Spectroscopically Probing Solvent-Mediated Folding in Dicarboxylate Dianions**

Torsten Wende, Marius Wanko, Ling Jiang, Gerard Meijer, Knut R. Asmis* and Angel Rubio*

Dicarboxylate salts play an important role in many areas of science including atmospheric, bio- and synthetic chemistry. For example, they are used as antitumor drugs^[1], building blocks for metal-organic framework materials^[2] and are found in aerosol particles comprising photochemical smog^[3]. Isolated dicarboxylate dianions are stable in the gas phase and serve as model systems for multiply charged anions.^[4, 5] The presence of two charge centers separated by a hydrophobic, aliphatic chain also makes them ideal for studying charge-screening and solvent-mediated effects.^[6] In the present study, we use gas phase infrared (IR) spectroscopy of microhydrated suberate (SA) dianion-water clusters, $\text{SA}^{2-}(\text{H}_2\text{O})_{0-28}$, together with quantum chemical calculations to establish relations between conformational changes and spectroscopic features. We then analyze how hydration can drive a conformational transition in a dianion and what role the hydrogen-bonded network plays.

Gas-phase action spectroscopy^[7] is a powerful tool to study the effects of microhydration on the configuration of dicarboxylate dianions, adding one water molecule at a time. Anion photoelectron spectra in combination with quantum chemical calculations^[6, 8, 9] found a delicate dependence of the conformation of the dicarboxylate dianion on the degree of hydration, the aliphatic chain length, as well as on temperature. A more detailed insight into the folding mechanism requires structural information, which is challenging to extract from the photoelectron data. IR photodissociation (IRPD) spectroscopy combined with high-level quantum chemical calculations on microhydrated anions^[10-12] is able to supply this information and thus leads to a considerably more detailed understanding of this hydration-mediated folding process at the molecular level.

Recent IRPD spectra of SA^{2-} and its monohydrate $\text{SA}^{2-}\cdot\text{H}_2\text{O}$

revealed, how the addition of a water molecule effects the spectroscopic signature of the dianion^[13]. The water molecule binds to one of the carboxylate groups of the quasi-linear dianion, causing characteristic shifts of the intense IR-active carboxylate stretching bands. In more detail, the two symmetric (ν_s) and two antisymmetric (ν_a) carboxylate stretching modes in SA^{2-} are quasi-degenerate, because each pair of modes is weakly coupled as a result of the large distance in-between the carboxylate groups. Addition of a single water molecule lifts this degeneracy and leads to a characteristic splitting of both bands (compare $n=0$ and $n=1$ spectra in Figure 1).

Figure 1. Experimental IRPD spectra (red) of $\text{SA}^{2-}(\text{H}_2\text{O})_n$ clusters with $n = 0-28$ in the region of the ν_s and ν_a carboxylate stretching modes. The spectra for $n=0$ and $n=1$ are taken from Ref. ^[13]. Simulated linear IR absorption spectra (blue) are shown for $n=0, 2, \dots, 16$.

In the present study we measured IRPD spectra of $\text{SA}^{2-}(\text{H}_2\text{O})_n$ up to $n=28$ and these are shown in Figure 1. The ions are produced in an electrospray source at room temperature and then cooled to cryogenic temperatures by many collisions with a buffer gas prior to

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irradiation with intense and tunable IR irradiation. As a probe we focus on the carboxylate stretching modes, which lie in the spectral region 1300-1650 cm^{-1} . The photodissociation cross section is plotted as a function of the photon energy. Inspection of the sequential shift of the IRPD bands as a function of the number of water molecules in the cluster (Figure 2, left) reveals that the ν_A band shifts to lower (1603 $\text{cm}^{-1} \rightarrow 1566 \text{ cm}^{-1}$) and the ν_S band (1344 $\text{cm}^{-1} \rightarrow 1404 \text{ cm}^{-1}$) shifts to higher energies with increasing number of water molecules. This sequential shift is nearly monotonic and decreases gradually with increasing n . The frequencies of aliphatic dicarboxylate dianions in bulk solution, e.g. pimelate ($\nu_A=1545 \text{ cm}^{-1}$, $\nu_S=1407 \text{ cm}^{-1}$)^[14] are reached for ν_S but not for ν_A (Figure 2), suggesting that the latter is more sensitive to longer range effects.

