Monitoring the Charge Distribution During Proton and Sodium Ion Conduction
Along Chains of Water Molecules and Protein Residues^a

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ABSTRACT

Quantum calculations are used to determine the level of delocalization of a cation as it translates along a chain of water molecules or of glycine residues. Charge dispersal is monitored via the molecular electrostatic potential and the dipole moment of the entire system. The positive charge is largely localized on the water molecule on which it is situated, but becomes more intense and extended as the proton moves along the chain. The positive charge is more delocalized in protonated polyglycine where it extends over at least an entire residue. Displacement of the proton along the chain intensifies the charge, and progressively polarizes the entire chain. This pattern of charge intensification is more profound in both the 3_{10} and α helical structures. A Na^+ cation behaves in much the same way as H^+ in terms of charge migration.

^adedicated to Menachem Gutman in celebration of his 80th birthday

keywords: Molecular electrostatic potential; dipole moment; α -helix; 3_{10} helix; proton hopping

INTRODUCTION

The migration of charge is one of the most widespread and important processes in all of biochemistry. Electron transfer is commonly compensated by simultaneous proton conduction across biomembranes ¹⁻³. The rate of proton conduction can be quite high, due to active pumping, in systems as diverse as bacteriorhodopsin ^{4,5}, ATP synthase ⁶, photosynthetic reaction centers ⁷, and cytochrome c oxidase ^{8,9}, some employing sophisticated proton-collecting systems ¹⁰. The transfer of protons between groups on the surface of a protein appears to be a common feature, even of those proteins which do not act as proton pumps ¹¹.

In a general sense, the mechanism of proton conduction has engendered a large number of studies and a wealth of information concerning a host of biological systems ^{6, 12-18}. Our understanding has been supplemented by examination of nonbiological systems as well ¹⁹⁻²⁵. In addition to examination of proton transfer in enzymes such as chymotrypsin ^{26,27}, there have been a number of careful calculations involving small model units like NH₃, HCN, OH₂, and carboxylate, imine, and amide groups ²⁸⁻³³. In terms of more inorganic settings, proton transfers in semisandwich Re and Ru complexes have been examined ³⁴. Work has progressed to the consideration of aspects of proton transfer in excited electronic states ³⁵⁻⁴⁶ as well.

As a proton or other ion moves along its pathway, it is tempting to view the charge as fully concentrated upon it. That is, one might think that this ion contains the full charge of +1 or +2 as the case may be, and that the protein along which it is moving is electrically neutral. But that picture ignores the common phenomenon that when an ion lies close to, and especially if it engages in a weak noncovalent bond, with another entity a significant portion of the ion's charge is dispersed onto the latter. There remains the central question, though, of just how much of this charge is transferred to the protein. Another tantalizing issue relates to the degree of dispersal of the transferred charge. Just how far does this charge extend? Taking the example of a proton that engages with the peptide O atoms of a protein as it migrates, how much of the proton's charge is transferred to the protein? And is this transferred charge limited to the O atom, to the C=O, the entire peptide unit, or does it extend even further? And as a peripheral matter, does the amount of charge transfer remain constant throughout the conduction process, or does it vary depending on how far along the proton is in its full transit?

Some of these questions can be addressed nicely by quantum chemical methods, which are well suited to analysis of the wave function and its attendant electron density. The position of the proton, or other ion, can be precisely specified, and its pathway carefully mapped out as it moves along. Analysis of the charge distribution at each step of the conduction is a straightforward matter, leading to a precise analysis of the concentration and extent of the excess charge.

It is to these questions that the present work turns. Proton conduction along a chain of water molecules is considered by two distinct mechanisms, monitoring the charge concentration at each step. A protein is simulated by a chain of glycine residues. This polypeptide is considered in several of the more common conformations observed in proteins. Specifically, an extended conformation similar to a strand of β -sheet is examined as are both the α and 3_{10} helices. In most of these scenarios, a proton is added to the system, but the Na^+ ion is considered as well to determine the sensitivity of the observations to the nature of the cation.

COMPUTATIONAL METHODS

Quantum calculations employed the Gaussian-09 set⁴⁷ of programs. Systems were constructed and optimized as described below in each section. Geometry optimizations made use of the 6-31G* basis set, followed by application of the more extended and polarized 6-31+G** set to analyze the wave function and molecular electrostatic potential (MEP), all at the SCF level. The latter represents the potential that would be felt by a positive point charge at a specific position.

