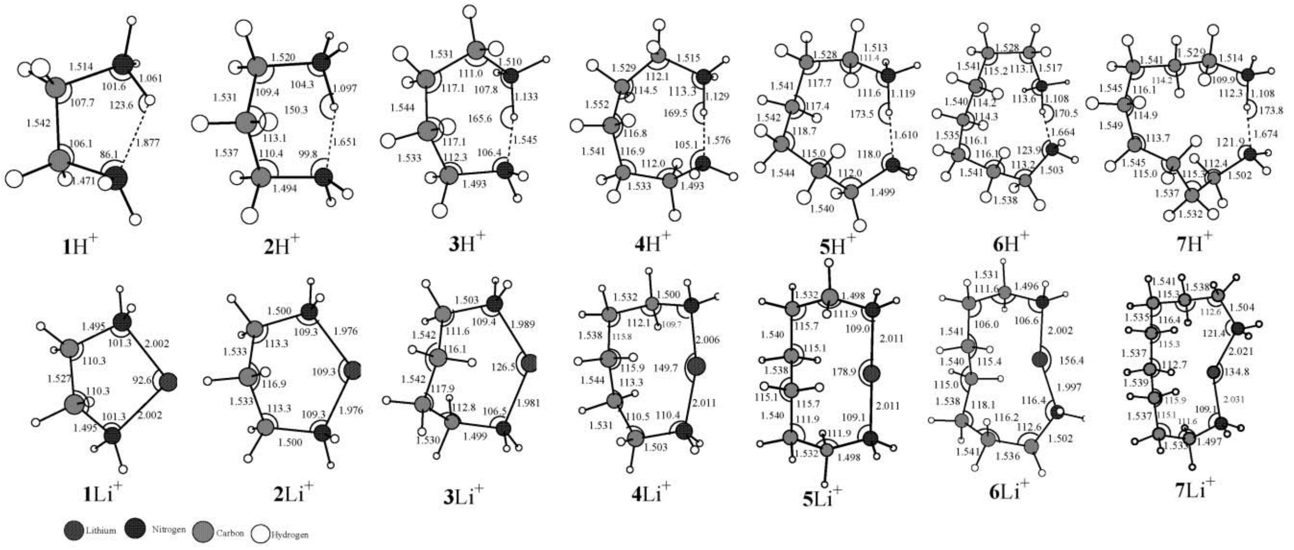

Fig. 2 B3LYP/6-311++G** optimised geometries of cyclic H$^+$ and Li$^+$ ion complexes of diamines. Bond lengths in Å and bond angles in degrees.

complexes prefer cyclic conformations, the nature of bridging and the energy differences between the mono and bidentate complexes are quite different.

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9 All the mass spectra were recorded using a Quattro LC triple–quadrupole mass spectrometer (Micromass, Manchester, UK) and the data were acquired using Masslynx software (version 3.2). The Electrospray ionization capillary voltage was maintained between 3.5 to 4.0 kV, and the cone voltage was kept at 5–10 V. Nitrogen was used as desolvation and nebulization gas. The source and desolvation temperatures were kept at 100 °C. The sample solutions were injected through an infusion pump (Harvard Apparatus, Kent, UK) at a flow rate of 10 μL min^{-1}. Argon was used as the collision gas for all CID experiments and the collision cell pressure was maintained at 3×10^{-4} mbar.
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11 In this ladder construction, most diamines are compared to at least three others. The $\ln(I_{Li^+\cdot L1}/I_{Li^+\cdot L2})$ values calculated for successful combinations are found to be reproducible. Based on this data, the lithium ion affinity ladder of the α,ω-diamines (**1**–**7**) is constructed. The $\ln(I_{Li^+\cdot L1}/I_{Li^+\cdot L2})$ values are internally consistent for the lithium bound heterodimers of diamines. For example, the value for $[\mathbf{4}\cdot Li\cdot \mathbf{1}]^+$ is 3.51, a very similar value is obtained by summing the $\ln(I_{Li^+\cdot L2}/I_{Li^+\cdot L1})$ values of three intermediate steps, *viz*. $\ln(I_{Li^+\cdot \mathbf{3}}/I_{Li^+\cdot \mathbf{1}}) + \ln(I_{Li^+\cdot \mathbf{2}}/I_{Li^+\cdot \mathbf{3}}) + \ln(I_{(Li^+\cdot \mathbf{4})}/I_{(Li^+\cdot \mathbf{2})}) = 1.91 + 0.08 + 1.58 = 3.57$. The $\ln(I_{Li^+\cdot L1}/I_{Li^+\cdot L2})$ values for other pairs are also consistent internally with a difference no larger than 0.2. Similarly, results were also obtained when the experiments were performed at different collision energy values (2, 4, 6, and 8 eV). This accord confirms that entropic effects, which tend to be non-additive, are indeed negligible with the diamines studied.
12 It was shown in the literature that T_{eff} is fairly similar for dimeric ions of chemically similar molecules, irrespective of the central ion holding the two molecules, when experiments are performed at identical conditions. The dissociation of proton bound heterodimers of diamines at different collision energies (2, 4, 6, and 8 eV) was studied for this purpose. Only diamines **2**, **4**, **5** and **6** could be used for this study and the difference in the PA values among the three diamines (**4**, **5** and **6**) is very small (± 0.5 kjoule mol^{-1}). This restricts the number of good references needed for this study and does not lead to a reliable T_{eff} value. Diamine **3** could not be used as a reference though the literature PA value suggests it can be used.
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