

Lectures on Electrostatics

Electrostatics is at the core of virtually all enthalpically driven non-covalent interactions in biological macromolecules. Charge-charge interactions, Van der Waals interactions, hydrogen bonds are all driven by electrostatic interactions. So it is useful to have a look at the fundamentals again.

In our calculations we will be using energy instead of force. This turns out to be a lot more convenient, because energy is a scalar quantity whereas force is a vectorial quantity, which would make all our calculations a lot more complicated.

Virtually all of the electrostatics that we will encounter when we deal with proteins, will come down to two types of problems or situations. Coulomb and Born. If you understand these two “problems” you will have a pretty good feeling for the role that electrostatics plays in determining protein structure and function.

Coulomb

The coulomb problem can be formulated like this: “How much energy do I have to expend (or do I gain) by bringing two charges together or by separating them”

Lets work through this problem. You should all remember Coulombs law. You should also remember that **energy is the integral of work over distance**. So the work we can do or have to expend to bring two charges to within a certain distance from one another is the integral of the coulombic force from infinity to a given distance r .

Here is coulombs law:

$$F_{coulomb}(r) = \frac{1}{4\pi\epsilon_0} \cdot \frac{q_1q_2}{r^2}$$

we can calculate the Coulombic energy that holds two charges together at a certain distance by calculating the amount of work we get out of or have to put into (negative work) separating them from that distance to infinity.

$$u_{coulomb}(r) = \int F_{coulomb}(r) dr = \int \frac{1}{4\pi\epsilon_0} \cdot \frac{q_1q_2}{r}$$

$$\int_r F_{coulomb}(r) dr = \int \frac{1}{4\pi\epsilon_0} \cdot \frac{q_1q_2}{r} + \frac{1}{4\pi\epsilon_0} \cdot \frac{q_1q_2}{r}$$

since

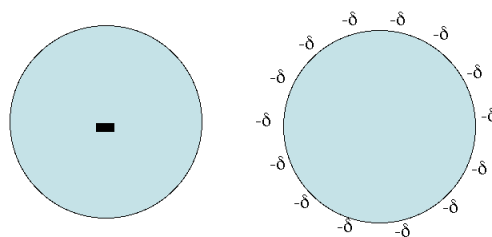
$$\frac{1}{4\pi\epsilon_0} \cdot \frac{q_1q_2}{r} = 0$$

$$\int_r F_{coulomb}(r) dr = \frac{1}{4\pi\epsilon_0} \cdot \frac{q_1q_2}{r} = u_{coulomb}(r)$$

Here are a few things that you should see right away. If you do not see these things, practice looking at equations and try to guess what they will do what they will do.

- The interaction energy of two charges falls only with $1/r$. This is very slow. We will see that hard-sphere collision energies go with $1/r^{12}$. This is what makes calculating electrostatic interactions so difficult.
- If we have opposite charges (+and-), we have to expend work (the work is negative) to separate the two charges, if the charges are like (-and- or +and+) we can extract work from the process of separating the two charges (the work is positive).
- The interaction energy goes with the square of the charge. If we double the charge we will quadruple the interaction energy

One thing that makes calculating electrostatic interactions easy though is the fact that for Coulombic interactions we can treat an ionized atom in which the charges are distributed with spherical symmetry as if this ion had the whole charge concentrated in its center.



For a point charge that is located outside the ion, the two charge configurations shown above exert the same electrostatic effect (provided of course that all the δ charges add up to 1).

The one thing we really want to know though is how big this interaction energy is. And this energy depends on the relative size of the interaction constant $\frac{e^2 N_A}{4\pi\epsilon_0}$, e the elementary charge of a proton, ϵ_0 and N_A .