RESULTS

1. Water Chain

A chain of eight water molecules was constructed. A full optimization of this system leads to a circular arrangement, rather than a linear chain. In order to ensure a proper alignment into a linear chain, the O atoms were forced to occupy a plane, and a zig-zag structure was achieved by setting all $\theta(\text{O-O-O})$ angles to 120° , with $\phi(\text{O-O-O-O})$ dihedral angles = 180° . The ensuing geometry optimization led to the structure portrayed in Fig 1a, where some variability is noted in the various H-bond (HB) lengths. Consistent with prior observations on related systems, the interior HBs tend to be a bit shorter than those on the periphery.

There are several means of proton conduction one can envision along this chain. The first might be thought of as the Nagle-Morowitz (NM) mechanism^{48, 49} of water wires in which a proton latches on to the first water in the chain. As depicted by the curved arrows in Fig 2, in the next step the proton on this water which was initially H-bonded to the second O atom, transfers across from O1 to O2, leaving a neutral terminal water and a H_3O^+ as the second link in the chain. This same process continues, with protons transferring across each pre-existing HB until it is the eighth and final water which is a hydronium, as indicated by the bottom of Fig 2.

The MEP of the initial configuration, with a H_3O^+ on the left end of the chain, is illustrated in the uppermost portion of Fig 3. The blue color indicates the extreme positive of +0.2 au, while the lowest potential shown in red is 0 au. (There is little in the way of negative potential since the entire system is positively charged.) The excess positive charge of the terminal hydronium on the left is indicated by the blue color surrounding it. Note that there is a bit of dispersal of the positive charge over the next two

waters as well, indicated by the light blue and green colors. The O atoms become more solidly red, less positive beyond this point. But it would be fair to say that the bulk of the charge, indicated by the dark blue region, is localized on the water to which the excess proton is attached.

The MEPs of the configurations as the proton migrates along the chain via this NM proton-hopping mechanism are shown in lower parts of Fig 3, for occupation of $n=3$, 6, and 8. The charge appears to migrate intact, in the sense that the most positive region in each case surrounds the hydronium, with a bit of lighter blue color spreading to the hydronium's two nearest neighbors. Similarly, the $n=8$ MEP looks very much like a mirror image of $n=1$.

Another mechanism one might envision for the proton conduction along the chain would be one that does not disturb the internal HB structure of the chain, leaving all bridging protons covalently bound to the O to their immediate left. As in the NM mechanism, the excess proton first binds to the leftmost water. But then it is this same non-bridging proton that hops to O2, then to O3, and so on, until reaching O8. In other words, the excess proton in each structure is a peripheral one, not involved in any HB itself. Such a mechanism would be unlikely in an isolated water chain as the motion of the proton from one molecule to another would take it through an area of high energy, essentially unbound to any water. On the other hand, this mode of transport becomes much more feasible when the chain of waters is surrounded by other H-bonding groups, as might occur for example in a proton-conducting channel within the confines of a membrane-spanning protein. It is worth studying this peripheral mechanism also for the comparison it offers with the conduction of cations other than H^+ , where the NM proton wire mechanism is not possible, as examined in some detail below. The MEPs of the same four attachment points of $n=1$, 3, 6, and 8 are displayed in Fig 4 for this peripheral proton conduction mechanism.

The diagrams look basically similar to those corresponding to the NM hopping mechanism in Fig 3 in that the dark blue positive region migrates along with the excess proton. But a closer inspection reveals certain differences as well. As the proton moves from left to right, the dark blue region gradually becomes larger. For example, this color covers only the very first H_3O unit when $n=1$, but ranges over the adjacent water as well for $n=8$. One can see differences in the least positive regions as well. When $n=1$, the right end of the chain shows much less red color than does the left end when $n=8$. In other words, as the proton migrates from left to right, there is increasing polarization, wherein the protonated end becomes more positive and the opposite end less so, as compared to $n=1$.

This enhanced charge separation via this mechanism is reflected also in the dipole moments. As indicated by the first entry in Table 1, the dipole moment of the neutral water octamer is 16.6 D, with its positive end pointing toward $n=8$. It is reduced by 40.2 D, and turned in the opposite direction, to -24 D,

upon protonation of the first residue. This change in moment is displayed in the next column of Table 1. Placement of the excess proton on $n=8$ in the context of the NM mechanism enlarges the moment of the neutral by 10.8 D. The same placement on $n=8$ via the peripheral process, however, raises this quantity by 41 D, to 58 D. In other words, the peripheral process raises the moment about four times more than does the NM mechanism.

