The Role of Electrostatic Effects in Organic Chemistry

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The introduction of substituents into organic compounds often leads to charge shifts and significant dipole moments. This may have important consequences for structure, energy, and reactivity. A quantity frequently used to describe the polar nature of substituents is the electronegativity, first defined by Pauling (*1*). The electronegativities of the first- and second-row elements are given in Table 1 (*2, 3*). They cover a wide range. Fluorine is the most electronegative and sodium and lithium are the least electronegative. Despite its importance, however, the electronegativity of substituents has not received much attention in many organic chemistry textbooks. The purpose of this review is to make organic chemists more aware of charge distributions in molecules and the associated electrostatic effects (*4*).

Bond Dissociation Energies

The strengths of chemical bonds are usually expressed as bond dissociation energies (BDEs). As a result of recent experimental work, relatively precise values of BDEs for many organic compounds are known (*5*), and some of them are summarized in Table 2. In the series methylamine, methanol, and methyl fluoride there is a marked increase in the CH_3–X BDE, which parallels the increasing difference in electronegativity between the carbon and the substituent. This effect was noted by Pauling many years ago as part of a general trend of increasing strength of covalent bonds as their polarity increased (*1*). In the case of methyl fluoride, the electronegativity of fluorine leads to a marked polarization in the sense C^+–F^-, and the increased strength of the bond presumably arises from coulombic attraction between the charges on carbon and fluorine. The polarization is much less for the C–N bond in methylamine because of the smaller electronegativity of nitrogen. This leads to the smaller BDE.

The decrease in BDE from ethane to methylamine probably arises from the change in hybridization. In ethane, the C–C bond is formed from two ~sp^3 hybrids at carbon, whereas in methylamine, the orbital from nitrogen to carbon has much more *p* character so as to place the lone pair in an orbital with as much *s* character as possible. Bond strengths increase with increasing *s* character (*6*), leading to the C–C bond being stronger than C–N.

It is interesting that with the second-row substituents, the C–Si bond is stronger than C–Cl and much stronger than C–S or C–P. Again, this is related to electronegativity differences. Silicon is electropositive with respect to carbon (Table 1), leading to strong polarization in the sense C^-–Si^+. This leads to internal coulombic stabilization and a relatively strong bond. The electronegativities of S and P are closer to that of C, and this results in relatively small bond dipoles and weaker bonds. With chlorine, there is significant bond polarization in the sense C^+–Cl^- and again there is an increase in BDE.

It is well known that C=O double bonds are much stronger than C=C double bonds. The heat of hydrogenation of a carbonyl group is about -14 kcal/mol (*7*),

whereas that of a C=C is about -28 kcal/mol. This translates into a C=O π bond strength of about 84 kcal/mol vs. 64 kcal/mol for C=C. It is probably another manifestation of the electronegativity of oxygen, which affects the σ and π parts of the double bond approximately equally. The large polarization of C=O vs. C=C leads to the increased strength of the bond.

Stabilization of Polyfluorinated Compounds

The unusual stability of carbon tetrafluoride is well known (*8*). It is seen in the uphill energy change for the reaction

$$CF_4 + 3\ CH_4 \rightarrow 4\ CH_3F \qquad \Delta H = +53$$

where ΔH is in kcal/mol. Although it is not possible to carry out this reaction in the laboratory, the overall energy change may be calculated knowing the experimental heats of formation of the reactants and products (*9*). Further, each step in the successive removal of fluorines from carbon tetrafluoride is endothermic:
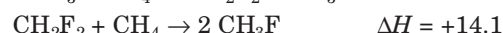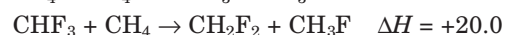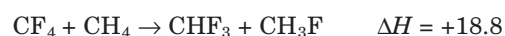
$$CF_4 + CH_4 \rightarrow CHF_3 + CH_3F \qquad \Delta H = +18.8$$
$$CHF_3 + CH_4 \rightarrow CH_2F_2 + CH_3F \qquad \Delta H = +20.0$$
$$CH_2F_2 + CH_4 \rightarrow 2\ CH_3F \qquad \Delta H = +14.1$$

