Guanidinium Ion Self-Consistent Field Calculations: Fluoro, Amino, and Methyl Single Substituents

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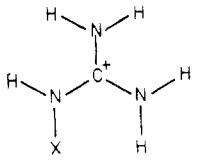
Rotational barriers of NH_2 and NHX groups are calculated for the single substituted guanidinium ion, where X is F, NH_2, or CH_3. The geometries and the net atomic charges are also calculated.

In a recent paper[1] we presented a theoretical study of the electronic structure of the guanidinium ion $C^+(NH_2)_3$ (**1a**). Here we extend that work to single substituted guanidinium ions.



1a, X = H
b, X = F
c, X = NH_2
d. X = CH_3

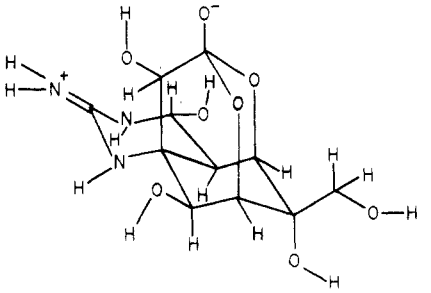
We chose fluoro (**1b**), amino (**1c**), and methyl (**1d**) substituents. These model a range of electronic donor–acceptor behavior that much influences the role played by guanidinium ions in several important experiments.

NMR measurements[2] have been used to study substituent effects on guanidinium rotational barriers. Barrier changes of a few kilocalories per mole have been rationalized partly in terms of substituent interaction with the Y-aromatic charge distribution characteristic of the guanidinium ion. The calculational results presented here illuminate such rationalizations. Moreover, we find in certain cases that intramolecular hydrogen bonding is an additional factor controlling the rotational barrier changes.

In a series of voltage-clamp experiments[3] with giant squid axons it has been shown that amino-substituted guanidinium, as well as guanidinium itself, is capable of passing through sodium channels in the nerve membrane. Methylated guanidinium ion, however, is incapable of passage. This fact has been central to the structural model hypothesis for the sodium channel "pore" controlling selective ion passage.

In the case of free guanidinium, which is planar, the molecule fits neatly through the rectangular 3 × 5 Å "pore" in the sodium channel. A methyl substituent increases the molecular width and prevents passage. As our results indicate, however, the geometry of amino-substituted guanidinium is remarkably similar to that in the methylated case. Presumably the amino-substituted guanidinium can reduce its effective width by forming strong hydrogen bonds on passing through the sodium channel. Our analysis of the charge carried by the amino group lends support to this hypothesis.

A matter intimately related to the permeability experiments is the mechanism of action for tetradotoxin,[4] also a substituted guanidinium molecule (**2**). The toxin affects



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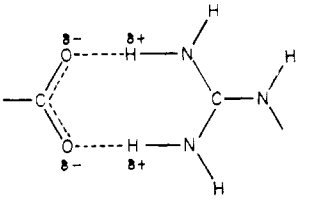
nerve function. The guanidinium moiety enters a sodium channel, and the "substituent fragment" attaches by hydrogen bonds to a protein in the cell wall of the nerve membrane. The net result is blockage of the sodium channel to the passage of ions and hence inhibition of nerve function.

It often occurs that apparently trivial substitutions dramatically affect the biological activity of chemical compounds. Therefore, one wishes to know whether such changes are capable of affecting the geometric and/or electronic structure of the guanidinium moiety which is presumed to bring the toxin into position in the sodium channel. Our results indicate that even strong substituent effects leave the geometry of the guanidinium moiety essentially unaffected. The electron distribution, however, can show large reorganizations over the fixed geometrical framework.

The amino acid arginine is also a substituted guanidinium. Light conversion by bacteriorhodopsin involves motion of protons across the purple membrane of "*Halobacterium halobium*". A guanidinium carboxylate complex (attached to arginine) is thought to act as a charge-transfer relay for protons[5] (**3**). (Interestingly the



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carboxylate ion group seems to be involved in the inter-

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(3) B. Hille, *J. Gen. Physiol.*, **59**, 637 (1972).
(4) R. Keynes, *Sci. Am.*, **240**, 126 (1979).
(5) L. Packer, S. Tristam, J. M. Herz, C. Russell, and C. L. Borders, *FEBS Lett.*, **108**, 243 (1979).

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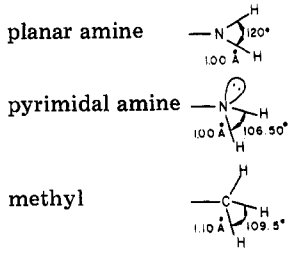
Table I. Fixed Geometrical Parameters



action of the guanidinium cation and the sodium channel pore, the carboxylate ion being a source of high electric field.)

