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Short communication

# Gas-phase structures of solution-phase zwitterions: Charge solvation or salt bridge?

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ABSTRACT

Sodium and lithium adduct ions of a synthetic guanidiniocarbonylpyrrole-derivative are examined in the gas phase. A wavelength tunable free electron laser (FEL) was used for photo-dissociation spectroscopy experiments in the infrared (1400–1800 $\text{cm}^{-1}$). The photo-dissociation spectra are compared to calculated IR spectra of structures identified by theory. All photo-dissociation spectra acquired are strikingly similar, indicating that all ions adopt analogous gas-phase structures. Additionally, the respective sodium adduct ions were examined with ion mobility mass spectrometry (IMS). Although computational efforts succeeded in finding a charge solvated conformer that matched both the photo-dissociation spectra and the IMS data, the predicted global minimum was a salt-bridge structure.

## 1. Introduction

In this contribution we present a study on synthetic, amphoteric guanidiniocarbonylpyrrole carboxylate molecules, which are zwitterions in polar solutions and develop a strong tendency towards oligomerization in, e.g., water or dimethylsulfoxide [1]. It has been shown that the self-association properties of these compounds are critically dependent on the length of the aliphatic spacer. In solution (NMR) and in the gas phase (electrospray mass spectrometry), large oligomer aggregates are found for members of the series presenting short methylene-chains ($n = 1, 2$), whereas compounds with relatively long alkyl-chains prefer to remain monomers or form at best dimers ($n = 3–5$) [1,2]. Obviously, intramolecular coulomb interactions are outbalancing intermolecular interactions in the case of the latter, whereas the opposite is true for the former. The unique clustering properties of this class of compounds motivated us to study the gas-phase behavior in more detail. For that purpose a representative analyte with a relatively long side chain ($M_4$), was selected to probe whether a salt-bridge (SB) structure, present in the solution phase, is conserved in the gas phase (Scheme 1) or whether a charge solvation (CS) structure is more stable.

Recent studies of alkali metal cationized arginine and other amino acids, suggest that zwitterionic structures are favored with increasing size of singly charged metal ions [3,4]. As a consequence we chose to study the $M_4$ complex with the small sodium ion in order to minimize the preference of the metal cation for the formation of a gas-phase zwitterion. The methyl ester $M_4Me$ was included in the study to provide a charge solvation structure for reference. Lithiated molecular ions of $M_4$ and $M_4Me$ were also examined since the lithium cation strongly favors the formation of charge solvation structures in the gas phase [2,3] and thereby provides a valuable data set for comparison.

## 2. Materials and methods

The wavelength tunable free electron laser (FEL) for infrared experiments (FELIX) [3–5] was used for the spectroscopic experiments. Structure assignment of the ions was achieved by comparison of the recorded spectra with spectra calculated at high levels of theory (DFT and ab initio). Additionally, collision cross sections of the molecular ions of interest were determined by ion mobility mass spectrometry (IMS) measurements and compared to calculated values of ion structures identified by theory.

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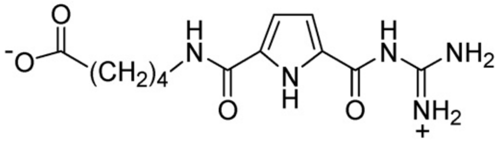

**Scheme 1.** Zwitterion structure of analyte $M_4$ in polar solution; note that the index 4 denotes the number of methylene groups in the alkyl-chain. Intramolecular interactions are neglected in the depicted structure for reasons of clarity.

### 2.1. *Compounds*

The synthesis of the guanidiniocarbonylpyrrole carboxylate compounds $M_4$ and its methyl ester $M_4Me$ was accomplished as reported in Ref. [1]. The solvents (methanol, dimethylsulfoxide) and the alkali metal salts ($NaCF_3COO$ and $LiCF_3COO$) used to generate the desired molecular ions of $M_4$ and $M_4Me$ were used as purchased by Sigma–Aldrich (Hamburg, Germany). Distilled water was used to dissolve the alkali metal salts for preparation of stock solutions.

### 2.2. *Computational modeling*

Arbitrary CS and SB structures of all molecular ions were chosen as input structures for a conformation search using MacroModel 8.1 (Schroedinger Inc., Portland, OR). 5000 LCMM steps were performed, each followed by minimization using the Merck Molecular Force Field (MMFF94s). Candidate structures with low MMFF energy were selected for subsequent higher level calculations which were performed on the DFT and MP2 level of theory as implemented in Gaussian 03 applying the 6-311++G(2d,2p) basis set on all atoms [6]. All relevant sodiated and lithiated molecular ion structures, the respective IR-spectra and the energetic ordering identified by theory are located in the supporting information.

