Ca and F bonding and polarization
From small molecules to biology and medicine

Making the connection
Purpose: In biology and in medicine, calcium and fluorine have critical roles. Their influence is mediated by short-range and long-range interactions. How can small-molecules (experiments, effective potentials, and ab-initio calculations) help to understand their unique properties?

Spectroscopic connection: Ionization potentials, dissociation energies, Rydberg levels, excited states, and Stark effects are spectroscopic values. They open windows to molecular and atomic chemical properties based on fragment electric properties.

Larger molecules: Calcium ion is hidden and released as a neurotransmitter. Why Ca? Developing effective potentials including polarizabilities from experiment and ab-initio calculations take us from experimentally-accessible ranges to bond-stretching and bond-breaking, and to non-covalent trapping.

Context: Atomic properties and empirical Thole polarization damping has long been used for molecular dynamics. New effective fragment methods + DFT now predict behavior of large systems, but mostly omitting heavier atoms.
What is the role of Calcium in biology?

A. Calcium ion is the switching agent for many processes through a calcium-release ion channel that triggers activity.
   1. Very high levels in the forebrain,
   2. In skeletal muscle
   3. In non-REM-type sleep and memory consolidation
   4. Other signaling in the central nervous system
   5. In lymphocytes, stomach, kidney, lungs, adrenal glands, thymus, and other organs.

B. Ca\(^{2+}\) concentration must be kept low in the intracellular fluid. High concentration would lead to inorganic precipitation. Because of this hazard, Ca is held / sequestered by calsequesterin in the sarcoplasmic reticulum, a cell compartment, in a typical case, and dispensed by calmodulin.

C. The major Ca\(^{2+}\) ion-channel protein is very large (2.2 MDa), but its structure has been determined by cryo-electron-microscopy, currently the best method of determining structure of very large molecules. There are many other Ca proteins.
Sequestering of Calcium ion in the SR by calsequestrin. Ca release is modulated by calmodulin (CaM). Ca release triggers **multifunction Ca kinase proteins** (CaMK, CaMKII) that engineer energy activation of target proteins (in the heart, ..., etc. and **extraordinarity high in the forebrain**).

1. Berchtold MW et al. (2000) **Calcium ion in skeletal muscle**: its crucial role for muscle function, plasticity, and disease. Physiol Rev. 10.1152/physrev.2000.80.3.1215

**Calcium ion triggers are involved in every movement, every heartbeat, in sleep, and in conscious thought. Ca rates are 1 ms, Mg slower at up to 100 ms.**
Life chooses Ca for availability, flexibility, and speed.

**Similarity:** Mg, Ca, Zn, Sr each have \(^1\text{S}_0\) ground states and \(^1\text{S}_0\) \(\text{M}^2+\) ion. (\(\text{Zn}^{2+} \neq ^3\text{F}_4 \text{Ni}^0\)). And the 4 compete for absorption in the diet.

**Abundance:** Mg, Ca are more abundant than Zn or Sr. (Ni is the limit of star nucleogenesis (minor exceptions)). And Ca is very strong in supernovae, first in emission and then absorption.

**Bonding:** Low empty s,d,p orbitals in Ca increase covalent and non-covalent geometric flexibility in. Ca sequestration involves up to 7 interactions holding the \(\text{Ca}^{2+}\) ion.

**Speed:** Multiple bonds make the hold weaker. Mg bonding to water is stronger. If Mg were used, we would think 10X slower (Ca 1-10 ms, Mg 100 ms).

**Too Similar: Sr is like Ca:** Chernoybl released \(\beta\) emitter Sr-90 which replaces Ca in milk and bone and is undetectable outside the body. Fukushima released 0.1-1 PBq Sr-90 in cooling water to the ocean. (1PBq =10\(^{15}\) decays/s). (food-chain contamination)
A single Ca-F bond is examined by removing F\(^-\) from CaF\(_2\) making CaF\(^+\). Comparing CaF\(^+\) to Ca\(^{2+}\)\cdot F\(^-\) shows that charge flows from F\(^-\) to several Ca\(^{2+}\) empty s and d orbitals to reduce the effective charge on the Ca and F atoms.

Electron density from F\(^-\) can go into the lowest Ca\(^+\) states, which are 4s, 3d, 4p, ...

Thanks to the Klaus Schulten group at UIUC for VMD used to create the image. Klaus sadly no longer with us.
Fluorine is an “innocent ligand” (but Oxygen is not)

Bonding in compounds isoelectronic to CaF$^+$

F is either bonded F$^-$, or neutral F$^0$.

Not oxygen! O can be Coulomb stabilized in an ionic bond to include O$^{2-}$ character.

Effective charges on atoms in Ca bonds are further from integer charges than NaF, KF due to d orbitals.

But look how KF begins to look like CaF$^+$ at short bond length!

CaF$^+$, KF, NaF, show that bonded fluorine does not affect the oxidation state of the metal, it is “innocent.”