Table 1. Electronegativities

| Element	Electronegativity	
	Pauling	Allred–Rochow
H	2.20	2.20
Li	0.98	0.97
Be	1.57	1.47
B	2.04	2.01
C	2.55	2.50
N	3.04	3.07
O	3.44	3.50
F	3.98	4.10
Na	0.93	1.01
Mg	1.31	1.23
Al	1.61	1.47
Si	1.90	1.74
P	2.19	2.06
S	2.58	2.44
Cl	3.16	2.83

Table 2. Bond Dissociation Energies, kcal/mol at 25 °C

Bond	BDE	Bond	BDE
CH_3–CH_3	89.4±0.3	CH_3–SiH_3	89.6±2.1
CH_3–NH_2	85.7±1.5	CH_3–PH_2	~70
CH_3–OH	92.2±0.2	CH_3–SH	74.4±0.8
CH_3–F	109.6±2.0	CH_3–Cl	83.3±0.3

The stability of carbon tetrafluoride has usually been explained in terms of no-bond, double bond resonance structures (*10*)
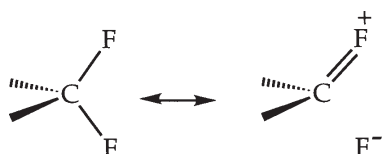
or of the donation of charge density from a fluorine lone pair into the s* orbital of an adjacent C–F bond (*11*)
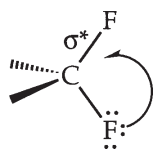
In the valence-bond formulation, each fluorine is both a donor and an acceptor, and it is difficult to see how this can lead to stabilization. In the MO picture, the energy of the lone pair on fluorine is low, corresponding to its low basicity, and the energy of the C–F σ* orbital is relatively high. Thus one would not expect a strong interaction between these orbitals. What then is the source of the stabilization of carbon tetrafluoride?

Here it is worth examining the physics of electronic stabilization of molecules. The energy of any atom or molecule may be expressed as

$$E = \Sigma T + \Sigma V_{nn} + \Sigma V_{ee} + \Sigma V_{ne}$$

where ΣT is the sum of the kinetic energies of all of the electrons, ΣV_{nn} is the sum of the repulsions among the positively charged nuclei, ΣV_{ee} is the sum of the repulsions among the electrons, and ΣV_{ne} is the sum of the attraction between the electrons and the nuclei. For a system to be stable, its total energy must be negative. The first three terms are all positive; only the last has a negative sign. Since the total energy must be negative for a stable molecule, the last term must have a larger absolute magnitude than the sum of the other three terms, to provide the stabilization that allows the formation of atoms and molecules.

The energy may also be written as $E = T + V$, where T is the sum of the kinetic energies of the electrons and V is the sum of all of the potential energy terms. The virial theorem (*12*) further states that for any molecular system at its equilibrium geometry, $V = -2T$. Thus $E = V/2$, and we need only be concerned with the potential energy terms. To make a molecule more stable, it is then necessary to increase the nuclear–electron attraction or decrease the electron–electron repulsion. It is not clear that either of the above explanations for the stability of carbon tetrafluoride can be cast in these terms.

It is interesting to examine the charges at fluorine in the series from methyl fluoride to carbon tetrafluoride (Table 3). Three ways of calculating charges were used (*13*). In the first (AIM), the charge density derived from large basis set ab initio calculations was integrated over properly chosen volume elements (*14*). The second (NPA) (*15*) is closely related to the commonly used Mulliken population analysis (*16*), but is better defined and not strongly dependent on the level of theory used in obtaining the electron populations. The third (GAPT) makes use of the changes in dipole moment when the molecule undergoes molecular vibrations (*17*). Numeri-

cal values for the fluorine charge vary somewhat between methods because of the different definitions that were used. Nevertheless, all of these quite different ways of assigning charges agree that the charge on fluorine is independent of the number of fluorines attached to carbon. This has also been found in an approach that compares the charge densities at the atoms directly (*18*), and by an experimental study of the dipoles created when carbon tetrafluoride undergoes molecular vibrations (*19*). Intuitively, one may have expected the fluorine charge to decrease with increasing substitution, but the calculations make it clear that this is not the case.