### 2.3. *Electrospray*

Analytes $M_4$ and $M_4Me$ were dissolved in dimethylsulfoxide (DMSO) and the stock solutions were subsequently diluted with methanol to give $10^{-4}$ M solutions (5:95% DMSO/methanol). These solutions were used for the FELIX experiments. Abundance optimization of the sodiated precursor ions was achieved by drop wise (1–3 μL) addition of a 1 mM solution of $CF_3COONa$ in $H_2O$ to the solutions of $M_4$ and $M_4Me$. An analogous sample preparation procedure was used to optimize the abundance of $[M_4+Li]^+$ and $[M_4Me+Li]^+$ precursor ions.

### 2.4. *Free electron laser for infrared experiments*

Experiments were conducted on a 4.7 T FT-ICR mass spectrometer equipped with an electrospray ionization (ESI) source at the front end. The radiation of the free electron laser enters the FTICR-MS from the back through a ZnSe window allowing IRMPD experiments of stored ions to be performed. The instrument used for the FELIX study and general experimental methods have been described in detail elsewhere [7,8]. Sodiated and lithiated molecular ions of $M_4$ and $M_4Me$ were generated by infusing respective solutions of the analytes prepared as described above. The solutions were infused at a flow rate of ~10 μL min$^{-1}$ into the ESI source (Z-spray, Micromass, UK). The electrospray needle was held at voltages around +3 kV. Ions were accumulated in a storage hexapole (≤3 s) prior to extraction through a quadrupole bender, an RF-octopole and finally transferred into the ICR cell. Electrostatic switching of the dc bias of the octopole allows ions to be captured in the ICR cell without the use of a gas pulse, thus avoiding collisional heating of the ions.

For FELIX, spectra were recorded over the wavelength range of 1400–1800 cm$^{-1}$. Pulse energies at the instrument were around 35 mJ per macropulse of 5 μs duration. The full width at half maximum bandwidth of the laser was typically 0.5% of the central wavelength. All precursor ions were irradiated for 3 s, corresponding to interaction with 15 macropulses. FELIX spectra were generated by detection of the precursor ion depletion and the production of fragment ions, in this case the loss of guanidine at each IRMPD wavelength.

### 2.5. *Ion mobility mass spectrometry*

Ion mobility data were obtained on a custom-built electrospray quadrupole mass spectrometer equipped with a drift cell [9]. Ions exiting the source capillary enter an ion funnel where they are focused and guided towards the drift cell. Near the funnel exit, ions are stored and periodically pulsed into the ion mobility cell. Ions drift through the cell under the influence of weak uniform electric field while undergoing thousands to millions of collision with the buffer gas helium held at a pressure of ~5 mbar. Ions exiting the cell are mass analyzed and detected as a function of arrival time. For known experimental conditions (pressure, temperature, electric field, cell length), the ion–helium collision cross section is readily deduced from the ion arrival time distribution [10]. Employing a projection approximation model [11], experimental collision cross sections are compared to theoretically evaluated cross sections of candidate structures obtained by molecular mechanics or electronic structure calculations.

## 3. Results and discussion

FELIX-spectra were recorded over the wavelength range of 1400–1800 cm$^{-1}$. The characteristic CO stretching mode, which is diagnostic of either SB or CS structures, is located in this region [3,4]. Examination of Fig. 1 indicates that all spectra of the sodiated and lithiated precursor ions exhibit a similar set of five rather unresolved bands. All spectra show a remarkable similarity in four of the major bands (at ~1460, 1520, 1560 and 1625 cm$^{-1}$). This striking similarity over the entire IR-region, in which the stretching modes of C–O and C–N and bending modes of N–H and O–H are found, suggests that closely related conformations of all precursor ion species are present [3,4]. Only the band at the blue end of the scale shows a significant dependence on structure. The FELIX-spectra of both $M_4$ methyl ester precursor ions, i.e., $[M_4Me+Na]^+$ and $[M_4Me+Li]^+$

