Solvent-Mediated Folding

DOI: 10.1002/anie.201006485

Spectroscopic Characterization of Solvent-Mediated Folding in Dicarboxylate Dianions**

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Dicarboxylate salts play an important role in many areas of science, including atmospheric chemistry, biochemistry, and synthetic chemistry. For example, they are used as antitumor drugs[1] and as building blocks for metal–organic framework materials,[2] and they 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] Herein, we use gas-phase infrared (IR) spectroscopy of the microhydrated suberate dianion (SA^{2-}, $^{-}OOC(CH_2)_6COO^{-}$) together with quantum chemical calculations to establish relationships 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 conformation 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, and the temperature. 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 $SA^{2-}\cdot H_2O$ revealed how the addition of a water molecule affects the spectroscopic signature of the dianion.[13] The water molecule binds to one of the carboxylate groups of the quasi-linear dianion, thus causing characteristic shifts of the intense IR-active carboxylate stretching bands. The two symmetric (ν_S) and two antisymmetric (ν_A) carboxylate stretching modes in SA^{2-} are in each case quasi-degenerate, because each pair of modes is weakly coupled as a result of the large distance between the carboxylate groups. Addition of a single water molecule lifts this degeneracy and leads to a characteristic splitting of both bands (compare the spectra for $n=0$ and $n=1$ in Figure 1).

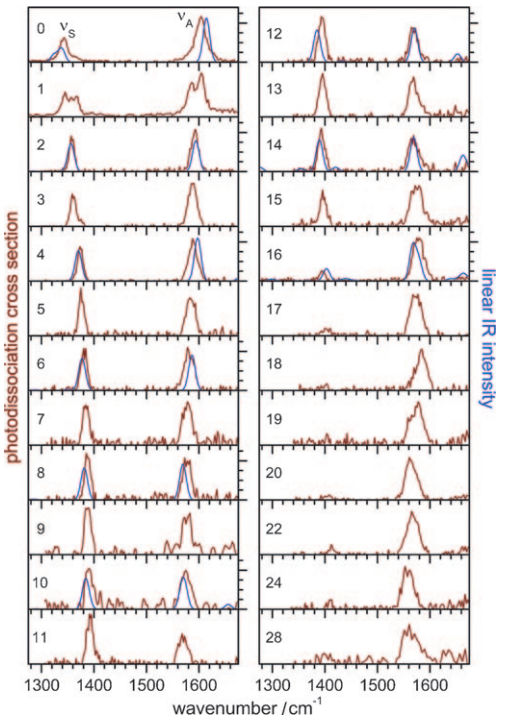

Figure 1. Experimental IRPD spectra (red) of $SA^{2-}(H_2O)_n$ clusters with $n=0$–28 and simulated linear IR absorption spectra (blue) for $n=0$, 2,.., 16 in the region of the ν_S and ν_A carboxylate stretching modes. The spectra for $n=0$ and $n=1$ are taken from Ref. [13].

We measured IRPD spectra of $SA^{2-}(H_2O)_n$ up to $n=28$ (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 irradiation with intense and tunable IR radiation. As a probe, we focus on the

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[**] We thank the Stichting voor Fundamenteel Onderzoek der Materie (FOM) for beamtime and the staff for support and assistance. This research is funded by the European Community's Seventh Framework Programme (FP7/2007-2013, grant nr. 226716), the Spanish MEC (FIS2007-65702-C02-01), the "Grupos Consolidados UPV/EHU del Gobierno Vasco" (IT-319-07), and CIC NanoGUNE (grant no. CSD2006-53). L.J. thanks the Alexander von Humboldt Foundation for a postdoctoral scholarship.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201006485.

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→1566 cm^{-1}) and the ν_S band to higher energies (1344→1404 cm^{-1}) with an increasing number of water molecules. This sequential shift is nearly monotonic and decreases gradually with increasing values of n. The frequencies of aliphatic dicarboxylate dianions in bulk solution, for example, pimelate (ν_A = 1545 cm^{-1}, ν_S = 1407 cm^{-1}),[14] are reached for ν_S but not for ν_A (Figure 2), thus suggesting that ν_A is more sensitive to long-range solvent effects than ν_S.

