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Abbott, Helen E; Hey, John C; Britton, Melanie M; Johnston, Roy L

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Effects of Hydration on the Conformational Behaviour of Flexible Molecules with Two Charge Centres

Helen E. Abbott, John C. Hey, Melanie M. Britton* and Roy L. Johnston†

School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom

* corresponding author

† deceased 16th August 2019

Abstract

The hydration behaviour of alkyl-diammonium di-cations and alkyl-dicarboxylate di-anions, of varying alkyl chain length, was examined using basin-hopping global optimisation techniques. For every di-ion investigated, a conformational transition from linear to folded is observed at a critical hydration number, n^* , specific to each di-ion. A step-wise hydration study has been undertaken for alkyl-dicarboxylate di-anions in finite water clusters containing one to twelve water molecules, and low energy structures have been examined for larger water clusters. An even number of carbons in the alkyl chain gives rise to more stable conformations in unhydrated, implicitly solvated and explicitly solvated conditions. This work provides valuable information on how the hydration of ammonium and carboxylate ions influence larger biomolecules' conformations.

1. Introduction

The presence of ionic functional groups are critical for the hydration of large biomolecules.^{1,2} In proteins and peptides containing the 20 naturally occurring amino acids, there are only three types of ionic group present: the ammonium, guanidinium and carboxylate groups.³ An insight into biological processes can be gained by understanding how peptides and proteins behave in aqueous solutions. This can be achieved by investigating the extent of interactions between these ionic groups and water.^{1,4,5} Alkyl-dicarboxylate di-anions, $[\text{O}_2\text{C}(\text{CH}_2)_m\text{CO}_2^-]$ (DC_m) and alkyl-diammonium di-cations $[\text{H}_3\text{N}(\text{CH}_2)_m\text{NH}_3^+]$ (DA_m), in which the two distinct charge centres are separated by a hydrophobic, flexible alkyl $(\text{CH}_2)_m$ chain, can act effectively as simple models for peptides.⁶ Solvent-mediated folding processes can be understood by studying the stepwise hydration of these types of di-ions in the gas phase.^{3,6-12}

Several theoretical and experimental studies^{9,11-16} have previously been undertaken to understand the interaction of these di-ions with finite water clusters $(\text{H}_2\text{O})_n$. Hydrated DA_m were methodically studied by Jahangiri *et al.*¹³ for $m = 5 - 10$ and $n = 10 - 40$ using molecular dynamics (MD) simulations. For small numbers of water molecules (n), the two charged ends of the DA_m were found to be hydrated by two separate, small water clusters.¹³ This is in agreement with the experimental results of Kebarle and coworkers¹⁷ who measured the stepwise binding energies of DA_m where $n = 1 - 6$. Jahangiri *et al.*¹³ found that as n is increased, a conformational transition occurs, wherein the DA_m folds and both charged ends of the molecule are hydrated by a single, larger water cluster. Demireva *et al.*¹⁴ also observed this conformational transition using infrared photodissociation experiments with $\text{DA}_7(\text{H}_2\text{O})_{<12}$. The number of water molecules at which this conformational transition occurs is the critical hydration number (n^*). As the alkyl chain length of DA_m increases, n^* was found to increase, with more water molecules required to form a water bridge between the terminal ionic groups.¹³

This phenomenon has also been observed experimentally and computationally for micro-solvated $\text{DC}_m(\text{H}_2\text{O})_n$ molecules, where $m = 6$ and $n = 1 - 20$, by Yang *et al.*⁶ They found, using a combination of photoelectron spectroscopy and MD simulations, that each water molecule adds to alternate ends of the linear DC_6 di-anion. A conformational transition occurs when $n = 16$, because the two negatively charged ends are screened and brought closer together via a water bridge, while the increased number of hydrogen bonds overcomes the Coulombic repulsion present between the two charge centres.⁶ This leads to the flexible backbone adopting a bent configuration with both carboxylate groups embedded within a single water cluster.

Infrared photodissociation (IPRD) spectroscopy has been combined with quantum chemical simulations to study $DC_m(H_2O)_n$, for $m = 2, 4, 6$ in micro-solvated conditions.¹⁶ The conformational transition was reported. This was indicated by both the computational simulations and a reduction in the intensity of the symmetric carboxylate stretching modes observed in the experimental IRPD spectra. The n^* values were again found to increase with increasing m .¹⁶

In this study, we undertake a computational, systematic investigation of the evolution of the conformational and energetic behaviour of DA_m and DC_m , with flexible backbones consisting of 3 - 11 methylene units, as they undergo stepwise hydration. The relationship between conformational behaviour with alkyl chain length has been explored for di-ions in unhydrated, implicitly solvated, and explicitly solvated conditions. We examine DA_m and DC_m over a larger range of alkyl chain lengths (m) than has been previously reported and determine, for the first time in many cases, their respective critical hydration numbers (n^*), which is defined as the number of water molecules present when the folded conformation is first observed as the putative global minimum (GM). Furthermore, this study demonstrates the suitability of the basin-hopping Monte Carlo algorithm^{18,19} for studying the hydration of flexible, multi-charged systems.

2. Methods

DA_m and DC_m molecules, with alkyl chain lengths $m = 3 - 11$, were modelled using the standard parameters found in the ff99SB atomistic force field,^{20,21} within the AMBER simulation package.²² The AMBER force field was chosen because we perform a large number of local minimisations during our global optimisations for exploring the complex landscapes of these water clusters, and ff99SB is a computationally inexpensive force field which has a proven track record. We have verified that a number of the minima found using ff99SB correlate to minima on the DFT landscape by performing local minimisations using the B3LYP xc functional with the aug-cc-pVDZ basis set²³ as implemented with the Gaussian09 package.²⁴ Water clusters, $(H_2O)_n$ where $n = 1 - 25$, were modelled using the TIP4P rigid body potential²⁵ which was chosen because of its computational efficiency. Furthermore, TIP4P water clusters have been studied extensively,²⁵⁻³⁰ with good putative GM determined up for up to 36 water molecules,²⁹ and are in reasonable agreement with both *ab initio* calculations, as well as experiments, for systems up to 12 molecules.³¹ The H-O-H bond angle is fixed at 104.52° and the H-O bond lengths are fixed at 0.9572 \AA . The lone pair on the oxygen atom, which is fixed at 0.15 \AA

from the O atom, along the H-O-H bond angle bisector, acts as a pseudoatom and the site of the oxygen's charge.^{28,32} Potential parameters are shown in Table 1.