Consider going from methyl fluoride to methylene fluoride:
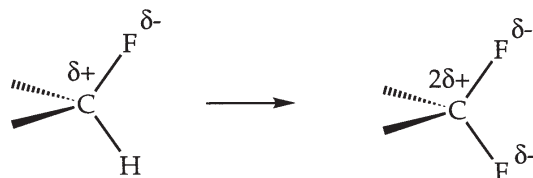
In methyl fluoride, the C–F bond was strengthened by the attraction between C^+ and F^-. The second fluorine doubles the charge at carbon and further strengthens both the original C–F bond and the new C–F bond. This bond-strengthening effect continues through carbon tetrafluoride, where the charge at carbon is 4 times that in methyl fluoride. At the same time, the increased attraction between C and F leads to a decrease in bond length, from 1.383 Å in methyl fluoride to 1.320 Å in carbon tetrafluoride. Thus the high stability of polyfluorinated compounds arises from the increased coulombic attraction caused by the increased positive charge at carbon.

These conclusions may be checked by examining the effect of silicon substitution. Remember that the C–Si bond of methylsilane was unusually strong as a result of the polarization C^-–Si^+. Here, the negative charge at carbon should increase with increasing silicon substitution, leading to increased stability of polysilated carbons. Although $C(SiH_3)_4$ is not known, its energy may be calculated by ab initio methods leading to the energy change:

$$C(SiH_3)_4 + 3\ CH_4 \rightarrow 4\ CH_3SiH_3 \quad \Delta H = +13\ kcal/mol$$

Again the reaction is unfavorable, this time by 13 kcal/mol, indicating stabilization of $C(SiH_3)_4$. The effect is smaller than for CF_4, but the bond lengths are longer and the difference in electronegativity is less, and one would expect a smaller energy change.

These ideas may be further checked by examining FCH_2SiH_3. Here, fluorine attracts electrons from carbon, while silicon donates electrons. As a result, the carbon should be close to electrical neutrality, leading to little internal coulombic stabilization. The reaction

$$FCH_2SiH_3 + CH_4 \rightarrow CH_3F + CH_3SiH_3 \quad \Delta H = -7\ kcal/mol$$
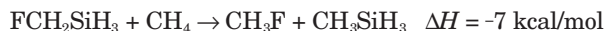
is now found to be exothermic, indicating that the products are better stabilized than the reactants.

Table 3. Atomic Charges at Fluorine

| Compound	AIM	NPA	GAPT
CH_3F	-0.743	-0.429	-0.550
CH_2F_2	-0.744	-0.429	-0.576
CHF_3	-0.744	-0.421	-0.576
CF_4	-0.737	-0.405	-0.551

Amide Resonance and Other Interactions with Carbonyl Groups

Amides have significant C–N rotational barriers, which are generally attributed to resonance structures of the type (20)
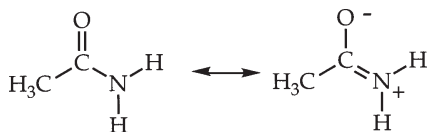
This interaction will be lost on a 90° rotation about the C–N bond, and it is known that in the gas phase the energy increases by about 13 kcal/mol for such a rotation (21).