The entries in parentheses in Table 1 refer to a highly idealized situation in which the change in moment is computed by simply placing a unit point charge at the precise position of the excess proton, allowing no perturbation of the charge density of the system. For example, if a positive point charge were placed at the position of the proton at $n=1$, it would lower the dipole moment by 38 D, whereas an increase by a like amount would result from a point charge at $n=8$. These changes are a bit larger in magnitude in the context of the peripheral mechanism, due to a slightly different positioning of the excess proton. The actually computed moment changes for the full system are fairly similar to those expected for simple motion of a point charge, with the obvious exception of $n=8$ for the NM mechanism.

The reason for this large discrepancy is that the conduction of the proton from left to right in the context of the NM mechanism is not merely the motion of a single proton. After the full transit from $n=1$ to $n=8$, the chain is left with all OH groups pointing to the left instead of to the right. That is, as shown in Fig 2, the chain has altered its configuration from $\text{OH}\cdots\text{OH}\cdots\text{OH}$ etc to $\text{HO}\cdots\text{HO}\cdots\text{HO}$. The completion of the full conduction process requires the rotation of all of these OH groups around to the original configuration, which would add to the dipole moment change in the last column of Table 1. This point was discussed earlier⁵⁰ where calculations showed that the proton conduction process indeed accounts for only part of the full charge transfer.

2. Polyglycine

A. Extended Conformation

One of the most common local geometries adopted by a protein is a β -sheet wherein adjacent strands engage in H-bonding with one another. In order to achieve this structure, the polypeptide backbone of each strand is an extended one. When octaglycine ($\text{NH}_2(\text{CH}_2\text{CONH})_7\text{CH}_2\text{CHO}$) was fully optimized the terminal amide with its NH_2 group tended to curl around, so this problem was avoided by restricting the terminal $\phi(\text{NCCN})$ dihedral angle to 180° . The ensuing optimization yielded a fully extended structure, with all $\phi(\text{NCCN})$ and $\psi(\text{CCNC})$ angles equal to 180° , as exhibited in Fig 1b. This structure was protonated at each of the eight carbonyl O atoms in turn. The proton was placed 0.97 Å from the O in question, with $\theta(\text{COH})=105^\circ$, and dihedral angle (HOCN) set equal to 180° .

The MEPs for several placements of the excess proton are exhibited in Fig 5. As may be seen the blue region, corresponding to +0.2 au, encompasses not only the OH group itself, but extends to the carbonyl C atom and the two atoms bonded to it. In other words, it would be misleading to consider the excess proton as the seat of the full charge, but rather this charge is dispersed at least to encompass the entire residue on which it lies. Notably, the extent of this blue positive region experiences a degree of expansion as the excess proton moves from left to right, hopping from one carbonyl O to the next. The rightmost blue region for n=8 is a bit more extended than it is for n=1. Similarly, the opposite end of the chain from the proton (left end for n=8 and right for n=1) becomes a bit redder, less positive, as the hopping reaches its righthand terminus.

The dipole moment of the neutral octaglycine is 13.7 D, oriented with its positive end toward n=8. Placing a proton on the first residue reduces this quantity to -37.6 D, a reduction/reversal of 51 D. When the proton is situated on the other end, the moment rises by 63.5 D to 77.2 D. The much larger change of moment associated with the position of the proton on the far right end, as compared to the left, is confirmation of the intensification of polarization as the proton migrates to the right. Note that these moment changes compare reasonably well with the idealized increments arising from motion of a simple point charge.

B. 3_{10} Helix

Whereas beginning a geometry optimization from an extended structure leads to the geometry described above, if instead one takes as a starting point a generally helical conformation, a full optimization leads to a 3_{10} helix. The (ϕ, ψ) angles vary a bit from one residue to the next but average roughly (-65°, -20°), the values anticipated for a typical 3_{10} helix. As displayed in Fig 1c, the $\text{NH}\cdots\text{O}=\text{C}$ HBs fit the 1-3 pattern characteristic of this helix, and these HB are roughly 2.3 Å in length.

As in the case of the extended conformation, a proton was added to each O atom in turn, with the same geometrical considerations of bond length and angle as indicated above for the extended structure. The MEPs of the same four locations of the proton are displayed in Fig 6. There is clear evidence of an intensification of the blue area as the proton moves along the chain. The dark blue region is rather small for n=1, covering only the OH group. By the time this proton has reached terminal residue n=8, this region is considerably larger, including more than a full residue. At the same time, the regions at the other extreme transition from mildly positive (green) to negative (red), despite the overall positive charge of the entire system.