Table 1. TIP4P water parameters.

Molecule	Site	ϵ / kcal mol ⁻¹	σ / Å	q / e
TIP4P H ₂ O	O	0.648	3.2	0
	Lone pair	0	0	-1.04
	H	0	0	0.52

Global optimisation was performed on the di-ion water complexes using the basin-hopping (BH) Monte Carlo algorithm^{18,19}, as implemented in the GMIN package.³³ The putative GM, the structure with the lowest energy, of each system was found using the BH technique. The coordinates of the low energy structures and the putative GMs discussed in this study can be found in the data depository (see *Associated Content*).

For each $D_m(\text{H}_2\text{O})_n$ (where D_m stands for DC_m or DA_m) system, low energy structures were generated from a short BH run (10,000 steps). The 10 lowest energy, unique structures were used as the starting point for ten longer BH runs (100,000 steps), in order to find the putative GM. In this investigation, the Monte Carlo geometry perturbations were carried out in blocks of 100 moves of the same type. Three move classes were used: rotations, translations and short, high temperature MD runs. During the rotation moves, all molecular fragments within the cluster are rotated by a random angle between $\pm\pi$ radians. For the translation moves, a random molecule has a random displacement applied to it relative to the rest of the cluster. 1000 steps were used in the MD simulations and were run at 1000 K with a time step interval of 0.001 ps. Implicitly solvated di-ions were modelled using the continuum electrostatic Born hydration model³⁴ (external dielectric constant = 80.4 f m^{-1}), which uses a pairwise de-screening approximation, as implemented in the SANDER simulation package.^{22,35} Analyses of the systems were performed with cpptraj³⁶ and in-house-built codes.

The total conformational energy, including intra-molecular and inter-molecular interactions, of the hydrated di-ion $D_m(\text{H}_2\text{O})_n$ with an alkyl chain length of m and n water molecules, is defined as $E(m, n)$. The hydration energy ($E_{\text{hyd}}(m, n)$) for $D_m(\text{H}_2\text{O})_n$ is calculated as:

$$E_{\text{hyd}}(m, n) = E(m, n) - \left(E(\text{frozen } D_m) + E(\text{frozen } \text{H}_2\text{O}_n) \right) \quad (1)$$

where $E(\text{frozen } D_m)$ is the energy of the isolated di-ion, with its conformation fixed (frozen) to that in the $D_m(\text{H}_2\text{O})_n$ complex, and $E(\text{frozen } (\text{H}_2\text{O})_n)$ is the total energy of the water cluster(s), with the same conformation as in the $D_m(\text{H}_2\text{O})_n$ complex.

The second difference in energy ($\Delta_2(m, n)$) for $D_m(\text{H}_2\text{O})_n$ is calculated as:

$$\Delta_2(m, n) = 2E(m, n) - \left(E(m-1, n) + E(m+1, n) \right) \quad (2)$$

where a more positive value of $\Delta_2(m, n)$ indicates a less stable conformation. Boltzmann weightings are applied to various properties according to the formula:

$$\bar{\chi} = \frac{\sum e^{\Delta U_i \beta} \chi_i}{\sum e^{\Delta U_i \beta}} \quad (3)$$

where $\beta = 1/k_B T$ and the difference between the putative GM and the minimum, i , is denoted by ΔU_i . The weighted mean is taken over all structural isomers of unique energy found in all basin-hopping runs for each size of system. A theoretical temperature of $T = 300$ K was used to maintain consistency with our previous computational studies, and provide an insight into behaviour at approximate ambient temperature.

The DC_m series where $m = 3 - 11$ were investigated in unhydrated conditions using DFT calculations in order to clarify certain results. The conformational energy of each di-anion was calculated using the B3LYP xc functional with the aug-cc-pVDZ basis set³⁷ as implemented with the Gaussian09 package.²⁴

3. Results

3.1 Unhydrated Di-ions

3.1.1 Alkyl-diammonium Di-cations

The unhydrated DA_m series were found to all have positive conformational energies (Supporting Information: Figure S1) due to Coulombic repulsive forces between the two charged ends. The

smallest di-cation ($m = 3$) has the highest positive energy value; the two ammonium charge centres are closer together and therefore experience the strongest, destabilising Coulombic repulsions. As the alkyl chain length increases, the conformational energy decreases and becomes less positive (Supporting Information: Figure S1). The Coulombic repulsive forces become less dominant as there is greater separation between the charged ends. The putative GM conformations of DA_m were observed to be linear, with all C-C-C-C dihedral angles in the *trans* configuration. The two ionic groups are therefore the maximum distance apart, thus fully reducing the Coulombic repulsive forces.

3.1.2 Alkyl-dicarboxylate Di-anions

All putative GM structures were found to be linear with positive conformational energies which decrease as the alkyl chain length increases (Figure 1a). For the DC_m series, an even number of carbons in the alkyl chain results in a more stable conformation as shown in Figure 1b. This effect has been previously reported in the literature for DC_m and was attributed to a twist in the conformations of DC_m when m was odd.^{38,39} However, in our study no twist in the alkyl chains is observed in the putative GMs. The odd-even effect can be attributed to the energy contribution from electrostatic forces (Supporting Information: Figure S4b) and is also observed in results generated from DFT calculations (Supporting Information: Figure S46).