All these quantities participate in the formula for the interaction energy in a simple multiplicative form, so that it is convenient to pull them together into a single quantity which happens to have a numerical value that is easy to memorize.

$$\frac{e^2 N_A}{4\pi\epsilon_0} = 1.386 \cdot 10^{24} \text{ J} \cdot \text{m} \cdot \text{mol}^{-1} = 333 \text{ kcal} \cdot \text{\AA}^{-1} \cdot \text{mol}^{-1}$$

The charge interaction energy of an NaCl ion pair with a contact distance of 2.8Å then is.

$$u(\text{NaCl}, 2.8 \text{ \AA}) = \frac{e^2 N_A}{4\pi\epsilon_0} \cdot \frac{1}{r} = \frac{1.39 \cdot 10^{24} \text{ J} \cdot \text{m} \cdot \text{mol}^{-1}}{2.8 \cdot 10^{10} \text{ m}} = 496 \text{ kJ} \cdot \text{mol}^{-1} = 119 \text{ kcal} \cdot \text{mol}^{-1}$$

This is a huge number!!!! Compare this to the measly 0.6 kcal/mol we got for T_S we got in our tetra-hedron example.

More importantly even at r=20 Ang (the diameter of a typical protein domain) we still get ~17 kcal/mol for the Na Cl interaction

From this simple calculation we can already see that electrostatic interactions are both strong and long-range (unless there is a solvent). So we cannot simply deal only with the interactions with nearest neighbors but we have to deal with all the charges out to essentially infinity.

Bjerrum Length, comparison of u to RT.

One way of thinking about just how strong and long range the interaction between an ion pair is, is to calculate how far away two charges have to be so that the attractive (or repulsive) energy that wants to drive the charges to a particular configuration is equaled by the randomizing effects of the thermal energy. The distance at which these two energies equal one another is called the Bjerrum length.

$$E^0_{thermal} = k_B N_A T = \frac{e^2 N_A}{4 \pi \epsilon_0 r_{bjerrum}} = u^0(r_{bjerrum})$$

with

$$e = 1.6 \cdot 10^{19} C$$

$$\epsilon_0 = 8.85 \cdot 10^{12} F \cdot m^{-1}$$

$$N_A = 6.023 \cdot 10^{23} mol^{-1}$$

Solving for $r_{bjerrum}$ we get

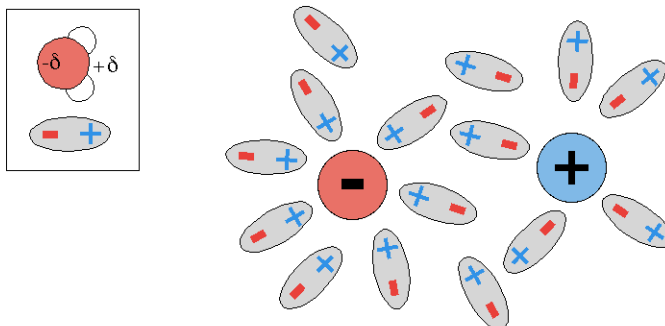
$$r_{bjerrum} = \frac{e^2}{4 \pi \epsilon_0 k_B T} = 56 \cdot 10^9 m = 560 \text{ \AA}$$

So if we are looking at an ion pair that is much closer to one another than $r_{bjerrum}$ then we can essentially ignore the thermal effects. The electrostatic interaction will dominate. If they are much farther apart than $r_{bjerrum}$ we can ignore the electrostatics effects. So with a typical protein being of the order of 30 – 50 Å in diameter, we virtually always have to take the interaction of all charges into account, even if we are dealing with something as huge as the ribosome.

Dielectric constant, Effects on Bjerrum length

So far our calculations have assumed that our interacting ions are in a vacuum, but of course they are not. In all biologically relevant reactions our ions are not in a vacuum but in some kind of “solvent” environment. What would the effect of such a solvent be? Lets think about a polar solvent like water. From an electrostatic viewpoint water looks like a little dipole. The end of the oxygen carries a partial negative charge and the side with the

two hydrogens carries a positive charge. If we now place an ion into this solvent, what will happen? Of course the dipoles will align to complement the ionic charge. The water molecules will rotate so that their positive poles point towards the negative ions and their negative poles point away from anions and vice versa for positive ions. The net effect is that the ions do not feel each other's presence as strongly. Or put differently, the other ions seem to be farther away.