With regard to the dipole moment, this quantity amounts to 30.4 D prior to protonation, with its positive end at n=8. This direction, as well as magnitude, is entirely sensible based upon the direction of the various

HBs within the helix. Adding a proton at $n=1$ essentially eliminates the moment, reducing it to -1 D. Placing the proton on the other end, in contrast, enhances the moment by 27 D, raising it to 57 D.

Protons are not the only charged species that migrate within or along proteins. As another, and much larger, cation the Na^+ species was considered. As in the case of the proton, the sodium was placed on each carbonyl O in turn along the length of the 3_{10} helix. The $\theta(\text{C-O-Na})$ angle was chosen to be 105° , and the (N-C-O-Na) dihedral angle 180° . The $\text{R}(\text{O-Na})$ length was taken as 2.23 Å, the optimized distance when Na^+ is placed in the vicinity of a water molecule.

The MEP of the helix as the Na^+ migrates from left to right is exhibited in Fig 7. The large size of the sodium ion disperses its charge quite a bit, leaving a green contour on its exterior surface for $n=1$. Note however, that the area surrounding the cation turns from green to blue as it progresses in its path, i.e. becoming progressively more positive. Not only the sodium, but also the residue to which it is attached turns from green to blue. In other words, the charge of the cation is dispersed over a broad region, including at least one full residue. As in the previous cases, the opposite end of the chain from the migrating cation is considerably less positive when $n=8$ than when $n=1$, evident by the red color for $n=8$ as compared to the green for $n=1$.

As indicated above, the dipole moment of the neutral 3_{10} helix is 30.4 D. Placement of the Na^+ on the left end reduces this quantity to -1.9 D, quite similar to the same positioning of the proton. Also similar is the moment when the Na^+ has migrated along the entire length of the helix, up to 56.7 D. Whether H^+ or Na^+ , the moment enlarges for $n=8$ very similarly to the simple situation where the cation contained a full unit charge. On the left end, however, with $n=1$, the moment change is reduced by some 10-14% as compared to the idealized unit charge. This pattern is consistent with the MEP view of smaller positive charge when the cation is on the left end of the chain.

C. α -Helix

More common in proteins than the 3_{10} helix is the corresponding α structure. The latter is distinguished by a 1-4 HB pattern, compared to 1-3 in the former. Because of the smaller number of HBs in the octapeptide resulting from the transition from 3_{10} to α , a full geometry optimization leads back to the former structure. In order to force the optimization to progress to a true α -helix, the various (ϕ, ψ) angles were restricted to $(-50^\circ, -50^\circ)$. The resulting geometry is displayed in Fig 1d. Comparison with the 3_{10} helix in Fig 1c indicates HBs that are a bit longer on average.

Very much like the 3_{10} case, the MEP pattern in Fig 8 also indicates increasingly large polarization as the proton moves from left to right. The blue region grows far more intense and larger in extent, encompassing 2 full residues when $n=8$. And the opposite end from the proton changes from green on the

far right when $n=1$ to red on the far left when $n=8$. Switching the subject cation to Na^+ leads to the MEPs in Fig 9 which again shows the potential around the cation becoming more positive as it migrates to the right, turning from green to blue. This positive area again encompasses not only the Na but also the residue to which it is bound.

The dipole moment of the neutral α -helix is 32.5 D, 2 D larger than that of the 3_{10} geometry. This quantity is reduced by nearly 30 D when either cation is placed on the first residue, and increases by 21 D when on $n=8$. As in the earlier 3_{10} case, the latter increase closely matches that assuming a pure unit charge, whereas the dipole diminishes for $n=1$ by less than the unit charge would do. This distinction is again indicative of the lesser charge separation when the ion is positioned on the left side of the helix.

SUMMARY AND DISCUSSION

The combination of molecular electrostatic potentials and dipole moments provide insights into the manner in which charge propagates along a chain of water molecules or glycine residues as an added ion traverses the chain. The charge is fairly well localized upon the water molecule to which the proton is attached, particularly in the context of the Nagle-Morowitz proton hopping mechanism. When the excess proton is peripheral to the chain, it tends to diffuse its charge over a bit more of an extended region, most notably as it arrives near the terminus of the $\text{OH}\cdots\text{OH}\cdots\text{OH}\cdots$ chain. This higher concentration of positive charge on the right end of the chain is complemented by a less positive left end, providing a picture of a more polarized chain.