Substituent effects on charge distributions give an indication of how substituents will affect hydrogen bond formation. This is because hydrogen bonds are essentially electrostatic interactions. The structure of arginine indicates that its guanidinium fragment will be affected in a manner analogous to that in methyl substitution. In that case, our population analysis indicates charges on hydrogen atoms which would make them favorable donors in hydrogen bond formation.

Our charge distributions also accord with NQR measurements[6] on guanidinium ferroelectric crystals on guanidinium acetate which contain strong hydrogen bonds.

The calculations presented here are based upon the Hartree–Fock approximation, the appropriateness of which for examining guanidinium ions has been discussed in our previous paper.[1] The computer program used is the standard GAUSSIAN-70 program[7] available from QCPE. The basis of orbitals is STO-6-31G, the same one that we used previously for free guanidinium ion, in order to make comparisons between the ion and its substituted forms as meaningful as possible. The results presented correspond to partial geometrical optimization of the total energy.

In calculations of the sort presented here one must always face the question of how many geometrical parameters to determine variationally. One temptation is to optimize every bond distance and bond angle. This has the advantage of removing prejudices based on "chemical intuition". The disadvantage in this for molecules of the size treated here and for the number of different calculations performed is that of consuming a prohibitive amount of computer time and effort. Here we have adopted a frankly pragmatic compromise in which we optimize only those parameters which are rather directly related to substituent effects of interest to us. The parameters we have chosen not to optimize are of two types: (1) NH distances and HNH angles of the basic guanidinium moiety; (2) the distances and angles within the methyl and amine substituents. The parameters of the first type were given values equal to those obtained by complete optimization in the free guanidinium ion.[1] Parameters of the second type were given their standard experimental values.[8] A summary of the geometrical parameters held fixed is given in Table I.

All the remaining parameters were variationally optimized. These include the following: (1) the bond distance between substituent and the nitrogen atom, N_3, to which it is attached; (2) the orientation of CH_3 and NH_2 substituents with respect to the guanidinium ion plane; (3) all NCN angles of the guanidinium moeity; (4) all CN bond distances in the guanidinium moiety; (5) the XNC angles for each of the substituents, where X = F, NH_2, or CH_3; (6) the H_4N_2C angle for each substituent.

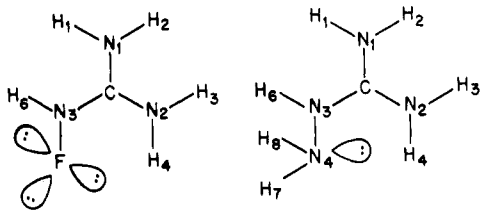
Table II. Selected Optimized Geometrical Parameters[a]

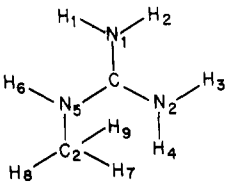
molecule	parameter: $d(XN_3)$, Å	$<XN_3C$, deg	$<H_4N_2C$, deg
F	1.36	115	115
NH_2	1.42	120	120
CH_3	1.48	120	120

[a] The $CN_{1,2,3}$ distance is 1.33 Å and the NCN angle 120° in all cases.

The variationally determined geometrical parameters are summarized in Table II.

As in the case of guanidinium, the fluorine substituted ion is planar in its ground state (4). Although not required





by symmetry, we find all the CN bond distances and NCN bond angles to be equal and to have the values 1.33 Å and 120°, respectively. This preservation for the ground state of the planar guanidinium "Y" framework occurs with each of the three substituents we have studied. The NF bond distance is 1.36 Å, which is an ordinary value for an NF single bond. Interestingly, the angles FN_3C = 115° and H_4N_2C = 115° and the distance FH_4 = 2.12 Å indicate the presence of a hydrogen bond.

In the case of the ground-state, amino-substituted ion, the hydrogens of the amino group arrange themselves symmetrically above and below the plane of the ion, and the lone pair of the pyramidal amino nitrogen lies in the plane and points in the direction of a neighboring planar hydrogen (5). The distance between the amino nitrogen and its nearest neighbor, planar hydrogen, is 2.34 Å and is appropriate for hydrogen bonding.

In the ground state for the methyl-substituted ion, methyl hydrogens arrange themselves symmetrically above and below the molecular plane, leaving the third in the plane and pointing away from the hydrogen which is attached to N_2 (6). The NC bond distance involving the methyl is 1.48 Å. The distance between the methyl carbon and its neighboring hydrogen attached to N_2 is 2.34 Å. This distance may be consistent with a weak electrostatic interaction.

Our results for the rotational barriers are displayed in Table III.