Another way to estimate the magnitude of "amide resonance" is via group transfer reactions of the type (22)

$$\Delta H = +19.6 \text{ kcal/mol}$$

$$\Delta H = +23.4 \text{ kcal/mol}$$

$$\Delta H = +17.9 \text{ kcal/mol}$$
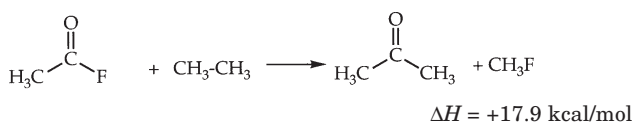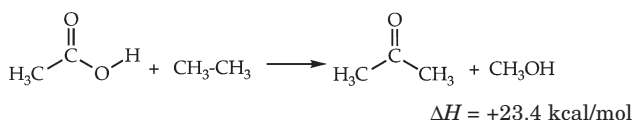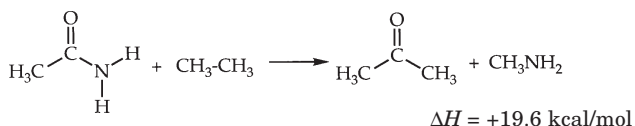
Here the carbonyl–X bond is split and each part is attached to a methyl group, giving a measure of the strength of the bond. The energy change for acetamide is significantly larger than the rotational barrier. The energy change for acetic acid is even larger than for acetamide, despite the lower basicity of the oxygen lone pairs that should make it less effective than nitrogen in π-electron donation. In agreement with this expectation, the rotational barrier for acetic acid (11 kcal/mol) is less than that for acetamide. Only half of the group transfer energy may be associated with the π interaction. In the case of acetyl fluoride, it is difficult to see why there should be any significant π interaction because the fluorine lone pairs are well stabilized by the relatively large positive charge at the fluorine nucleus and are not available for bonding. Thus some factor other than π-electron donation from lone pairs must be involved in these group transfer reactions.

It may be noted that all of the group transfer reactions have two compounds, ethane and acetone, in common and they will not contribute to differences in ΔH. We may then concentrate on the difference between the C–X bonds in the acetyl derivatives and the methyl derivatives. This suggests comparison of the bond dissociation energies of the carbonyl derivatives with those of the corresponding methyl derivatives (Fig. 1).

We should first eliminate the π-electron interaction in acetamide, acetic acid, and thioacetic acid. This may be done by calculating the bond dissociation energies of the 90° rotated forms where the π-interaction has been removed. Then, for the set of substituents PH$_2$, SH, Cl, NH$_2$, OH, and F (solid circles) where the hybridization is
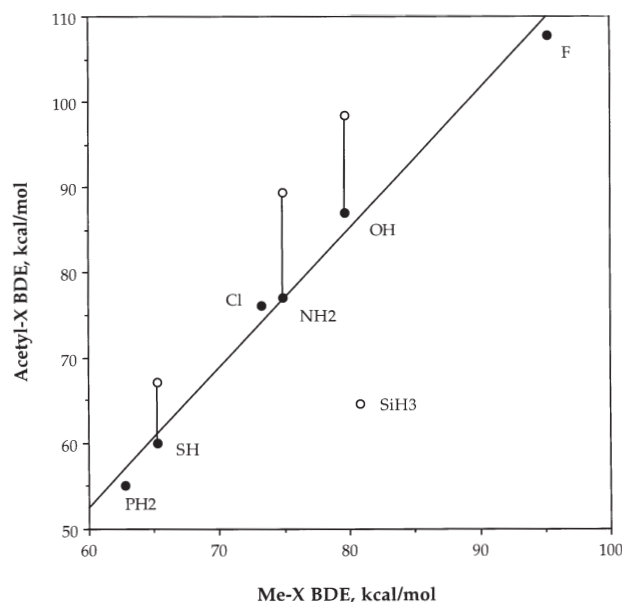

Figure 1. Comparison of acetyl–X and methyl–X bond dissociation energies. With X = SH, NH$_2$, and OH, the open circles are for the planar structures and the solid circles are for the 90° rotated structures in which the π interaction has been eliminated. The slope of the line is 1.6.

roughly constant and the electronegativity increases, there is a good linear relationship between the acetyl–X and methyl–X BDEs. The most interesting thing about the correlation is that the slope is 1.6. Thus the acetyl compounds are more sensitive to the electronegativity of the substituent than are the methyl derivatives.

