Substituent effects in BAPTA-based ion binding: A computational investigation

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Significance

Ion binding stabilizes biological molecules.

Figure 1. Parvalbumin (above) is a Ca^{2+}-dependent binding protein. Ca^{2+}-binding capacity is critical for regulating Ca^{2+} concentrations in human systems. Graphics by Hanbae Vedrani, PhD 3rd year, Edington Lab.

- Ions interact with biomolecules to influence function & reactivity.
- Metal ions stabilize protein conformations, which facilitates signaling and catalysis.
- Chelators model metal-binding sites by mimicking binding environments.
- Parvalbumin (left) is an example of an ion-dependent protein that regulates intracellular signaling.

How do metal ions influence different electrostatic binding environments?

Objective:

Spectroscopic profiles to be correlated with metal ion selectivity.

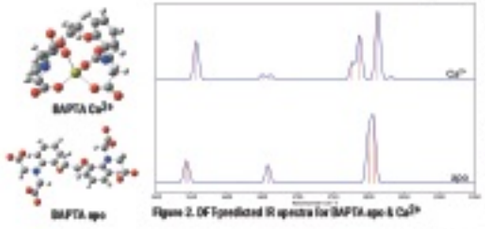
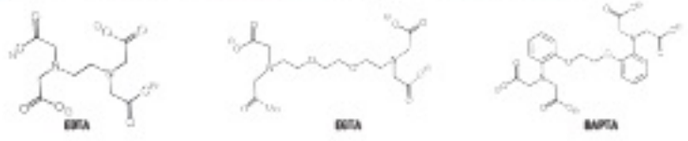


Figure 2. DFT-predicted IR spectra for BAPTA apo & Ca^{2+}

- BAPTA is a polycarboxylate chelator that exhibits ion selectivity & fast kinetics.
- BAPTA is selective for Ca^{2+} over Mg^{2+}.
- BAPTA forms the basis of photolabile derivatives that enable optically-triggered binding kinetics.



Binding affinities and k_{off} rates of EDTA, EGTA, BAPTA[1-5]

Chelator	Ca^{2+} affinity (k_D,μM)*	Mg^{2+} affinity (k_D,μM)*	$k_{off}^{Ca^{2+}}$ (10^6/(M.s))
BAPTA	4.4	~0.9	20.0
EGTA	8.5×10^{-6}	~5.2	0.5
EDTA	~0.2	~17.0×10^3	~79.0

EDTA, EGTA and BAPTA have similar Ca^{2+} binding affinities but differ in Mg^{2+} binding affinities and kinetics.

Methods

IR spectroscopy is sensitive to picometer-scale structural changes within chelators upon metal binding.

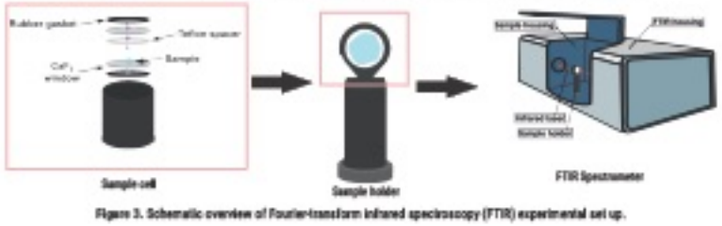


Figure 3. Schematic overview of Fourier-transform infrared spectroscopy (FTIR) experimental set up.

Methods

Density Functional Theory predicts ion-chelator binding interactions.

- Quantum mechanical model used to predict electronic structures and vibrational modes of molecules by numerically simulating electron wavefunctions.

Basis Set	Functional Theory
Def2svp	M06

Results

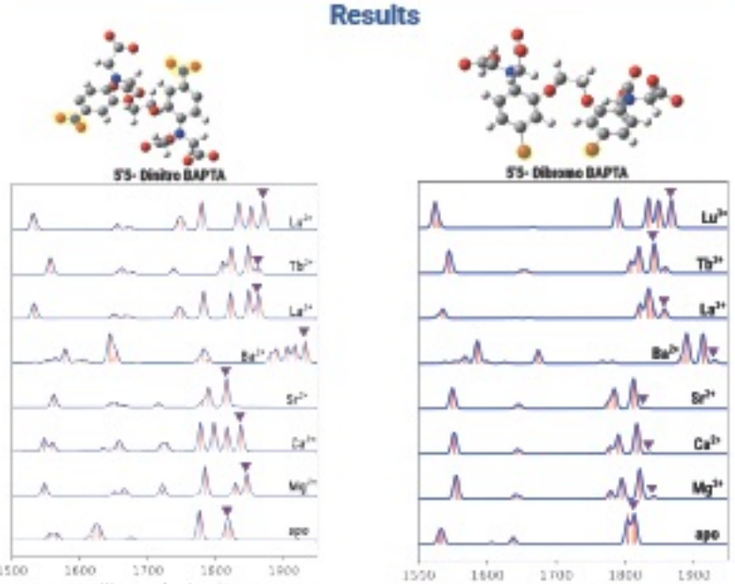


Figure 4. Calculated IR vibrational modes of 5'5-Dinitro BAPTA from 1500-1900 wavenumbers. Red lines show discrete DFT-predicted vibrational frequencies. Blue traces are convolved stick plots calculated from the DFT frequencies. Magenta inverted triangles show the highest-frequency carboxylate asymmetric modes.