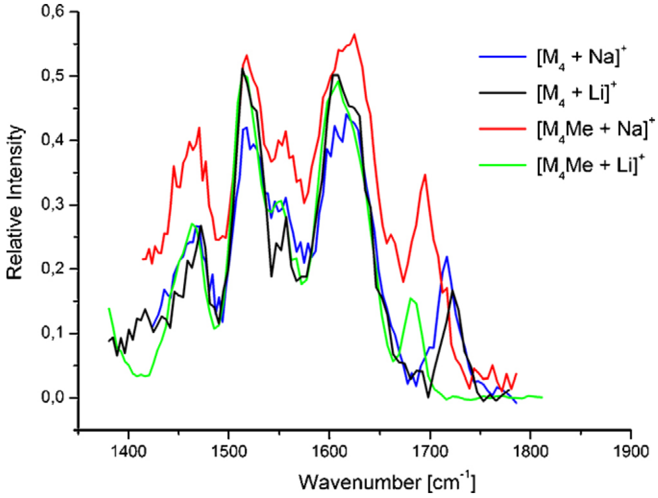

**Fig. 1.** FELIX-spectra of the molecular ions $[M_4+Na]^+$, $[M_4+Li]^+$, $[M_4Me+Na]^+$, and $[M_4Me+Li]^+$.

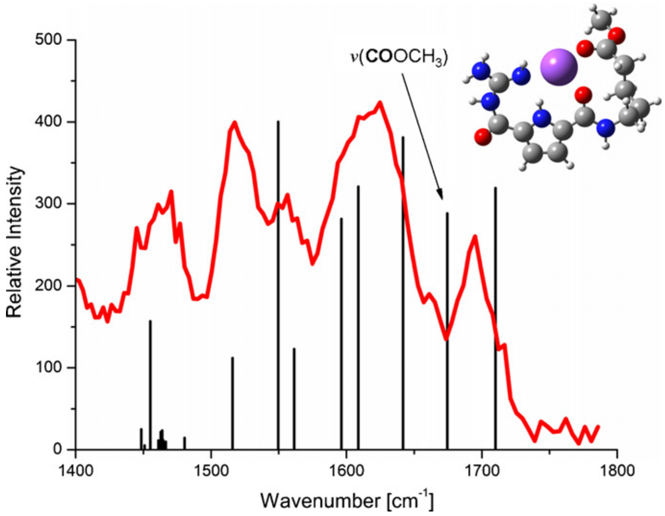

**Fig. 2.** FELIX-spectrum of $[M_4Me+Na]^+$ compared to the calculated spectrum of the lowest-energy conformer of $M_4Me$, i.e., CSc3 (shown schematically: sodium: purple; oxygen: red; nitrogen: blue; carbon: grey; hydrogen: white). Frequencies are scaled by a uniform factor of 0.98 found to be best suited for the level of theory applied [14]. The calculated signal intensities and their position differ from those found in the FELIX spectrum. These discrepancies are often encountered, but do not invalidate the assignment [15–19].

exhibit the CO stretching mode substantially red shifted in comparison to the analogue absorption of the carboxyl acid moiety in the respective precursor ions of $M_4$ (Figs. 1–3). In Fig. 2, the calculated spectrum of the most stable charge solvation structure (CSc3) of $[M_4Me+Na]^+$ is compared with the respective FELIX spectrum. It is apparent that this charge solvation structure is also a good match for the recorded FELIX spectrum of $[M_4+Na]^+$ as shown in Fig. 3. However, the assignment of an individual structure for this set of molecular ions proved to be a complex task as Fig. 4 illustrates. All relevant structures of the sodiated conformers named in Fig. 4 are depicted in the supplementary material (Fig. 1S). Additionally, an analogue set of figures illustrating the interpretation of the FELIX data of the lithiated analytes is provided as well.

After thorough inspection of the figures presented, it is apparent that $[M_4Me+Na]^+$ and $[M_4+Na]^+$ adopt the same charge solvation structure (CSc3). Due to the pronounced similarity of all FELIX-spectra and the structure assignment for the sodiated molecular ions it is reasonable to assume that the molecular ions formed with the very small lithium cation are also charge solvated. However, for both molecular ions of $M_4$ DFT and MP2 calculations predict SB structures to be more stable than any CS conformer identified (see Table 1S in the supplementary material).

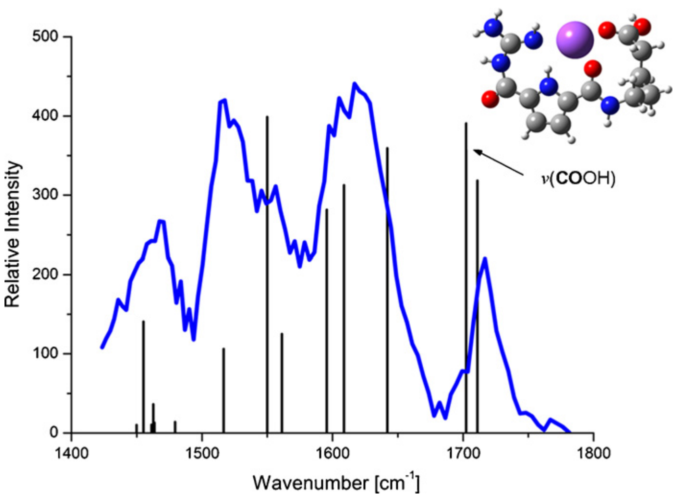

**Fig. 3.** FELIX-spectrum of $[M_4+Na]^+$ compared to the calculated spectrum of the CSc3 conformer of $M_4$ (shown schematically with the same color scheme as in Fig. 2). Frequencies are scaled by a uniform factor of 0.98 found to be best suited for the level of theory applied [14].