Oxygen is a “non-innocent” ligand. With Ca, the O charge can be O$^-$ or O$^{2-}$. Even though EA(O$^-$) is negative (-7.6 eV), oxygen can be driven to O$^{2-}$ in CaO by short range Coulomb stabilization.
Fluorine

1. 20% all drugs on the market contain at least one fluorine
2. Few natural compounds contain fluorine
3. Innocence
   a. Single bond only, but enhanced electron withdrawal.
   b. No exposed lone pairs or empty orbitals. Spherical symmetry of F⁻ persists (our result)
   c. No low-lying electronic states of F⁻
   d. Convenient and useful for
      a. Adjust the biological persistence of the drug by making incremental changes to electric properties
      b. Create a drug similar to another one but the same function

Judicious placement of fluorine in a candidate compound can markedly affect potency, increase metabolic stability and enhance membrane permeability. (no functional change)


An example: The antibiotic “Cipro”

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Fragment-based methods can be useful for large-molecule dynamics

Stability of Properties

Multipole moments and polarizabilities can be stable properties in similar environments because

1. In polar groups, internal fields are large, and determine electronic structure. They dominate fields from fragments that are not directly bonded.
2. Work by the Zanni and Boxer groups give one example
   A. Carbonyl group vibrations can be Stark-shifted in an active site, but C=O bond-force constant is not changed by solvent interactions.
3. These concepts are being used in current developments of effective fragment potential and molecular orbital methods. *

Ca and F are out of the usual list H, C, N, O.
Ca is more complex; Fluorine perhaps simpler.

Methods
1. Intramolecular atomic charges and polarizabilities are obtained from molecular multipole moments. (calculated and experimental values).
2. Energies from perturbation by single test charge lead to values for higher polarizabilities.
   A. Point charge creates fields and field gradients and so respond to higher polarizabilities.
   B. Integration of the point-charge interaction energy on spherical shells using spherical harmonics, gives polarization-modified effective multipole moments
   C. The $1/r^n$ dependence of the effective multipole moments gives higher-order molecular polarizabilities.

Look at Ca and F in two molecules:
The bare single Ca-F bond (CaF$^+$) and the bent pseudo-Jahn-Teller CaF$_2$
A few results for the bare single Ca-F bond (CaF⁺)
Quenching of F⁻ dipole polarizability as the bond shortens

The low and near-constant Ca dipole polarizability indicates that it is not far from Ca²⁺: free Ca²⁺ pby is 3.25; while Ca⁺ pby is 76.1, so Ca mostly Ca²⁺, as assumed in biology.

F⁻ remains almost spherical, but pby decreases smoothly because of exchange repulsion.
Quadrupole rather than dipole polarizability on Ca is better

First 3 multipole moments of CaF$^+$

Either dipole or quadrupole pby on Ca can match dipole, quadrupole and octupole curves.

At equilibrium $R$, only the quadrupole pby can match the hexadecapole! Also it is consistent with the 3d levels lower than the 4p in Ca.
Quadrupole rather than dipole polarizability on Ca is unusual, but works

**Polarizabilities**

- $H_{Q_2,Q_1}$ model of $A_{zzz}(Ca)$
- $H_{Q_2,Q_1}$ model of $\alpha_{zz}(F)$

**Induced Moments**

- $H_{Q_2,Q_1}$ model of quadrupole on Ca
- $H_{Q_2,Q_1}$ model of dipole on F

As the bond shortens, more negative charge moves to Ca. $Q_2(Ca)$ is negative.
The “transition-metal in waiting” character of Ca makes CaF$_2$ especially interesting. It is a bent, pseudo-Jahn-Teller molecule.

1. Koput and Roszczak find a barrier of about 60 cm$^{-1}$ and predict an interesting rot-vib spectrum. Brenda Winnewisser is thanked in the acknowledgements.
2. Garcia-Fernandez, P., Isaac B. Bersuker and Jame E. Boggs have compared many explanations and found pseudo-Jahn-Teller to be the best.

We have made a number of ab-initio calculations for CaF$_2$, but the model needs development, and additional calculations are required.

All of the calculations have been done with CFOUR (cfour.de). John Stanton has allowed us to use the 2018 development version, which has allowed charged-perturbed calculations to be made rapidly and accurately
• Ca and F are highly important in biology and medicine, but the importance of F is largely in what it does NOT do (no change to function), while for Ca its importance is what it does do (neurotransmitter).

• F is a probe and a nearly structureless sink/source for electron density.

• Calcium is in many places. The coordination number of Ca$^{2+}$ is 1 to 8 (!) due to high flexibility in bonding from low-lying s, d, p orbitals.

• The high ion charge of Ca$^{2+}$ means that the electron density does not like to slide away from the center (dipole polarization), but if forced to accept some charge, Ca$^{2+}$ will become egg-shaped.

• No information is ready yet on CaF$_2$ atomic properties.
References follow


Reference to bonding data on CaO, KF, NaF data will be added.

Coordination number of Ca is 1 to 8. but mostly 2 to 7. Wang, X., M. Kirberger, F. Qiu, G. Chen and J.J. Yang(2009), Towards predicting Ca2+-binding sites with different coordination numbers in proteins with atomic resolution. Proteins. 75(4): 787-98, DOI: 10.1002/prot.22285.