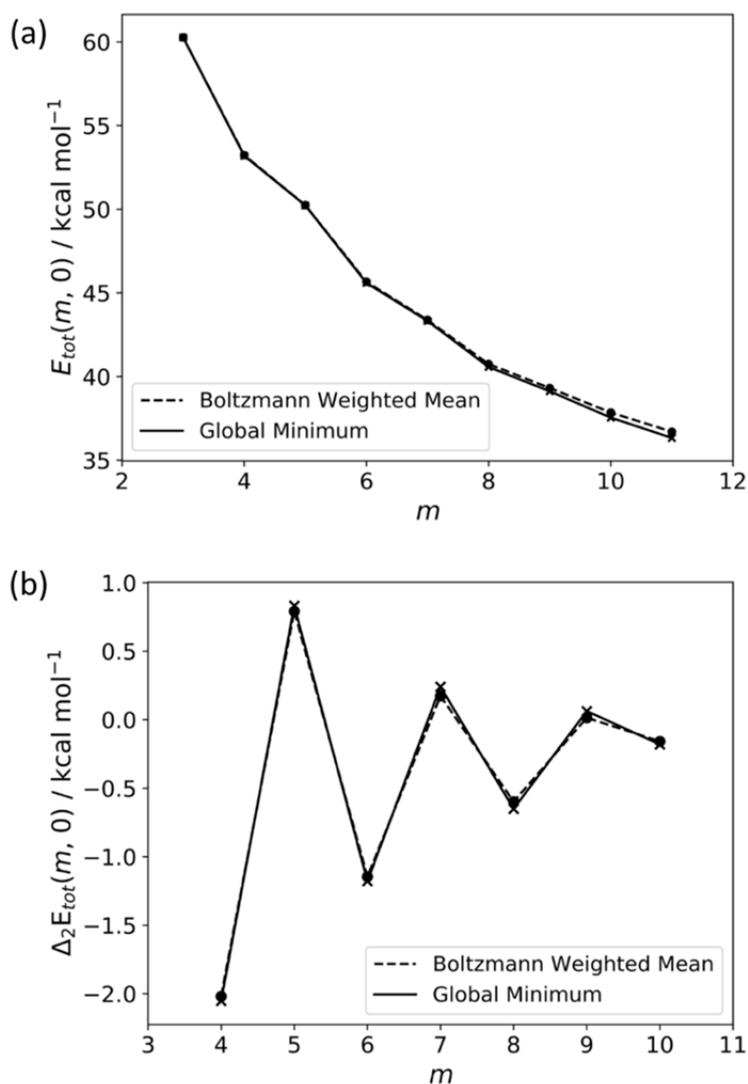


Figure 1. a) A plot of the conformational energies as a function of carbon chain length for unhydrated DC_m with $m = 3 - 11$. b) A plot of second difference for the conformational energies of unhydrated DC_m with $m = 4 - 10$.

3.2 Explicitly Hydrated Di-ions

3.2.1 Alkyl-diammonium di-cations

A series of DA_m , where $m = 3 - 11$ in water clusters of $n = 1 - 25$, were investigated and their n^* values are listed in Table 2. It can be seen that as m increases, n^* also increases. For all of the di-cations studied, a single value for n^* was determined, with the exception of $m = 3$. The values for m

= 5 - 10 have been compared with those found experimentally¹² and computationally¹³, which are listed in Table 2, and are found to be lower.

Table 2. Values of the critical hydration number as a function of alkyl chain length for DA_m.

	<i>n</i>* (this work)	<i>n</i>* (literature)
3	9-11	
4	11	
5	11	17 (ref 13)
6	13	19 (ref 13)
7	14	20 (ref 13), 21 - 23 (ref 12)
8	16	27 - 29 (ref 13), 24 - 26 (ref 12)
9	18	27 - 29 (ref 13)
10	22	27 - 29 (ref 13), 27 - 29 (ref 12)
11	22	

A detailed hydration study of DA₅ was undertaken to fully explain the conformational behaviour illustrated in Figure 2. The conformational energies of DA₅(H₂O)_{1 - 12} decrease linearly with increasing *n*, as the added water molecules stabilise the charged ammonium terminal groups (Figure 3a). In the range *n* = 1 - 10, sequential hydration occurs as seen in previous investigations.^{13,14} Two small water clusters hydrate each ammonium end, with hydrogen bonds forming between the oxygen atom of water and the hydrogen atom of the ammonium group. When *n* < 10, for even values of *n* the system is symmetrical because the water molecules add to alternate charged ends: and a relatively more stable conformation is observed as seen in Figure 3b. The conformation of DA₅(H₂O)_{1 - 10} is linear with an average distance between the terminal ammonium groups, *R*_{NN}, of ~ 7.66 Å (Supporting Information: Table S1). The hydrophobic alkyl chain is left unhydrated.

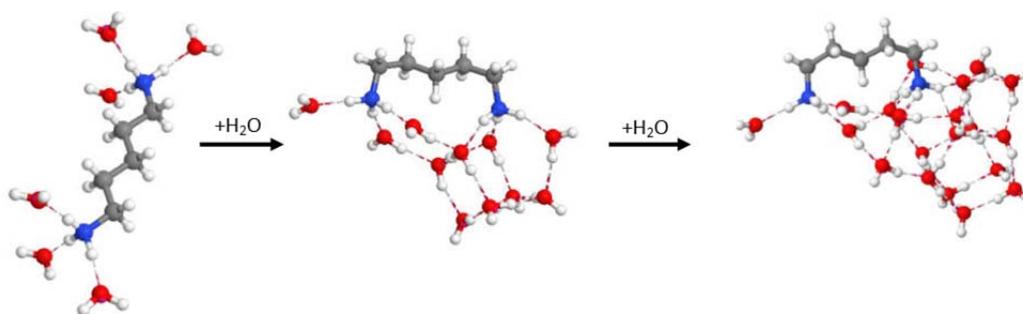


Figure 2. Putative GM structures of $DA_5(H_2O)_n$ where $n = 6, 11$ and 20 (from left to right) in which the positions of the oxygen (red), nitrogen (blue), carbon (grey) and hydrogen (white) atoms are indicated. Representations of the hydrogen bonds have been added as dashed lines, to better demonstrate the water network present in each system.