Figure 2. Center of the ν_S and ν_A bands (left) and intensity ratio $I(\nu_S)/[I(\nu_S)+I(\nu_A)]$ (right) for microhydrated $\text{SA}^{2-}(\text{H}_2\text{O})_n$ clusters as a function of n . Experimental values (red circles), as well as computed values for linear (green diamonds) and folded (blue triangles) geometries are shown. Error bars indicate the standard deviation (Table S1). Lines connecting the symbols are drawn to guide the eye. Dotted lines indicate absorption frequencies in solution.

While the sequential band shifts are rather regular in nature, the behavior of the band intensities shows a pronounced size dependence. This is best seen in Figure 1 for the IRPD spectra of $n \geq 14$, where the intensity of the ν_S band drops significantly at $n=16$ and remains low throughout the spectra of the larger clusters. A more quantitative analysis, involving the normalized intensity $I(\nu_S)/[I(\nu_S)+I(\nu_A)]$ is plotted in Figure 2 (right). The ratio increases from 32% at $n=0$ to above 50% at $n=11-12$, after which it drops down to 11% at $n=16$ and remains small for all larger water clusters.

To elucidate the origin of this behavior, we determined the minimum energy structures for both linear and folded geometries for even n up to $n=16$ (see Suppl. Mat.) and derived IR spectra (Figure 1, blue traces) from calculated harmonic vibrational frequencies and IR intensities. All simulated IR spectra of the folded geometries show a strong reduction in intensity of the IR-active ν_S mode, whereas the ν_A mode remains strong and decoupled, like in the linear configuration (Figure 2, right). As shown in Figure S3, this trend is independent of the particular structure of the water cluster. Note, minor deviations between the experimental IRPD cross sections and the calculated linear absorption spectra are expected, due to the multiple photon nature of the absorption process^[15].

The IR intensity of a vibrational mode is proportional to the square of the change in dipole moment μ when the geometry is displaced along the corresponding normal coordinate ($|d\mu/dQ|^2$). Displacement along the ν_A mode causes a strong charge transfer

(CT) between the two carboxylate O-atoms, as it breaks the symmetry of the resonance structure. Due to the local character of this CT, it is independent of the geometry of the polyethylene chain and hence unaffected by the folding. This is in contrast to excitation of ν_S , where a smaller, but long-range, CT between the carboxylate moiety and the chain occurs, which is sensitive to changes in dihedral angles upon folding (Figure 3). Furthermore, this CT between the hydrophobic and hydrophilic moieties responds strongly to hydration and it will be affected by the mutual polarization of the carboxylates. Apart from the static polarization, we also find a subtle resonance effect due to the interaction of the fluctuating dipoles induced by excitation of ν_S (Figure 3). We isolated this effect for $n=12$ by calculating the spectrum with isotopically labeled oxygen on one of the two carboxylates to decouple the two resonating COO stretching modes. As a result $I(\nu_S)$ decreases in the linear and increases in folded case (Table S4).

Figure 3. Natural population analysis (NPA) difference charges induced by displacement along ν_S modes for linear (left) and folded (right) $n=12$ clusters (water molecules not shown). $|d\mu/dQ|$ is given in 10^{-2} a.u., intensity I (in parentheses) in km/mol.

While the relation between cluster size and folding is clearly established, the investigation of the folding mechanism in the low-temperature regime remains challenging. Both experiments and classical molecular dynamics (MD) simulations face the problem that a thermodynamic equilibrium between linear and folded structures cannot be obtained at cryogenic temperatures^[6, 9]. As suggested by Wang *et al.*^[6, 9], this is due to a folding barrier that originates from the long-range Coulomb repulsion between the charged moieties, which is counteracted by additional hydrogen bonds that form in the folded structures (Table S2). Our MD simulations support this model in several respects. Even at 230 K, we find low folding/defolding rates. A typical folding event in the MD trajectory (see Suppl. Mat. for a movie for $n=16$) shows a three-step process. First, SA^{2-} rests in an intermediate state where the separation between the carboxylates is reduced by isomerization of two C-C bonds, i.e., the outermost C-C-C-C dihedrals assume a value of ca $\pm 65^\circ$. Then, the first hydrogen bond forms between the two separate water clusters, and finally, the formation of additional hydrogen bonds allows for a third C-C isomerization, which defines the folded state (Table S3).