It would be extremely cumbersome to calculate the energy for every interaction between each of the solvents partial charges with each other and with the ions (though we could). Instead we use an experimentally determined parameter that treats the solvent as a continuum. This constant is the dielectric constant usually called D by which we multiply the distance between the two ions.

$$u(r)_{\text{vacuum}} = \frac{1}{4\pi\epsilon_0} \cdot \frac{q_1 q_2}{r}$$

while

$$u(r)_{\text{solvent}} = \frac{1}{4\pi\epsilon_0} \cdot \frac{q_1 q_2}{D_{\text{solvent}} r}$$

so

$$u(r)_{\text{solvent}} = u(r)_{\text{vacuum}} / D_{\text{solvent}}$$

or

$$u(r \cdot D_{\text{solvent}}) = u(r)_{\text{vacuum}}$$

So this constant does exactly what we intuitively wanted it to do. The energy between two ions in a solvent at a given distance is the same as the interaction energy would be in vacuum at a distance D times larger than the distance in the solvent.

Another way to think about it is that our graph of $u(r)$ vs. r is compressed along its r axis by a factor of D .

So how big is this dielectric constant for different solvents Here is a Table:

Solvent	T(°C)	D
Heptane	0	1.958
Heptane	30	1.916
Methanol	25	33
Formamide	20	109
HCN	0	158

HCN	20	114
Water	0(liquid)	88
Water	25	78.54

Obviously D varies very little from vacuum (where it is 1) to aliphatic/non-polar solvents, but varies dramatically between non-polar solvents and polar ones like water.

In water ions experience each other, as if they were 80 times as far apart. So their Bjerrum length is now

$$r_{bjerrum/solvent} = r_{bjerrum/vacuum} / D_{solvent}$$

so

$$r_{bjerrum/water} = 560 \text{ \AA} / 78.5 \approx 7 \text{ \AA}$$

That's a huge change, now thermal motions dominate if two mono-valently charged ions are separated by more than $\sim 10 \text{ \AA}$. Which is only a few ionic radii. Also the energy for the interaction of Na^+ and Cl^- at contact radius is now.

$$u(r)_{\text{NaCl/water}} = \frac{1}{4\pi\epsilon_0} \cdot \frac{q_1 q_2}{D_{water} r} = \text{kcal} \cdot \text{mol}^{-1}$$

at 2.8 \AA

$$u(r)_{\text{NaCl/water}} = u(r)_{\text{NaCl/vacuum}} / D_{water} \approx 1.5 \text{ kcal} \cdot \text{mol}^{-1}$$

This is very much closer to the energy we have seen in our tetrahedron game.

Notice how the dielectric constant for HCN and water changes noticeably with temperature, while it barely changes over a larger temperature range in heptane. Do you have an idea why the increase in temperature results in a drop in D ?

Coulomb interactions in proteins, practical considerations

As you have seen coulombic interactions fall off very slowly with distance (this is true even in solvents with high dielectric constants). So on the scale of a protein, pretty much any charge interacts with every other charge. We have also seen that the strength of the interaction is very much dependent on the dielectric constant of the medium that separates the two charges. As you will learn later in the course proteins contain a core made up largely from aliphatic and aromatic side chains, giving the protein interiors dielectric constants of 4-8. The surface of the protein -on the other hand- is highly polarizable with a dielectric constant close to or greater than water where the dielectric constant further depends on the flexibility of the protein. So the medium through which charge-charge interactions in proteins occur are very heterogeneous so it is next to impossible to determine an appropriate D for a protein. As a result, calculating electrostatic interaction energies in proteins is exceedingly difficult, even if (and this is -as you will see- a big "if") you know all the charge states of all your ionizable groups.

Interaction between chemical potential and electrostatic potential

I will cover this just qualitatively. Think about the following situation, you have an ionizable group on the surface of an uncharged protein. Lets say it's a glutamic acid and the proton is trying to float away from the surface. First it will have to break the bonding energy with the glutamic acid but then it also has to overcome the electrostatic energy between it and the glutamic acid group.

Now imagine that there is another group right next to the glutamic acid lets say it is a aspartate (already negatively charged) Now if the proton wants to diffuse away it needs to work against the electrostatic pull of both the glutamate and the aspartate ions. It also creates a repulsive energy between the two negative charges. In other words the presence of a negative charge nearby makes it much harder for the glutamic acid to become deprotonated, so its pKa will shift up. On the other hand if we have several positively charged groups around the glutamate, the proton will pop right off, driven away by the repulsive electrostatic energy and the pKa will go way down. This is a very simple example of chemical tuning. This is how proteins make specific groups act differently than they would in isolation. This is a big part of protein catalysis etc.