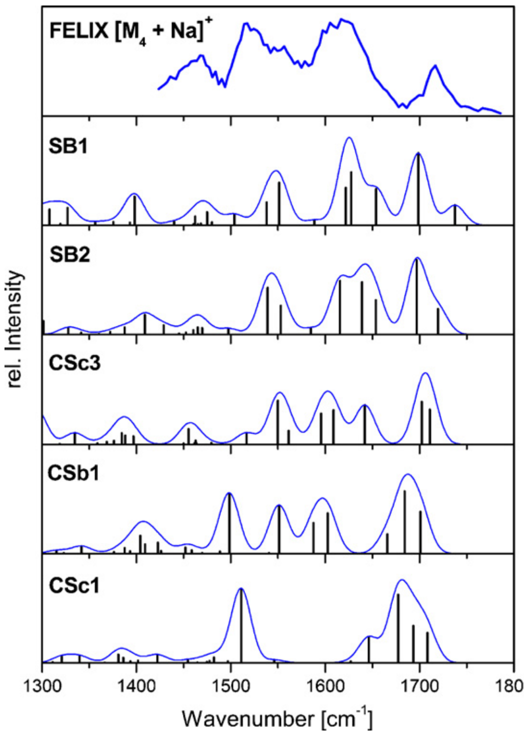

**Fig. 4.** FELIX spectrum of $[M_4+Na]^+$ and calculated spectra of the most stable salt bridge and charge solvation isomers. All relevant gas-phase structures of $[M_4+Na]^+$ predicted by theory (SB1, SB2, CSb1, CSc1 and CSc3) are depicted in Fig. 1S in the supplementary material.

To further test our interpretation IMS-based cross section measurements were conducted to independently probe the structures of the molecular ions in the gas phase (see Table 1) [10,12]. A comparison of the experimental data with theoretically evaluated cross sections for DFT structures indicates good agreement for structure CSc3, the best FELIX match for both $[M_4+Na]^+$ and $[M_4Me+Na]^+$. This completely independent measurement strongly supports the spectroscopic evidence that all systems adopt a charge solvation structure in the gas phase.

**Table 1**

Experimentally determined (IMS) [10,12] and theoretically calculated collision cross sections [11,13] of relevant ion structures of $[M_4+Na]^+$ and $[M_4Me+Na]^+$. Experimental error of IMS cross section measurements: ±2 Å$^2$.

| | Cross section [Å$^2$] |
|---|---|
| $[M_4+Na]^+$ | |
| Experiment | 110[a] |
| SB1[b] | 106 |
| CSc3[b] | 112 |
| CSb1[b] | 121 |
| $[M_4Me+Na]^+$ | |
| Experiment | 119[a] |
| CSc3[b] | 118 |
| CSb1[b] | 127 |
| CSc1[b] | 116 |

[a] Experimental error ±2 Å$^2$.

[b] Structures given in the supporting information.

## 4. Conclusion

In summary, the experimental results, both spectroscopic and IMS, of the guanidiniocarbonylpyrrole carboxylate derivatives correlate convincingly with the characteristics of a charge solvation structure identified by theory. Although the selected analytes possess a pronounced amphoteric character in the gas phase, they adopt charge solvation conformations when cationized by lithium or sodium ions. The formation of salt-bridge structures, present in solution, thus depends on the stabilization properties of polar solvent molecules and potentially on the nature of the cationizing metal ion. Apparently the interaction of the guanidinium and carboxylate groups with the sodium ion is not strong enough to overcome the lack of a solvent shell and salt bridges are not formed in these systems in the gas phase. It is noted that the energetic ordering of the gas-phase structures of $M_4$ predicted by computational modeling (DFT and MP2) appears to be substantially off, favoring SB structures rather than CS structures in gaseous sodiated and lithiated molecular ions.

The results presented in this communication are part of a systematic and multidimensional study of gas-phase molecular ions of a large series of similar compounds only differing in the length of the alkyl side-chain, which will be finalized soon.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijms.2008.12.011.

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