For the $n=14$ complex, Wang *et al.* have shown that linear and folded structures are in an equilibrium at 108 K^[6, 9]. While at higher temperatures, the linear form is more stable, a negative folding energy E_f of -1.7 kcal/mol was extrapolated for the 0-K limit. This information can be used to assess quantum chemical calculations on the minimum energy structures. To investigate the folding energetics, we performed CEPA/1 calculations (with ZPVE correction from PBE). Compared with the experimental estimate for

$n=14$, the method underestimates E_f by 4.4–4.6 (1.1–1.3) kcal/mol using a double- ζ (triple- ζ) basis set, respectively. Assuming the same error for $n=12$, the linear structure would be more stable by merely 1–2 kcal/mol at 0 K (Table 1).

Table 1: Decomposition of the folding energy E_f (kcal/mol).^[a]

n	$E_{\text{Coul}}^{[b]}$	SA	water	SA-water	ZPVE	E_f
12	26.5	23.0	5.6	-33.7	2.7	-2.4
14	38.7	31.1	24.0	-63.0	1.8	-6.1
16	23.2	18.6	3.5	-31.5	2.6	-6.8

[a] CEPA/1 calculations (aug-cc-pVDZ basis set and MP2/TZVP geometries); ZPVE from PBE/aug-cc-pVDZ. [b] Bare Coulomb interaction of the COO⁻ fragments (including intermolecular CT).

A decomposition of E_f based on fragment calculations is shown in Table 1. The Coulomb repulsion between the carboxylates increases by 20–40 kcal/mol upon folding, which essentially constitutes the folding energy of the bare SA²⁻, when omitting the water molecules in the calculation. The rise in energy is compensated by the interaction between the SA²⁻ and the water cluster and reflected in the formation of additional hydrogen bonds, mostly between the dianion and the water molecules (Table S2). Surprisingly, the water–water interaction does *not* contribute to folding, as the energy of the water cluster is not lowered by folding, when SA²⁻ is omitted in the calculation.

The present results show that (1) the intensity of the IR-active symmetric carboxylate stretching mode represents a sensitive probe to distinguish between linear and folded dicarboxylate dianions, because this mode strongly responds to the coupling between the carboxylate group and the saturated chain. (2) In contrast, the frequencies of the carboxylate stretching modes are more sensitive to the local hydrogen bonding network. Higher resolution techniques can exploit this to directly determine detailed structural information. (3) The stabilization of the folded dianion structures is essentially due to the formation of additional *solute-solvent* (rather than solvent-solvent) hydrogen bonds. Therefore, the folded structures should also persist in much larger microhydrated clusters at sufficiently low temperature. The present findings should have important implications for probing the structure of dicarboxylic acids and their ions in the condensed phase, as well as for remote sensing applications used, e.g., in atmospheric measurements.

Experimental Section

The IRPD experiments are carried out using a ring electrode trap/time-of-flight, TOF, mass spectrometer^[16, 17], temporarily installed at the “Free Electron Laser for Infrared eXperiments”, FELIX, facility^[18] at the FOM Institute Rijnhuizen (The Netherlands). Gas phase anions are produced in a commercial Z-spray source from a solution of suberic acid (1 mM) and NaOH (2 mM) in a 20/80 water/acetonitrile mixture. Parent ions are mass-selected in a quadrupole mass filter (Figure S1) and focused into a ring electrode ion trap. To allow for continuous ion loading and ion thermalization, the trap is continuously filled with He gas (~0.01 mbar) at an ion trap temperature of 15 K. After filling the trap for 99 ms all ions are extracted from the ion trap and focused both temporally and spatially into the center of the extraction region of an orthogonally mounted linear time-of-flight (TOF) mass spectrometer. Here, they interact with the IR laser pulse prior to the application of the extraction voltages. FELIX is operated from 1250 – 1800 cm⁻¹ with a bandwidth of ~0.3% RMS of the central wavelength and average power of 30 mJ/pulse. IR spectra are recorded by monitoring all ion intensities simultaneously as the laser wavelength is scanned. The

photodissociation cross section σ is determined from the relative abundances of the parent and photofragment ions, I_0 and $I(v)$, and the frequency dependent laser power $P(v)$ using $\sigma = -\ln[I(v)/I_0]/P(v)$.^[15]

