Cations Bind Only Weakly to Amides in Aqueous Solutions

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Supporting Information

ABSTRACT: We investigated salt interactions with butyramide as a simple mimic of cation interactions with protein backbones. The experiments were performed in aqueous metal chloride solutions using two spectroscopic techniques. In the first, which provided information about contact pair formation, the response of the amide I band to the nature and concentration of salt was monitored in bulk aqueous solutions via attenuated total reflection Fourier transform infrared spectroscopy. It was found that molar concentrations of well-hydrated metal cations (Ca\textsuperscript{2+}, Mg\textsuperscript{2+}, Li\textsuperscript{+}) led to the rise of a peak assigned to metal cation-bound amides (1645 cm\textsuperscript{-1}) and a decrease in the peak associated with purely water-bound amides (1620 cm\textsuperscript{-1}). In a complementary set of experiments, the effect of cation identity and concentration was investigated at the air/butyramide/water interface via vibrational sum frequency spectroscopy. In these studies, metal ion–amide binding led to the ordering of the adjacent water layer. Such experiments were sensitive to the interfacial partitioning of cations in either a contact pair with the amide or as a solvent separated pair. In both experiments, the ordering of the interactions of the cations was: Ca\textsuperscript{2+} > Mg\textsuperscript{2+} > Li\textsuperscript{+} > Na\textsuperscript{+} ≈ K\textsuperscript{+}. This is a direct cationic Hofmeister series. Even for Ca\textsuperscript{2+}, however, the apparent equilibrium dissociation constant of the cation with the amide carbonyl oxygen was no tighter than ~8.5 M. For Na\textsuperscript{+} and K\textsuperscript{+}, no evidence was found for any binding. As such, the interactions of metal cations with amides are far weaker than the analogous binding of weakly hydrated anions.
Materials and Methods

\[ \text{C}_3\text{H}_7\text{CONH}_2 \]

Amide group

carbonyl oxygen

Hydrated cations

\[ \text{Ca}^{2+} \]
ATR FTIR Measurements

To suppress the contribution to C=O, NH$_2$ fully exchanged with ND$_2$

![Diagram](image)

**a)**  
D$_2$O  
1620 cm$^{-1}$  

**b)**  
5 M NaCl in D$_2$O  
no variation in intensity

**c)**  
5 M CaCl$_2$ in D$_2$O  
split into two

Red shift, decreased
ATR FTIR Measurements

- Spectra with KCl and NaCl show no changes
In good agreement with a direct cationic Hofmeister series,

\[ \text{Ca}^{2+} > \text{Mg}^{2+} > \text{Li}^+ > \text{Na}^+ \approx \text{K}^+ \]
VSFS Measurements

- The presence of the salts affected the water orientation.
- A greater degree of cation adsorption over its counterion should correspond to increased water ordering.

2880 cm\(^{-1}\): the CH\(_3\) symmetric stretch
2940 cm\(^{-1}\): a Fermi resonance
3100–3600 cm\(^{-1}\): water region
3180, 3390 cm\(^{-1}\): the symmetric and asymmetric NH\(_2\) stretch modes.
VSFS Measurements

- The water structure peaks increase with CaCl$_2$ concentration.
- No effect is observed by adding NaCl.
VSFS from 300 mM butyramide with: (a) MgCl2, (b) LiCl, and (c) KCl.
O.S. strength values for the 3200 cm\(^{-1}\) peak as a function of salt conc.

- The VSFS data report on interfacial water structure ordering, while the FTIR data correspond to the carbonyl stretch of the amide moiety in bulk solution.
- In good agreement with a direct cationic Hofmeister series,

\[
\text{Ca}^{2+} > \text{Mg}^{2+} > \text{Li}^+ > \text{Na}^+ \approx \text{K}^+
\]
Conclusion

- Spectroscopic evidence for very weak binding behavior for Ca$^{2+}$ and Mg$^{2+}$, nearly statistical binding for Li$^+$, and exclusion for Na$^+$ and K$^+$ from the amide oxygen.