The carbonyl group is strongly polarized in the sense $C^+–O^-$ for *both* the σ and π components of the double bond (22). Now consider going from CH$_3$ to F as the substituent:

The fluorine will attract charge density from the carbon in much the same way as found with the fluorinated methanes. As a result, a strong C–F bond will be formed. But at the same time, the *increased positive charge at carbon will also strengthen the C–O bond*. Thus, an electronegative substituent at the carbonyl carbon will strengthen two bonds (C–X and C–O), whereas only one is strengthened with the methyl derivatives. This leads to the large slope in Figure 1. The effect is similar to the bond strengthening found on going from methyl fluoride to difluoromethane.

These results make it clear that both a π interaction and internal coulombic stabilization derived from the polarization of the σ bonds are responsible for the group transfer energies. With acetamide, about 13 kcal/mol may be attributed to the π interaction and 6 kcal/mol to the coulombic stabilization of the carbonyl group. With acetic acid, each of the terms contributes about 11 kcal/mol. With acetyl fluoride, the entire effect is due to the coulombic stabilization of the carbonyl group.

These conclusions may be checked in a couple of ways. First, the change in C–O bond lengths with substitution may be noted:

1.222 Å	1.220 Å	1.212 Å	1.185 Å
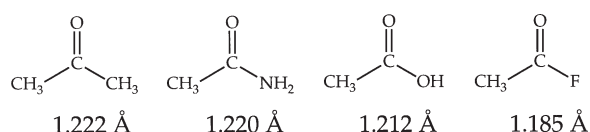
The shortening of the C–O bond with increasing electronegativity of the substituent would be predicted from the increased coulombic attraction between C and O. Also, the point for X = SiH_3 in Figure 1 may be noted. Here, the BDE for the acetyl compound is considerably smaller than expected from a correlation with the methyl–X BDEs. The same is true for X = CF_3 and NO_2. Thus in these cases, there must be a mechanism for destabilization. The element attached to the carbonyl group has a positive charge (viz., the Si of SiH_3, the C of CF_3, and the N of NO_2) and will give a repulsive interaction with the positively charged carbonyl carbon.

The polarization of the carbonyl group dominates its chemistry. In an investigation of amide "resonance" it was found that the charge density at the oxygen changes only slightly on rotation about the CN bond. Figure 2 shows the change in charge density at the carbonyl oxygen on going from the planar form to the 90° rotated form. Regions that have extra charge density in the planar form are indicated with dashed lines, and regions having extra charge density in the rotated form are in-

dicated by solid lines. It can be seen that the planar form has some excess π density, and the rotated form has some excess σ density. However, the net change is only 0.05 e (Table 4), which is too small to account for the rotational barrier (see below). This indicates that charge transfer from nitrogen to oxygen as suggested by the above resonance structures is not the major factor contributing to the rotational barrier in amides.

This can be understood if the amide resonance structures are written as
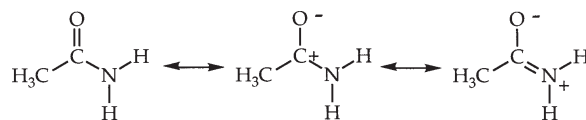
and the last two are taken as the principal contributing structures in determining the rotational barrier. The role of the carbonyl oxygen is to polarize the C=O bond, and the principal amide interaction is between the lone pair on nitrogen and the electron-deficient carbon. This is also the picture that emerges from a frontier MO (FMO) (23) consideration. The π MO of an amide has its largest coefficient at oxygen because of its higher electronegativity. Therefore the π* MO, into which the amide lone pair electrons would be donated, has its largest coefficient at carbon, and donation from N to the C=O group will largely be manifested at the carbon rather than at the oxygen.

Even this is not an adequate description because, besides donating π density to the carbon, the nitrogen withdraws σ density from the carbon as a result of its change in hybridization (sp^2 in the planar form and ~p in the 90° rotated form). Thus the stabilization of the planar amide structure is a rather complex phenomenon. Nevertheless, its essence is depicted in the right-hand two structures shown above.