MD simulations were performed with the CHARMM force field (glutamic acid parameters)^[19]. For successive structure selection and optimization, the SCC-DFTB method^[20], DFT (PBE/aug-cc-pVDZ) and CC2/aug-cc-pVDZ were used, the latter two as implemented in turbomole 6.1^[21]. CEPA/1 (aug-cc-pVDZ basis) calculations were performed with ORCA 2.7^[22]. Theoretical IR spectra show scaled (factor 1.0246) PBE/aug-cc-pVDZ frequencies. See Suppl. Mat. for computational details.

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IR-Spectroscopic Probe for
Characterizing Solvent-Mediated
Folding in Microhydrated Dicarboxylate
Dianions

Supplementary Material

Spectroscopically Probing Solvent-Mediated Folding in Dicarboxylate Dianions

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Computational Details

Structure Preparation

To obtain the minimum-energy structure for the folded and linear configurations, a multi-stage protocol was used. Only the complexes with even number of water molecules were considered. First, the configuration space was roughly sampled by 5 ns of molecular dynamics simulation (after 1 ns equilibration) using CHARMM with the TIP3P water model and force field parameters adopted from the CHARMM27 parameters for the glutamic acid side chain.^[1] The highest possible temperature was chosen at which no vaporization of water occurred. Due to overbinding of water (bulk water parameters) this was at 260 K. In these simulations, the linear configuration was strongly preferred for $n=0\ldots 16$. The same behavior was reported in a previous study that employed the Cornell ff94 force field and SPCE water model.^[2] As molecular mechanics (MM) water models with fixed point charges are parameterized for the liquid phase, the water dipole moments are too large for weakly coordinated water molecules in a gas-phase environment. On the other hand, the cooperative effects that are important when the water coordination increases upon folding are neglected due to the neglected polarizability. Therefore, it is not surprising that MM models predict the transition from linear to folded configurations for a larger number of water molecules. In addition, entropy has been suggested to bias the transition in the same direction.^[2, 3] To obtain structures with all possible levels of folding for $n=12\ldots 16$, the equilibrium was biased by scaling down the long-range Coulomb interactions linearly, for distances larger than 9 Å, down to zero at 12 Å. Linear and folded configurations were treated separately thereafter.

From each simulation, 500 random snapshots were optimized using the quantum mechanical (QM) method SCC-DFTB.^[4] Using ultra-tight optimization and appropriate energy thresholds, identical structures and local minima that are more than 5 kcal/mol higher in energy than the lowest one were discarded. The resulting minima (typically 20-200) were optimized with turbomole^[5] using the PBE functional,^[6] aug-cc-pVDZ basis set^[7] and the resolution of identity approximation. For the lowest-energy minima, zero point vibrational energies (ZPVE) were calculated (PBE/aug-cc-pVDZ) and their geometries were further optimized at the MP2/TZVP level of theory and their energies evaluated at the CC2/aug-cc-pVDZ level of theory.^[8] After manual assessment of structures and energies, the best structure was used as starting point for cycles of simulated annealing (0.5 ns for each cycle) at the QM level (SCC-DFTB). The initial temperature was adjusted to allow for topological changes in the water cluster, but preserving the high coordination of an ice-like “phase” (150-200 K). The same optimization/selection was then applied as described above. The procedure was stopped when the annealing did not produce any lower energy minimum.

For all the clusters with $n \leq 12$, except $n=4$, $n=8$, and $n=10$, the global minimum could be determined uniquely, as it is well separated in energy from the next higher one.

For $n=4$, an asymmetric (1+3) cluster was found energetically competitive, but its IR spectrum shows a clear splitting of the ν_s band (see Figure S2), which is not observed experimentally.