As the water cluster size is increased to $n = 11$, the two smaller water clusters merge together and DA_5 folds slightly ($R_{NN} = 5.73 \text{ \AA}$). The hydrophobic alkyl chain bends out of the cluster to avoid hydration, while the two charged ends are both hydrated in the larger single cluster. For $n \geq 11$, the single water cluster is positioned around one of the ammonium ends with no bridging water molecules. Instead, the molecules tend to form water bridges (a water molecule is hydrogen bonded to one ammonium group and to another water molecule which is, in turn, hydrogen bonded to the other ammonium group). The di-cation becomes fully folded by 20 water molecules in the cluster (Figure 2) with an R_{NN} value of 5.36 \AA (Supporting Information: Table S1).

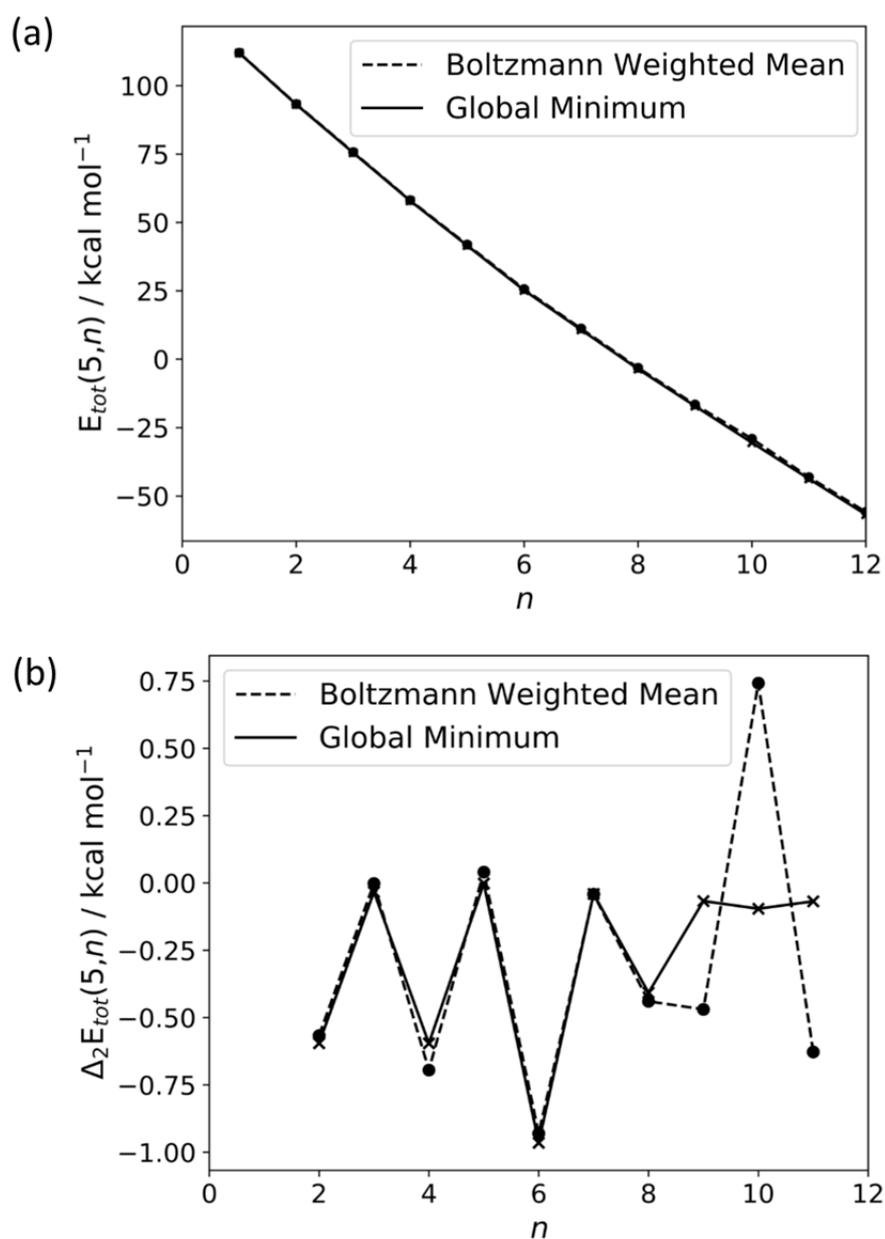


Figure 3. a) A plot of the conformational energies as a function of the number of water molecules for $DA_5(H_2O)_n$ with $n = 1 - 12$. b) A plot of second difference for the conformational energies of $DA_5(H_2O)_n$ with $n = 2 - 11$.

3.2.2 Alkyl-dicarboxylate Di-anions

The variation of conformational energies with increasing alkyl chain length (Supporting Information: Figures S24 - S35) follows the same general trend for the DC_m series in water clusters ($n = 1 - 12$) as previously seen for unhydrated conditions (Figure 1). The conformational energies decrease as the alkyl chain length increases and an even number of carbon atoms in the hydrophobic chain results in

a more stable conformation for $m < 9$. As water molecules were added to each DC_m , there was a decrease in the conformational energies as a result of extra stabilisation by the added water molecules of the carboxyl groups (Supporting Information: Figures S7 - S15).