In the same way, we may consider the old question of why acetic acid is more acidic than ethanol:

Here, the carbonyl group is written in the dipolar form to emphasize its polarization. It can be seen that the negative charge developed at the oxygen of acetate ion is adjacent to a positively charged carbon, leading to coulombic stabilization lacking in ethoxide ion. That is the
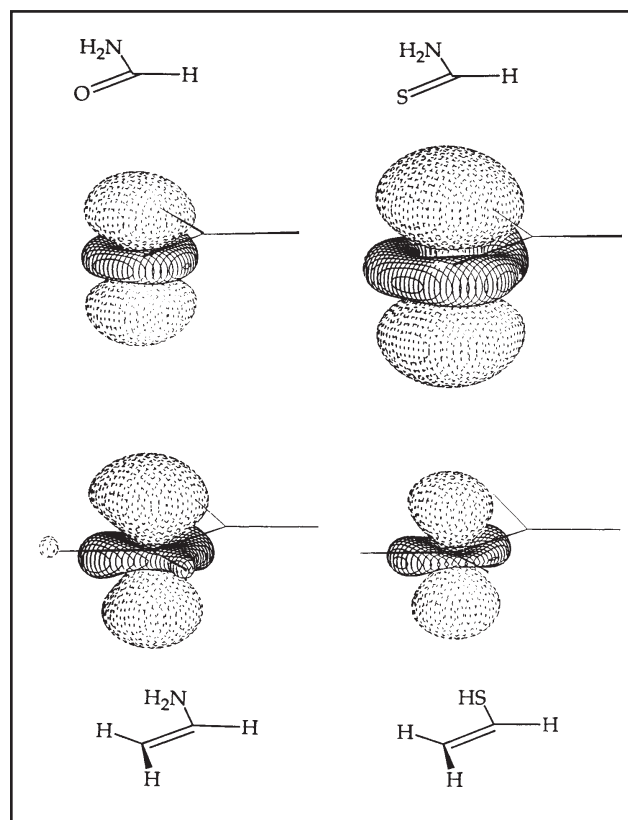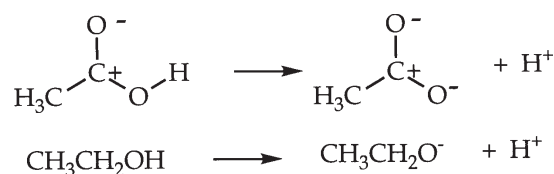

Figure 2. Charge density difference maps (planar–90° rotated) for acetyl derivatives (upper plots) and vinyl derivatives (lower plots). All are drawn at the same scale. Dashed contours indicate loss of charge density on rotation from the planar structures; solid contours indicate increase in charge density.

Table 4. Charge Shifts on Rotation about C–X Bonds

Compound	Group	π	σ	Total
Acetamide	O	-0.071	+0.036	-0.035
Acetic acid	O	-0.061	+0.022	-0.039
Thioacetic acid	O	-0.052	+0.020	-0.032
Vinylamine	CH_2	-0.103	+0.035	-0.074
Vinyl alcohol	CH_2	-0.067	+0.025	-0.042
Vinyl thiol	CH_2	-0.077	+0.028	-0.049
Formamide	O	-0.083	+0.035	-0.048
Thioformamide	S	-0.154	+0.052	-0.101

main reason for its increased stability and for the greater acidity of acetic acid (*24*). It is also interesting that in the ionization of acetic acid, the methyl carbon and the two oxygens retain their relative positions and the only structural change is a small motion of the carbonyl carbon into a position equidistant from the two oxygens (*25*).