For guanidinium one has three equivalent single rotational barriers. With the fluorine-substituted case, however, the reduction of symmetry implies that each of the single rotational barriers may be inequivalent. Hence the barrier magnitude for single rotation about CN_1 is 11.53 kcal mol^{-1}, about CN_2 is 19.31 kcal mol^{-1}, and about CN_3

(6) T. Oja, *J. Chem. Phys.*, 59, 2668 (1973).
(7) W. J. Hehre, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.*, 51, 2657 (1969).
(8) R. Weast, Ed., "Handbook of Chemistry and Physics", Chemical Rubber Publishing Co., Cleveland, OH, 1965, pp F-218–9.

Table III. Single Rotational Barriers (kcal mol^{-1})

molecule[a]	barrier[b] CN_1	CN_2	CN_3
H	14.73	14.73	14.73
F	11.53	19.31	19.70
NH_2	12.97	23.40	22.79
CH_3	13.47	15.21	16.78

[a] Refer to structures 1a-d. [b] Column headings refer to the energy barriers associated with rotation about the bonds CN_1, CN_2,a nd CN_3.

is 19.70 kcal mol^{-1}. One notes that compared to the guanidinium single barrier of 14.73 kcal mol^{-1}, the first of these barriers is reduced in magnitude, while the other two increase in magnitude. These barriers indicate the following (see Table IV for charge distributions). (a) The much reduced negative charge on N_3 is consistent with a smaller barrier about CN_1 (compared to that of guanidinium) because of decreased repulsion between N_3 and the negative charge differential which accumulates at N_1 with twisting at that position. (b) The favorable distance for hydrogen bonding between F and H_4 implies that rotation about either N_3 or N_2 will have the effect of breaking a strong hydrogen bond. This must be a major contributor to the elevation of these barriers in the substituted molecule as compared to those for the guanidinium ion. (c) Because F is highly electronegative, it will tend to localize the π charge in the CN_3 bond. This is consistent with the fact that the barrier about CN_3 exceeds that for CN_2.

As with fluorine, the amino substitution reduces molecular symmetry and renders the three rotational barriers inequivalent. Thus the rotational barrier about CN_1 is 12.97 kcal mol^{-1}, about CN_2 is 23.40 kcal mol^{-1}, and about CN_3 is 22.79 kcal mol^{-1}. The first of these barriers is reduced, and the others are increased when compared against those for the guanidinium ion. These trends indicate the following. (a) A reduction of negative charge on N_3 is consistent with a smaller barrier about CN_1 as was the case in fluorine. Here, however, the effect should be smaller (as actually occurs) because the amino reduces the charge on N_3 much less than does fluorine. (b) The favorable distance between the amino nitrogen and its neighboring planar hydrogen implies that rotation about either CN_2 or CN_3 will be at the cost of breaking a hydrogen bond. As with fluorine this elevates the associated rotational barriers. The size of the effect may be expected to be greater than with fluorine (as occurs) because the net negative charge on the amino nitrogen exceeds that for fluorine.

With methyl group substitution, the changes are much smaller because CH_3 more closely resembles the behavior of the H it replaces in guanidinium than does the F or NH_2. The energy of rotation about CN_1 is 13.47 kcal mol^{-1}, about CN_2 is 15.21 kcal mol^{-1}, and about CN_3 is 16.78 kcal mol^{-1}. In this case the barrier trends indicate the following. (a) A slight reduction in the negative charge on N_3 is consistent with the smaller, although only slightly so, barrier about CN_1. (b) There may be a weak electrostatic attraction between the methyl carbon and the nearest hydrogen attached to N. If so this would contribute to the small increase in both the CN_2 and CN_3 barriers. (c) The CN_3 barrier is slightly greater than for CN_2 in this case, the same trend as with fluorine. This is consistent with a tendency for localizing the double bond of CN_3, although the effect is not large.

In Table IV we list a population analysis for each of the substituted molecules. The numbers shown are net excess charges associated with the various atomic centers. For

Table IV. Net Atomic Charges

X[a]	C	N_1	N_2	N_3	H_1	H_2	H_3	H_4	H_5	H_6	C_2	F	N_4	H_7	H_8	H_9
H	+1.141	−0.918	−0.918	−0.918	+0.435	+0.435	+0.435	+0.435	+0.435	+0.435						
F	+1.168	−0.916	−0.917	−0.377	+0.448	+0.438	+0.450	+0.457		+0.473		−0.230				
NH_2	+1.235	−0.934	−0.924	−0.795	+0.434	+0.430	+0.425	+0.469		+0.428			−0.524	+0.382	+0.382	+0.218
CH_3	+1.186	−0.935	−0.939	−0.884	+0.430	+0.432	+0.432	+0.446		+0.427	−0.281			+0.218	+0.250	+0.218

[a] Refer to structures 1a-d.

the ground state, we see for all three substituted molecules a general trend indicating alternation of charge sign on moving outward from the molecular center. On consideration of the atoms of the guanidinium moiety, the central carbons are highly positive, the nitrogens are highly negative, and the hydrogens are highly positive. The substituents have the effect of reducing the negative charge on the nitrogen to which they are attached, the magnitude of this effect decreasing in the order F, NH_2, CH_3.