Table 3. Values of the critical hydration number corresponding with respective alkyl chain length for DC_m .

m	n^* (this work)	n^* (literature)
3	6	
4	9	13 (ref 16)
5	11	
6	12	16 (ref 6), 18 - 19 (ref 16)
7	12	
8	14	18 - 19 (ref 16)
9	15	
10	15	
11	19	

As shown in Table 3, the n^* values for hydrated DC_m increase with increasing chain length (m). The values at $m = 4, 6$ and 8 can be compared to those found experimentally,^{6,16} and are all found to be lower.

For $DC_5(H_2O)_n$ where $n = 1 - 12$, the conformational energy decreases with increasing water cluster size (Figure 4a). As the first ten water molecules ($n = 1 - 10$) are added, the conformation remains linear and the average distance between the carbon of the carboxylate groups, R_{CC} , is the maximum distance apart ($R_{CC} \sim 7.65 \text{ \AA}$), to minimise Coulombic repulsive forces. The terminal carboxylate groups are distinctly solvated by two small water clusters. It is observed that for even numbers of water molecules, the two small water clusters were of equal size due to alternating addition to each

charged end and the added stability of the symmetrical hydrogen bond network in the two terminal water clusters (Figure 4b). This alternating addition of water molecules to each charge centre for a $DC_m(H_2O)_n$ system was also observed by Yang *et al.*⁶

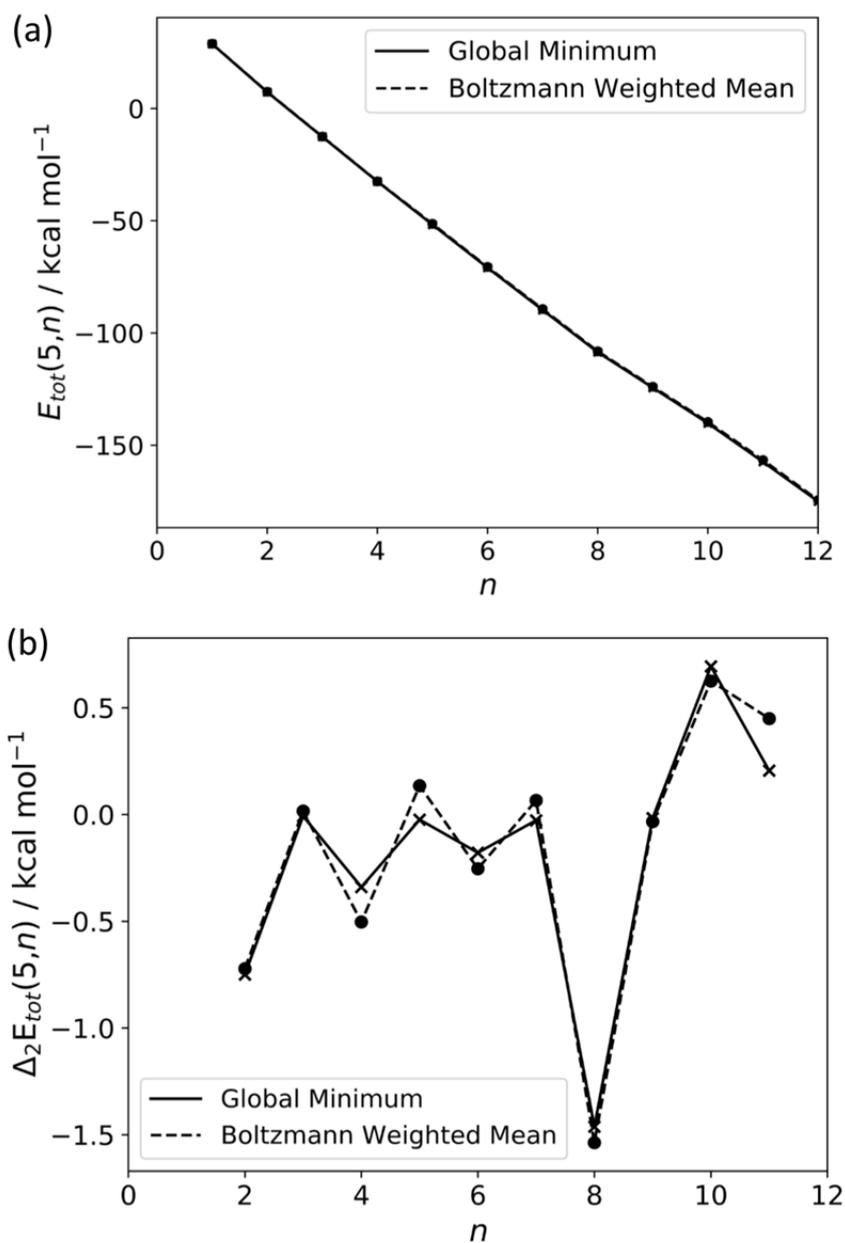


Figure 4. a) A plot of the conformational energies as a function of the number of water molecules for $DC_5(H_2O)_n$ with $n = 1 - 12$. b) A plot of the second difference graph for the conformational energies of hydrated $DC_5(H_2O)_n$ with $n = 2 - 11$.

A conformational transition occurs when $n = 11$ (Figure 5). The two previously separate water clusters merge and DC_5 folds in such a way that the two charged ends are hydrated in the single, resultant water cluster. The increased Coulombic repulsion between the two charged ends (R_{CC} value of $\sim 4.86 \text{ \AA}$) that occurs in the folded conformation is compensated for by the additional hydrogen bonds formed in the larger water cluster.^{3,6} The DC_5 is fully folded when $n = 20$ (Figure 5) with $R_{\text{CC}} \sim 4.63 \text{ \AA}$ (Supporting Information: Table S2). The water molecules form a strongly bound and extensive cage around the charged ends with the hydrophobic alkyl chain folded outside of the water cluster.