The peripheral conduction of a proton along an extended chain of polyglycine fits the pattern of the peripheral mechanism of water molecules. The charge is dispersed onto the entire residue on which the excess proton lies. As it moves from left to right, there is a noticeable, but not huge, magnification of the polarization of the chain, less positive on the left, and more so on the right. This growing polarization as the excess proton moves from left to right is enhanced in the 3_{10} and α helical conformations. Very similar patterns, even quantitatively so, were observed when the conducting ion is changed from H^+ to Na^+ .

The MEPs depicted above were evaluated for a potential with extrema of 0 and +0.2 au, as this range best illustrates the full range of MEP in these cationic systems. However, diagrams with other ranges show the same patterns. The same is true for the surface on which these potentials are measured, whether 1.0 or 1.5 times the vdW radius of the various atom.

It might be tempting to consider following the migration of charge via atomic charges. However, there would be a high level of arbitrariness introduced by such a protocol as various different means of assessing atomic charges in the literature typically provide vastly different values, and even signs can differ. Even within the context of a single charge calculation protocol, an analysis based on simple atomic charges is

unreliable. Taking the proton conduction along the 3_{10} helix as an example, the Mulliken charge of the migrating proton shows little variation with the residue on which it resides. This charge varies only within the tight range of 0.43 to 0.45, and is thus not a useful indicator of the location or magnitude of the charge, clearly at odds with the more objective electrostatic potential diagrams.

Attempts to quantify the charge via a sum of atomic charges would introduce an even larger degree of uncertainty. For example, the choice as to which atoms should be included is unclear. One could imagine using the OH group, or perhaps COH or NHCOHCH₂, with no clear resolution as to the most physical choice. And if one were interested in the extent of the positive charge originating from the excess proton, inspection of atomic charges would be less than insightful: in any given system all C and H atoms are assigned a positive atomic charge, and all O and N are negative, regardless of the precise position of the proton.

The protein models examined here are electrically neutral, and not zwitterionic, having uncharged groups on the ends of each chain. This model was chosen so as to best simulate the central regions of much longer polypeptide chains within the context of proteins.

As noted above, the MEPs were computed at the SCF level and thus did not explicitly include electron correlation. In order to examine if correlation might have a significant effect on these potentials, some were also computed at the M06-2X level, a DFT approach which includes electron correlation. The resulting MEPs were indistinguishable from the SCF MEPs presented above.

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Table 1. Dipole moments^a of neutral systems, and change in this quantity upon placing the indicated cation on the first and last residues, all in D.

			μ (neutral)	$\Delta\mu$ (n=1) ^b	$\Delta\mu$ (n=8) ^b
(H ₂ O) ₈	NM	H ⁺	16.6	-40.2 (-38)	+10.8 (+38)
	peripheral	H ⁺	16.6	-40.2 (-41)	+41.1 (+43)
(Gly) ₈	extended	H ⁺	13.7	-51.3 (-52)	+63.5 (69)
	3 ₁₀	H ⁺	30.4	-31.7 (-37)	+26.9 (28)
	3 ₁₀	Na ⁺	30.4	-32.3 (-36)	+26.3 (28)
	α	H ⁺	32.5	-27.9 (-34)	+21.6 (+22)
	α	Na ⁺	32.5	-29.9 (-34)	+20.4 (+22)

^aMoment in the direction of the chain, measured from center of mass

^bValues in parentheses refer to the placement of a positive point charge at the position of the cation, with no perturbation of the wave function.

Fig 1. Optimized geometries of a) linear chain of 8 water molecules, and octaglycine in b) an extended geometry, c) 3_{10} helix, and d) α -helix. NH...O H-bond lengths shown in Å.

Fig 2. Nagle-Morowitz (NM) mechanism for proton conduction along a chain of water molecules.

Fig 3. MEP of water chain with excess proton on indicated residue following the NM mechanism in Fig 2. Surface is drawn on the surface corresponding to 1.5 times the vdW radius of each atom. Dark blue and red regions correspond respectively to +0.2 and 0.0 au, with green and yellow intermediate.

Fig 4. MEP of water chain with excess proton on indicated residue in the context of the peripheral proton conduction mechanism.

Fig 5. MEP of $(\text{Gly})_8$ in its extended structure with excess proton on indicated residue.

Fig 6. MEP of $(\text{Gly})_8$ in 3_{10} helix with excess proton on indicated residue.

Fig 7. MEP of (Gly)₈ in 3₁₀ helix with Na⁺ on indicated residue.

Fig 8. MEP of (Gly)₈ in α -helix with excess proton on indicated residue.

Fig 9. MEP of $(\text{Gly})_8$ in α -helix with Na^+ on indicated residue.