For $n=8$, the two most stable clusters differ by 0.4 kcal/mol in energy and both yield good IR spectra. The spectrum of a third cluster (1.1 kcal/mol higher) agrees less well with experiment.

For $n=10$, the asymmetric (4+6) clusters are in the same energy range as the symmetric (5+5) one, and their spectra agree much better with experiment. They combine the very stable cubic hydrogen-bonded network (HBN) of the $n=12$ system on one side with the three HBN's of the $n=8$ system.

In the case $n=14$, four folded and four linear structures were found within a threshold of 1 kcal/mol. To propose the experimentally observed species, the energies were calculated at a higher level of theory and corrected for ZPVE (see section Folding Energy).

IR spectra

All IR spectra were calculated analytically with turbomole using the PBE functional and the aug-cc-pVDZ basis set. To facilitate the comparison of theoretical with experimental spectral shifts, a global scaling factor of 1.0246 for the C-O stretching frequencies was determined from the SA²⁻ spectrum without water.

Folding Energy

Different size consistent post-HF approaches (MP2, CC2, CEPA/1, CCSD) were benchmarked using the CCSD(T) method as a reference. Relative energies of different water clusters were best reproduced with the CEPA/1 method^[9] (Table S5), which also yields the lowest total energies (Table S8). With regard to folding energies, we considered the most relevant configurational change (C-C-C-COO⁻ isomerization) of the chain (Table S6) and, separately, the interaction between the two carboxylates in vacuo (Table S7). In both cases, CEPA/1 was superior. Merely for water binding energies (Table S8), the CEPA/1 method shows errors that are larger than for CC2 and MP2.

As the CEPA/1 method best reprocess CCSD(T) for cluster conformation energies and contributions to the folding energy, we calculated all folding energies and the identification of the lowest-energy structures with the CEPA/1 approach and the aug-cc-pVDZ basis set based on MP2/TZVP geometries, corrected by the ZPVE from PBE/aug-cc-pVDZ.

For explicitly correlated methods, E_f is slowly converging but systematically increases with the completeness of the basis set. For $n=14$, e.g., E_f from CEPA/1 (without ZPVE) is -9.8, -7.9, and -4.7 kcal/mol with the Aug-SV(P), aug-cc-pVDZ, and aug-cc-pVTZ basis set, respectively. This suggests that basis-set superposition plays a role, as the folded structure is more compact and thus profits more from basis-set superposition.

Electronic Properties

For the analysis of inter-molecular charge transfer (CT), atomic charges from a natural population analysis (NPA) were used, as implemented in turbomole. As local density functionals tend to overestimate CT, the HF wave function was used. To visualize the intra-molecular charge fluctuations associated with vibrational modes, NPA charges were employed using the density difference between the minimized and displaced structure, using the same method as for the corresponding IR calculation.

Table S1: Band positions and separations (both in cm^{-1}) of the ν_S and ν_A carboxylate stretching modes from the experimental and calculated vibrational spectra of $\text{SA}^{2-}(\text{H}_2\text{O})_n$ clusters with $n = 0-28$. The normalized band intensity $I_S/(I_S+I_A)$ and statistical errors for the experimental values are also listed.