Figure 5. Calculated IR vibrational modes of 5'5-Dibromo BAPTA from 1500-1900 wavenumbers. Red lines show discrete DFT-predicted vibrational frequencies. Blue traces are convolved stick plots calculated from the DFT frequencies. Magenta inverted triangles show the highest-frequency carboxylate asymmetric modes.

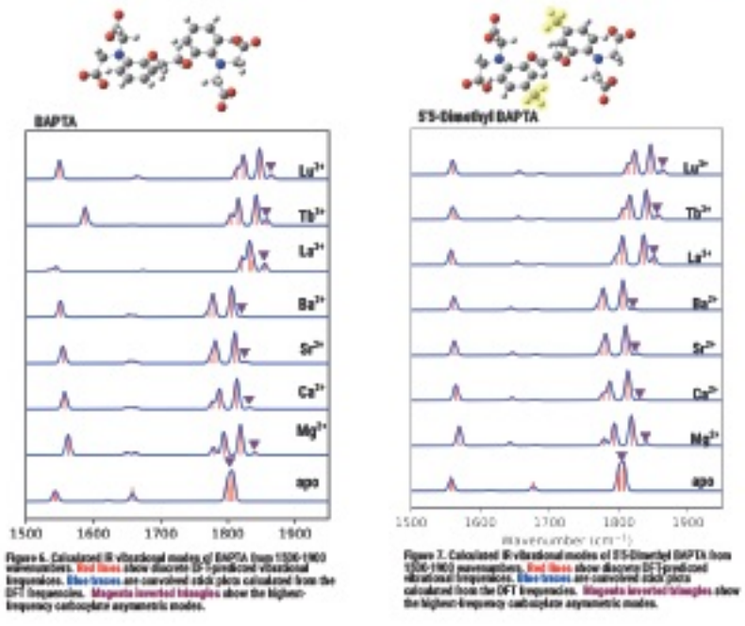


Figure 6. Calculated IR vibrational modes of BAPTA from 1500-1900 wavenumbers. Red lines show discrete DFT-predicted vibrational frequencies. Blue traces are convolved stick plots calculated from the DFT frequencies. Magenta inverted triangles show the highest-frequency carboxylate asymmetric modes.

Figure 7. Calculated IR vibrational modes of 5'5-Dimethyl BAPTA from 1500-1900 wavenumbers. Red lines show discrete DFT-predicted vibrational frequencies. Blue traces are convolved stick plots calculated from the DFT frequencies. Magenta inverted triangles show the highest-frequency carboxylate asymmetric modes.

Conclusions

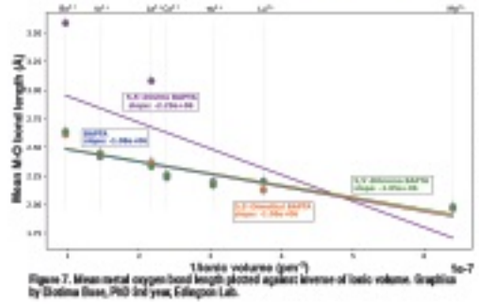


Figure 7. Mean metal oxygen bond length plotted against inverse of ionic volume. Graphics by Diotima Bose, PhD 3rd year, Edington Lab.

- Oxygen-metal bond length decreases with decrease in ionic volume.
- Dibromo and dimethyl groups have less effect on the BAPTA core in terms of bond length.
- Dinitro BAPTA, being more electron withdrawing, has greater effect on the oxygen-metal bond length (see **Figure 7**).

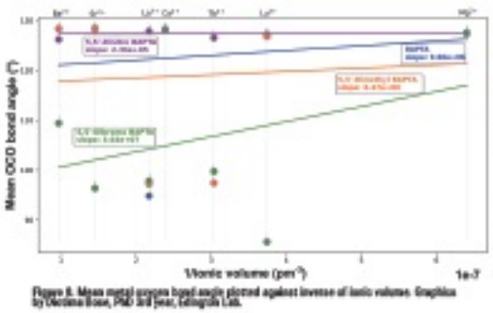


Figure 8. Mean metal oxygen bond angle plotted against inverse of ionic volume. Graphics by Diotima Bose, PhD 3rd year, Edington Lab.

- Bond angle increases with decrease in ionic volume
- The bond angle varies for BAPTA derivatives compared to BAPTA, suggesting that substituents on the aromatic influence the carboxylate arrangement.
- Variations in bond angles could explain selectivity for some metal ions over others.

BAPTA and 5'5-Dimethyl BAPTA show consistent ion-dependent shifts. 5'5-Dibromo and 5'5-Dinitro BAPTA do not.

- 5'5-Dinitro BAPTA (**Figure 4**) and 5'5 Dibromo BAPTA (**Figure 6**) deviate from the spectroscopic trends seen in BAPTA and 5'5-Dimethyl BAPTA
- Increased splitting may be from the electron-withdrawing groups, which alter the electrostatic environment by pulling electron density away from the carboxylate region.
- BAPTA (**Figure 6**) and 5'5-Dimethyl BAPTA (**Figure 7**) exhibit similar splitting and shifting patterns.

Future Work:

Validating DFT predictions about BAPTA derivatives with FTIR.

- Validate DFT vibrational calculations using FTIR spectroscopy of substituted BAPTA & metal ions.
- Monitor shifts in COO^- and related models to identify ion binding and coordination.
- Correlate substituent type with frequency shifts and binding strengths.
- Establish agreement between experimental FTIR and computational results.

References

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