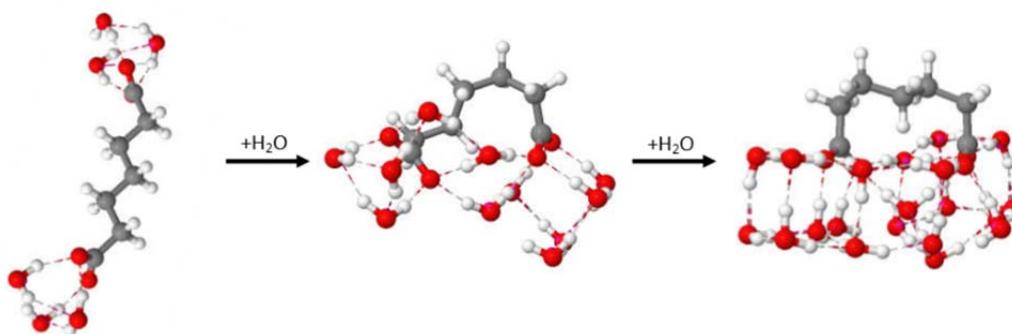


Figure 5. Putative GM structures of $\text{DC}_5(\text{H}_2\text{O})_n$ where $n = 6, 11$ and 20 (left to right) in which the positions of the oxygen (red), carbon (grey) and hydrogen (white) atoms are indicated.

Representations of the hydrogen bonds have been added as dashed lines, to better demonstrate the water network present in each system.

The hydration energies were calculated for $\text{DC}_5(\text{H}_2\text{O})_{1-12}$ and are shown in Figure 6. The hydration energies steadily decrease as each water molecule is added. There is a greater stabilisation observed at the critical hydration number, $n^* = 11$. This additional stability is also found for DC_m where $m = 3, 4, 6$ and 7 at their respective n^* value (Supporting Information: Figure S16 - S23).

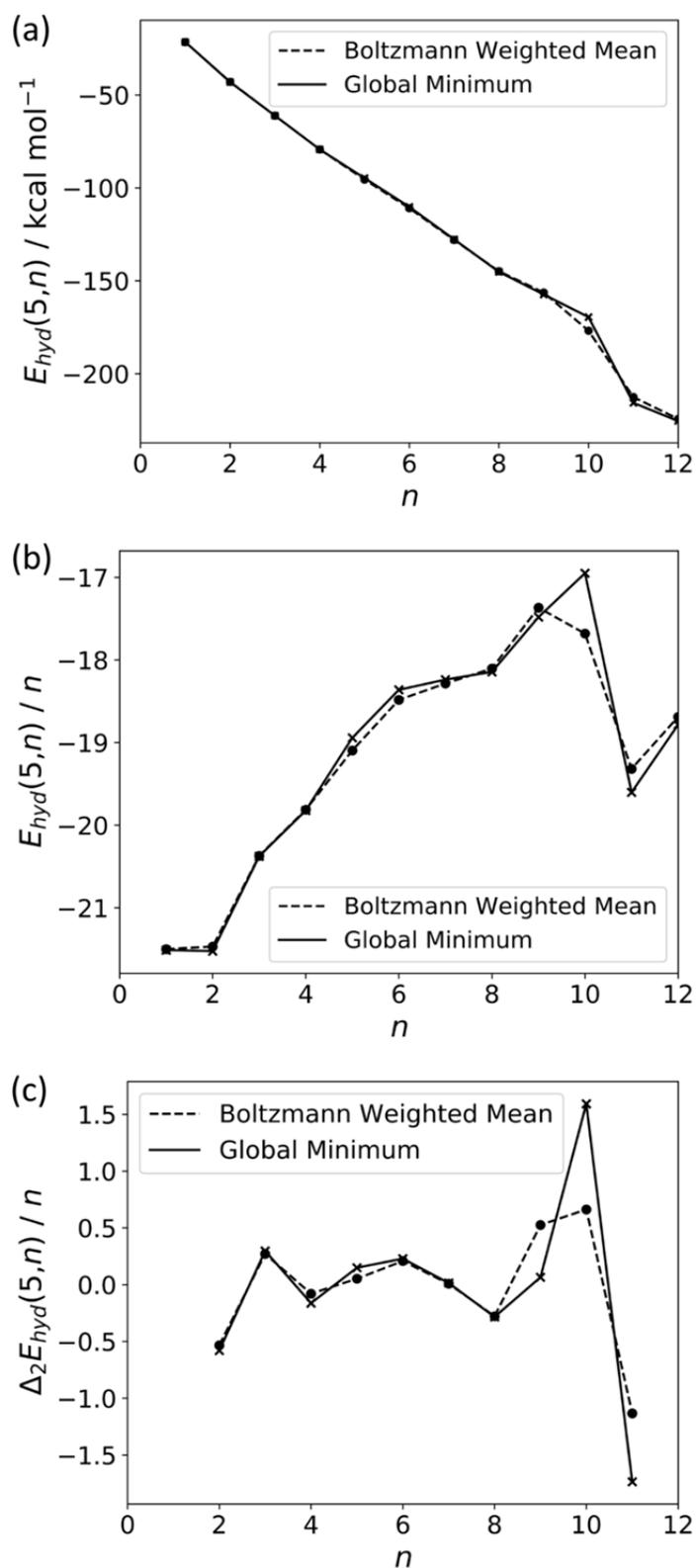


Figure 6. a) A plot of the hydration energies as a function of the number of water molecules present for $\text{DC}_5(\text{H}_2\text{O})_n$ with $n = 1 - 12$. b) A plot of the hydration energies per water molecule for $\text{DC}_5(\text{H}_2\text{O})_n$ with $n = 1 - 12$. c) A plot of second difference of the hydration energies of $\text{DC}_5(\text{H}_2\text{O})_n$ with $n = 2 - 11$.