Experiment ^a								Theory							
n	ν_S^b		$\pm^c$		$\nu_A - \nu_S$	$I_S/(I_S+I_A)$	$\pm^d$	linear				folded			
	ν_S^b	$\pm^c$	ν_A^b	$\pm^c$				ν_S	ν_A	$\nu_A - \nu_S$	$I_S/(I_S+I_A)$	ν_S	ν_A	$\nu_A - \nu_S$	$I_S/(I_S+I_A)$
0	1344		1603		259	0.32		1333	1614	281	0.33				--
1	1355		1599		244	0.35									
2	1358	11	1592	13	234	0.36	0.08	1356	1594	238	0.48				--
3	1362	8	1588	10	226	0.33	0.05								
4	1373	8	1589	11	215	0.35	0.04	1370	1598	227	0.42				--
5	1375	11	1585	12	210	0.40	0.12								
6	1380	12	1580	13	200	0.39	0.09	1377	1587	209	0.48				--
7	1384	15	1579	15	195	0.42	0.17								
8	1388	11	1578	12	190	0.44	0.17	1382	1569	188	0.47				--
9	1389	14	1573	18	185	0.45	0.26								
10	1394	16	1575	18	180	0.43	0.36	1385	1570	186	0.48				--
11	1394	13	1571	13	177	0.56	0.17								
12	1394	11	1569	11	175	0.52	0.13	1385	1570	185	0.49	1394	1574	179	0.23
13	1395	10	1571	13	176	0.44	0.08								
14	1392	12	1571	14	178	0.43	0.09	1390	1569	179	0.48	1404	1574	170	0.18
15	1394	15	1574	15	181	0.32	0.07								
16	1395	13	1578	11	183	0.11	0.04	1392	1582	190	0.44	1403	1572	168	0.19
17	1403	18	1573	12	170	0.12	0.08								
18	1397	20	1582	12	185	0.06	0.08								
19	1403	24	1574	13	172	0.10	0.13								
20	1406	19	1565	12	159	0.07	0.04								
22	1410	18	1567	13	157	0.09	0.05								
24	1412	20	1559	15	147	0.05	0.12								
28	1404	24	1566	13	162	0.03	0.17								

^a Experimental values for $n=0$ and $n=1$ from Ref. 13. ^b Weighted mean energy ($\bar{x}_w$). See Eq. S1. ^c Square root of the weighted mean square of the weighted deviations $MSWD_w$. See Eq. S2-3. ^d Error derived from standard deviation of background signal. See Eq. 4.

Experimental data points: (x_i, y_i) where y_i is the cross section at the energy x_i . y_i' refers to the background signal.

Weighted mean:

$$\bar{x}_w = \frac{\sum_{i=1}^n x_i y_i}{\sum_{i=1}^n y_i} \quad (\text{Eq. S1}).$$

Biased weighted estimator of the variance:

$$\sigma_{x_i}^2 = \frac{\sum_{i=1}^n y_i (x_i - \bar{x}_w)^2}{\sum_{i=1}^n y_i} \quad (\text{Eq. S2}).$$

Weighted mean square of the weighted deviations:

$$MSWD_w = \frac{\sum_{i=1}^n y_i}{\left(\sum_{i=1}^n y_i\right)^2 - \sum_{i=1}^n y_i^2} \cdot \sum_{i=1}^n \frac{y_i (x_i - \bar{x}_w)^2}{\sigma_{x_i}^2} \quad (\text{Eq. S3}).$$

Error in determining intensity ratio:

$$\Delta I = \frac{I_s}{I_s + I_a} \left(\frac{s_{noise}}{I_s} + \frac{2s_{noise}}{I_s + I_a} \right) \text{ with } s_{noise} = n \cdot \sqrt{\frac{\sum_{i=1}^n (y_i' - \bar{y}')^2}{n-1}} \quad (\text{Eq. S4}).$$

Figure S1: Quadrupole mass spectrum of gas phase anions produced in a commercial Z-spray source from a solution of suberic acid (1 mM) and NaOH (2 mM) in a 20/80 water/acetonitrile mixture.

Figure S2: Theoretical IR spectra of low-energy configurations (in ascending order of energy: red, green, blue, purple). By comparison with experiment, an asymmetric (1+3) water cluster can be ruled out for $n=4$, whereas for $n=10$, only the 4+6 clusters (red, purple, blue) reproduce the experimental spectrum.

Figure S3: Effect of folding on the calculated IR spectrum. Theoretical spectra (PBE/aug-cc-pVDZ) of the lowest-energy structures (ZPVE-corrected CEPA/1 energy within 1 kcal/mol of the global minimum).

Figure S4: Natural population analysis (NPA) difference charges induced by displacement along ν_A modes for linear (left) and folded (right) $n=12$ clusters (water molecules not shown). $|d\mu/dQ|$ is given in 10^{-2} a.u., intensity I (in parentheses) in km/mol.

Figure S5: Folded configuration of the $n = 12$ and $n = 14$ cluster.

Figure S6: Computed binding energy per water molecule (CC2/aug-cc-pVDZ), including ZPVE from PBE/aug-cc-pVDZ.