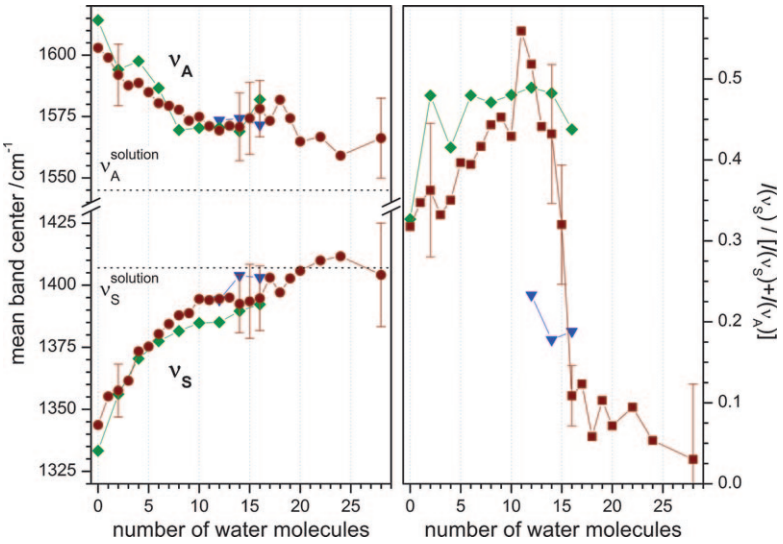

Figure 2. Center of the ν_S and ν_A bands (left) and intensity ratio $I(\nu_S)/[I(\nu_S)+I(\nu_A)]$ (right) for microhydrated $SA^{2-}(H_2O)_n$ clusters as a function of n. Experimental values (red circles) as well as computed values for linear (green diamonds) and folded (blue triangles) geometries are shown. Error bars indicate the standard deviation (Table S1 in the Supporting Information). Lines connecting the symbols are drawn to guide the eye. Dotted horizontal 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 effect 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 0.32 at $n = 0$ to above 0.50 at $n = 11$, after which it drops down to 0.11 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 values of n up to $n = 16$ (see the Supporting Information) 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 in the Supporting Information, this trend is independent of the particular structure of the water cluster. Note that minor deviations between the experimental IRPD cross sections and the calculated linear absorption spectra are expected, owing 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 oxygen atoms, as it breaks the symmetry of the resonance structure. Owing to the local character of this CT, it is independent of the geometry of the polyethylene chain and is hence unaffected by the folding. This situation 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 arising from 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 atoms (^{18}O) on one of the two carboxylate groups to decouple the two resonating COO stretching modes. As a result, the value of $I(\nu_S)$ decreases for the linear structure and increases for the folded structure (Table S4 in the Supporting Information).

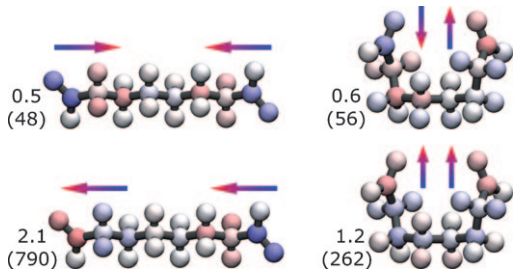

Figure 3. Natural population analysis (NPA) difference charges induced by displacement along ν_S modes for linear (left) and folded (right) $n = 12$ clusters (water molecules not shown). Blue: electron-rich, red: electron-poor, gray: neutral. $|d\mu/dQ|$ is given in 10^{-2} a.u., intensity I (in parentheses) in km mol^{-1}.

While the relationship 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 equilib-

rium between linear and folded structures cannot be obtained at cryogenic temperatures.[6,9] As suggested by Wang et al.,[6,9] this situation 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 in the Supporting Information). Our MD simulations support this model in several respects. Even at 230 K, we find low folding and unfolding rates. A typical folding event in the MD trajectory (see the Supporting Information for a movie for $n = 16$) shows a three-step process. First, SA^{2-} rests in an intermediate state in which the separation between the carboxylates is reduced by isomerization of two C–C bonds, that is, the outermost C-C-C-C dihedral angles assume a value of approximately $\pm 65°$. Then, the first hydrogen bond forms between the two separate water clusters, and finally, the formation of additional hydrogen bonds allows for isomerization of a third C–C bond, which defines the folded state (Table S3).

For the $n = 14$ complex, Wang et al. have shown that linear and folded structures are in 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^{-1} 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 and 1.1–1.3 kcal mol^{-1} when double-ζ and triple-ζ basis sets, respectively, are used. Assuming the same error for $n = 12$, the linear structure would be more stable by merely 1–2 kcal mol^{-1} at 0 K (Table 1).

Table 1: Decomposition of the folding energy E_f [kcal mol^{-1}].[a]

n	E_{Coul}[b]	SA	Water	SA^{2-}–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^{-1} upon folding, which essentially constitutes the folding energy of the bare SA^{2-} ion when the water molecules in the calculation are omitted. The rise in energy is compensated by the interaction between the SA^{2-} ion and the water cluster and reflected in the formation of additional hydrogen bonds, mostly between the dianion and the water molecules (Table S2 in the Supporting Information). Surprisingly, the water–water interaction does not contribute to folding, as the energy of the water cluster is not lowered by folding when SA^{2-} is omitted in the calculation.

The present results allow us to draw the following conclusions:

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 aliphatic 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 effect to determine more 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, for example, in atmospheric measurements.

Experimental Section

The IRPD experiments were carried out using a ring electrode trap and time-of-flight 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 were 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 were mass-selected in a quadrupole mass filter (Figure S1 ion the Supporting Information) and focused into a ring electrode ion trap. To allow for continuous ion loading and ion thermalization, the trap was continuously filled with He gas (ca. 0.01 mbar) at an ion-trap temperature of 15 K. After filling the trap for 99 ms, all ions were 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 mass spectrometer. Here, they interacted with the IR laser pulse prior to the application of the extraction voltages. FELIX was operated from 1250–1800 cm^{-1} with a bandwidth of approximately 0.3% root mean square (RMS) of the central wavelength and average power of 30 mJ pulse^{-1}. IR spectra were recorded by monitoring all ion intensities simultaneously as the laser wavelength is scanned. The photodissociation cross section σ was determined from the relative abundances of the parent and photofragment ions I_0 and $I(\nu)$ and the frequency-dependent laser power $P(\nu)$ using $\sigma = -\ln[I(\nu)/I_0]/P(\nu)$.[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 the Supporting Information for computational details.

Received: October 15, 2010
Published online: March 24, 2011

Keywords: carboxylic acids · hydrates · IR spectroscopy · molecular dynamics · solvent effects

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