3.3 Implicitly Solvated Di-ions

3.3.1 Alkyl-diammonium Di-cations

In implicitly solvated conditions, the conformational energies were all found to be negative due to the stabilisation of the DA_m by the simulated solvated conditions (Supporting Information: Figure S36). As the alkyl chain length increases, the conformational energies become less negative. As each successive methylene group is added to the alkyl chain, the hydrophobic interactions with the solvent increases which causes a destabilisation of the DA_m . The putative GM structures are all linear in order to minimise Coulombic repulsive forces between the two ammonium ends.

3.3.2 Alkyl-dicarboxylate Di-anions

The conformational energy becomes less negative as the alkyl chain length increases (Supporting Information: Figure S38a). This is, again, due to the increase of hydrophobic interactions with the simulated solvent as methylene groups are added to the backbone. An even number of carbons in the alkyl chain results in a more stable conformation (Supporting Information: Figure S38b). The effect is larger than that seen in unhydrated conditions and is dominated by the contribution from electrostatic interactions (Supporting Information: Figure S39).

4. Discussion

The n^* values reported here for DA_m and DC_m , for $m = 3 - 11$ (Tables 2 and 3) were all found to be lower than those reported by previous investigations.^{6,12,13,16} The difference in n^* values, between this work and these previous studies, is most likely due to the difference in temperature at which they were determined; this was 0 K in this study but 70 K, or higher, for the others. As a consequence, the effects of entropy are not taken into account in the calculations in this study, which is expected to lead to an increase in n^* .⁶

The average distances between terminal groups, R_{NN} for DA_m and R_{CC} for DC_m , on either side of n^* , are plotted in Figure 7. The conformational transition can be observed by the colour change, as n increases. A single transition, and hence value for n^* , is observed for all di-ions studied (Table 2 and 3), except DA_3 , where there is more than one transition between linear and folded conformations. This uncertainty in n^* , which led to us reporting a range of n^* values in Table 2, could be the result of the small differences in energy between linear and folded conformations at low values of m .

Figure 7 clearly illustrates that, as the alkyl chain length increases (m), n^* increases for both DA_m and DC_m . This is a result of the need for larger water clusters to bridge the charged ends of the larger di-ions and has been observed previously.¹³ It can also be seen that DC_m generally exhibit lower n^* values, than DA_m , and adopt a much more folded conformation, indicated by smaller R_{CC} values, compared to the corresponding R_{NN} values (Supporting Information: Tables S1 and S2). As a consequence, the alkyl backbone in the folded conformation of the di-anions is, therefore, more strained than the comparable DA_m (Figures 2 and 5). It is believed that these differences in structure are due to the additional stability of the DC_m .