Table S2: Number of hydrogen bonds in the linear and folded configuration.

n	config.	SA—water	water—water	total	total/ n
2	1	4	0	4	2.00
4	10	4	2	6	1.50
6	502	6	6	12	2.00
8	503, 504, 506	8	8	16	2.00
10	505 (sym.)	8	10	18	1.80
	502, 506, 507 (4+6)	8	11	19	1.90
12	linear	8	14	22	1.83
	folded	10	14	24	2.00
14	linear 2002	10	14	24	1.71
	linear 2004, 2006	10	16	26	1.86
	linear 2009 (6+8)	8	17	25	1.79
	folded 692, 688	11	17	28	2.00
	folded 541	12	16	28	2.00
	folded 700	11	16	27	1.93
16	linear	8	20	28	1.75
	folded	10	21	31	1.94

Table S3: Intermolecular charge transfer and geometric properties of the folded structure.^[a]

<i>n</i>	Min	CT ^[b]	sepa (Å) ^[c]	# iso ^[d]
12	a (a)	-0.22 (-0.18)	4.95	4
14	a (a)	-0.21 (-0.22)	4.48	3
	b (b)	-0.24 (-0.21)	4.47	3
	c (c)	-0.21 (-0.21)	4.44	3
	d (d)	-0.23 (-0.21)	4.48	3
16	a (a)	-0.25 (-0.21)	5.38	3

[a] MP2/TZVP geometries. [b] CT from SA to the water cluster, based on NPA charges (values from folded structure in parentheses). [c] Separation of the carboxylate carbon atoms in the folded structure. [d] Number of isomerized C-C bonds (C-C-C-C dihedrals of ca. +/-65°) in the folded structure.

Table S4: PBE/aug-cc-pVDZ intensities (km/mol) of the COO stretching modes for *n*=12.^[a]

	<i>I</i> (<i>v</i> _S)	<i>I</i> (<i>v</i> _A)	<i>I</i> (<i>v</i> _S)/ <i>I</i> (<i>v</i> _A)
linear, resonant	838	874	0.96
linear, non-resonant	384	438	0.88
folded, resonant	318	1071	0.30
folded, non-resonant	162	504	0.32

[a] In the off-resonant calculations, the mass of oxygen is set to 25 u on one carboxylate; the intensities refer to the decoupled modes of the other, unlabelled carboxylate.

Table S5: Water cluster conformation energies (kcal/mol): deviation from CCSD(T).^[a]

	min2002	min2003	min2004	min2006
MP2	0.33	0.36	0.30	0.31
CC2	0.44	0.36	0.37	0.43
CEPA/1	-0.20	0.01	-0.14	-0.17
CCSD	-0.27	-0.15	-0.20	-0.26

[a] The test system is $0.5 \cdot E(\text{CHOO} + 6 \text{ H}_2\text{O}) + 0.5 \cdot E(\text{CHOO} + 8 \text{ H}_2\text{O}) - E(\text{CHOO} + 7 \text{ H}_2\text{O})$ with four different 7 H₂O conformations.

Table S6: C-C-C-COO⁻ isomerization energies (kcal/mol) of the butyric acid anion: deviation from CCSD(T).

MP2	-0.14
CC2	-0.28
CEPA/1	0.04
CCSD	0.13

Table S7: Folding energy (kcal/mol) of SA²⁻ in vacuo: deviation from CCSD(T).^[a]

MP2	-1.24
CC2	-2.01
CEPA/1	0.35
CCSD	0.72

[a] Unrelaxed geometries obtained from the $n=16$ minimum-energy structures by deleting the water molecules.

Table S8: Carboxylate-water binding energies (kcal/mol): deviation from CCSD(T).^[a]

	H ₂ O	A ⁻	A ⁻ + 1 H ₂ O	A ⁻ + 2 H ₂ O	E _{bind} (1 H ₂ O)	E _{bind} (2 H ₂ O)
MP2	8.01	26.72	34.88	42.93	0.16	0.20
CC2	6.56	17.23	23.71	30.16	-0.08	-0.20
CEPA/1	2.65	11.83	15.24	18.45	0.76	1.32
CCSD	3.14	16.55	20.34	24.06	0.64	1.22

[a] The test system is the acetate anion (A⁻) and its complexes with one and two water molecules.

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