One may also notice in passing that for the amino substitution the guanidinium hydrogen involved in hydrogen bonding is very positive, thus presumably enhancing its role as a hydrogen donor in hydrogen bond formation. Comparing the hydrogens of the amino and methyl substituents indicates the former to be much more positive.

Summary and Conclusions

It appears that substitutions of the type modeled here do not much affect the planar "Y" framework of the guanidinium ion. They do, however, noticeably perturb the magnitude of single rotational barriers. The barrier changes, compared with the guanidinium case, are small for substitution by a methyl group, ±2 kcal mol^{-1}, but are larger for fluoro and amino substitution, ±10 kcal mol^{-1}. The range of barrier changes is not unreasonable judged against the NMR barriers that have been measured for guanidinium and substituted guanidinium. The charge analysis presented here does much to rationalize these barrier changes in terms of field effects, hydrogen bonds, and Y aromaticity.

The sp^3 hybrids of the methyl and amino substituents adopt similar orientations with respect to the molecular plane. Both substituents place a hydrogen symmetrically above and below the plane and, as one might think, enhance the width of the guanidinium molecule to the same extent. Importantly, however, the amino hydrogens are very positive, having a net charge of +0.382. Compare this charge to that of water (+0.394), computed by using the same basis as used here.[1] In so far as hydrogen bonds are largely electrostatic in character, these amino hydrogens will be good hydrogen donors in such bonds. The methyl hydrogens in contrast, however, are much less positive with net charges of +0.217 and +0.250 and cannot be expected to form hydrogen bonds. This contrast in hydrogen bonding is consistent with the relative effective width of the amino- and methyl-substituted guanidiniums in the sodium pore experiments mentioned earlier. The high net positive charge of the amino hydrogens is consistent with formation of strong hydrogen bonds in the sodium pore and a reduced effective width, allowing its passage through the pore. In fact, for the series X = H, NH_2, and CH_3, it is interesting that the measured permeability ratio[3] P_X/P_{NA^+} decreases monotonically (0.13 to 0.06 to 0.01), in good correlation with the monotonic decrease in net atomic charge on substituent hydrogen (+0.435 to +0.382 to +0.218).

It is significant that substitution (at least that studied here) does not have a large effect on the positive charge of those hydrogens attached to unsubstituted nitrogens in the guanidinium moiety. The charges were seen to go from a minimum value of +0.425 to a maximum value of +0.469. Hence these hydrogens maintain their suitability for acting as hydrogen donors to hydrogen bonds. This fact is of utmost importance in the chemistry of substituted guanidinium ions. Applying this to tetradotoxin, we cannot expect that substitutions on the toxin will much effect its guanidinium fragment's tendency to form hydrogen bonds. Insofar as substitutions effect toxin activity, such effects would seem to lie with other mechanisms. Applying this to arginine, one sees its guanidinium fragment will suitably bond with carboxyl groups as required by the light-conversion mechanism mentioned earlier.

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Coenzyme Models. 28. Facile Oxidation of Alcohols and Amines by 3-Hydroxy-*N*-methylacridinium Ion, a New NAD^+ Model Compound[1]

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The title compound (Ac^+OH) was synthesized for the purpose of developing a new NAD^+ model compound which is capable of oxidizing alcohols and amines. The absorption spectrum of Ac^+OH was similar to that of *N*-methylacridinium ion (Ac^+) in the acidic pH region and to that of 5-deazaflavin in the basic pH region. The absorption spectrum of the reduced form was analogous to that of 3-aminophenol. The reduced form which was prepared by $NaBH_4$ reduction was promptly reoxidized by molecular oxygen. With the aid of potassium *tert*-butoxide, Ac^+OH oxidized benzyl alcohol and cyclohexanol to the corresponding aldehyde and ketone in almost quantitative yields. In contrast, Ac^+ was totally useless as an oxidant under the same reaction conditions. Benzylamine was oxidized by Ac^+ to benzaldehyde in low yields (11–24%). On the other hand, the oxidation by Ac^+OH occurred in good yields (82–88%). When the reaction was carried out under an oxygen stream, the yield calculated on the basis of Ac^+OH was enhanced up to 1800–2200%. The results indicate that Ac^+OH acts as an effective turnover oxidizing agent and that the 3-hydroxyl group plays a crucial role in the redox reactions occurring on the acridinium nucleus. This is the first example of the facile oxidation of alcohols and amines which mimics the catalytic behavior of NAD^+ coenzyme.

In alcohol dehydrogenases, the interconversion of aldehydes (ketones) and alcohols occurs in conjunction with that of NADH and NAD^+ coenzymes. Since Westheimer's pioneering studies,[2] considerable interest has centered

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