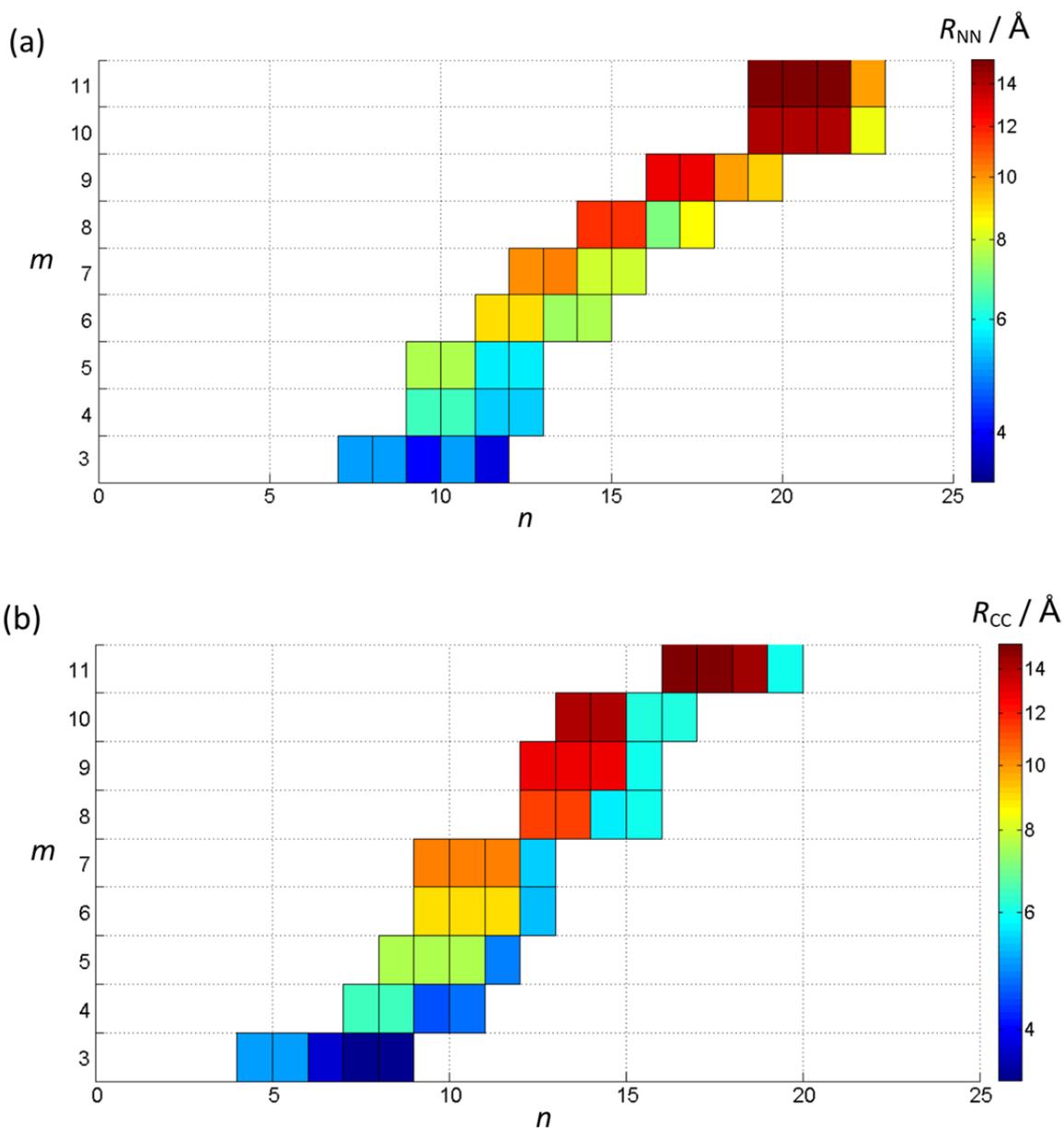


Figure 7. a) A plot of the average distance between the nitrogen atoms (R_{NN}) of the terminal ammonium groups for selected $DA_m(H_2O)_n$ as a function of alkyl chain length (m) and the number of water molecules added (n). b) A plot of the average distance between the carbon atoms (R_{CC}) of the terminal carboxylate groups for selected $DC_m(H_2O)_n$ as a function of alkyl chain length (m) and the number of water molecules added (n). The values of average distance between the terminal groups for the conformations can be found in Supporting Information: Table S1 and Table S2.

This additional stability of the DC_m , indicated by the more negative conformational energies (Figure 3 and 4) in all conditions considered, is due to the negative charge being more delocalised over the

carboxylate units. Furthermore, a higher number of hydrogen bonds is observed for DC₅ compared with DA₅ (Figure 8). This is, in part, because of the increased number of solute-solvent interactions in the DC₅ systems, where each oxygen atom, in the carboxylate groups, can form hydrogen bonds to more than one water molecule (Figure 5). Comparatively, each hydrogen atom of the ammonium group, in the DA₅ systems, can only form a single hydrogen bond (Figure 2). These factors are thought to aid the stabilisation of DC₅, and therefore other DC_{*m*} systems.

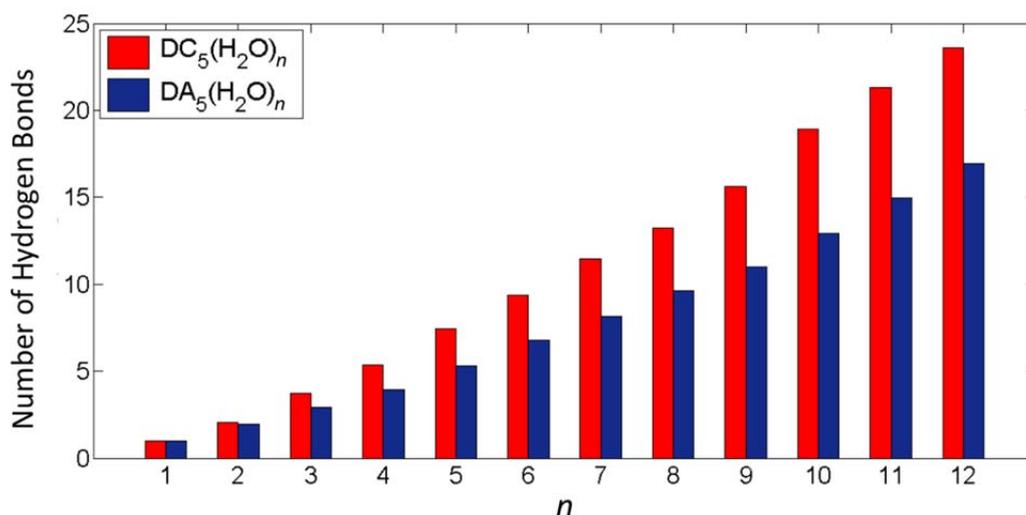


Figure 8. A plot of the average number of hydrogen bonds detected in the DC₅(H₂O)_n and DA₅(H₂O)_n systems as a function of the number of water molecules, *n* = 1 - 12.

Lastly, differences are observed in the structure of the water clusters surrounding DA_{*m*} and DC_{*m*} (Figure 2 and 5). It was observed that the water clusters formed pentagons in hydrated DA_{*m*}, but cubes were observed for DC_{*m*}(H₂O)_{*n*}, albeit in somewhat distorted forms. The shape of the water networks generated in this study have similar structural motifs to those previously observed in small, pure water clusters.^{26,29} It appears that, in this study, the selection of the structure of the water network, is influenced by the shape of the charged terminal group and solute-solvent interactions.

5. Conclusions

Basin-hopping has been used, for the first time, to systematically investigate the behaviour of DA_m and DC_m for a series of alkyl chain lengths in differently solvated conditions. Each series is found to follow similar conformational and energetic trends, which can be explained by considering inter- and intra-molecular interactions. For the DC_m series in unhydrated, implicitly solvated and explicitly solvated conditions, where an even number of carbons in the alkyl chain is found to exhibit a more stable conformation. The origin of this effect has been identified to be primarily due to electrostatic contributions. DFT calculations support the existence of the odd-even effect.

For every di-ion investigated, a linear to folded conformational transition is observed at a critical hydration number, n^* , resulting from a change in the hydration of the two charge centres. It is found that the n^* value is specific to each di-ion and is identified, for the first time, in the case of $m = 3, 4$ and 11 for DA_m and $m = 3, 5, 7, 9, 10$ and 11 for DC_m . Finally, this study demonstrates the suitability of the basin-hopping Monte Carlo algorithm^{18,19} for studying the hydration of flexible, multi-charged systems.

Associated Content

Supporting Information

The supplementary information contains the complete graphs associated with the results presented in this paper.

Data

The coordinates of the low energy structures and global minima can be found in the data depository <https://doi.org/10.25500/edata.bham.00000493>

Author Information

Corresponding Author E-mail: M.M.Britton@bham.ac.uk

The authors declare no competing financial interest.

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