The discussion above has emphasized the difference between the traditional picture of carbonyl group interactions and the observations based on charge density distributions. In this connection, it is interesting that there is a case in which the traditional amide resonance picture seems more appropriate. Thioformamide has a slightly larger rotational barrier than formamide (*26*), and the out-of-plane NH_2 bending mode is somewhat stiffer than that for formamide (*27*). An examination of the change in charge density at the sulfur on rotation about the C–N (Fig. 2, Table 4) shows that it is much larger than for formamide. Thus, the interaction may be represented by
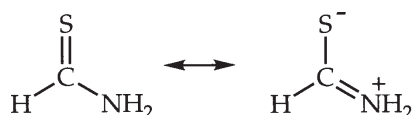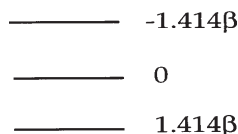

The FMO model does even better. Here, the π^* orbital will have similar coefficients at C and S because of the small difference in electronegativity. Thus, donation from nitrogen will result in charge transfer to both the C and S, the picture that emerges from an examination of the changes in charge density during C–N bond rotation (*27*).

With both the amides and thioamides, and with related compounds such as vinylamine, there is an energetic advantage in transferring some charge density from the nitrogen lone pair to an adjacent atom or bond. This reduces the electron repulsion between the lone pair electrons. Then why does the thioamide have more charge transfer from nitrogen to the terminal atom of the double bond than do amides? In amides, the carbonyl oxygen is essentially "saturated" with charge and cannot accept much more. However, there is an electron-deficient carbon that can interact with the nitrogen lone pair. In thioamides there is relatively little polarization of the C=S bond owing to the similarily in electronegativity between C and S. The sulfur may accept charge from nitrogen for two reasons: it has little extra charge to begin with; and because of its large size, it can accommodate a charge without a great increase in electrostatic energy.

Allyl and Vinyl Derivatives

In the usual Hückel MO picture, the π energy levels for the allyl system are given as

$$
\begin{array}{ll}
\rule{2cm}{0.4pt} & -1.414\beta \\[1em]
\rule{2cm}{0.4pt} & 0 \\[1em]
\rule{2cm}{0.4pt} & 1.414\beta
\end{array}
$$

Each MO can accept two π electrons, and so the allyl cation will have two electrons in the lowest level giving an energy of 2.83 β—considerably lower than the 2.0 β found for ethylene. (Here β is taken as having a negative value.) This might account for the well-known stability of an allyl cation. With the allyl radical and allyl

anion, electrons are added to the nonbonded level, which does not change the energy, suggesting that allyl radical and allyl anion should be comparably stabilized.

However, this ignores electron repulsion. Each added electron will repel the both the σ and π electrons already present, and as a result all of the MO energy levels will change. One of the main difficulties in interpreting the results of the full MO theory that includes electron repulsion is that there is at present no unique way to obtain the energies of the MOs so that the sum of the energies times the number of electrons in each MO will equal the total energy. Thus, it is not readily possible to specify how much each energy level changes on adding additional electrons.

There is an interesting difference in how electrons may be delocalized in allyl cation and anion. Electrons in the double bond of the cation may be delocalized into a region of lower potential energy, the empty *p* orbital. This will lead to decreased π energy and to stabilization. In the gas phase, an allyl cation will be stabilized with respect to one of the resonance structures in two ways: π-electron delocalization, and decreased electrostatic energy as the charge is spread over a larger volume element (i.e., over 3 carbons rather than 1, as in each of the resonance structures). Much of the electrostatic stabilization is lost in going to a solvent with a high dielectric constant. Allyl cation has a calculated rotational barrier of 33 kcal/mol, which is reduced to 27 kcal/mol in a medium of high dielectric constant. However, there are no experimental data with which to compare this (*28*). The tetramethylallyl cation has a calculated barrier to rotation about a C–C bond of 19.8 kcal/mol (*29*), somewhat larger than the experimental value (*30*). When the calculation is carried out for a medium with a high dielectric constant, it is reduced to 17.9 kcal/mol, in very good agreement with the experimental value.

The allyl anion is quite different. Here, there is no "hole" into which electrons may be delocalized. The electrons in the lone pair of one of the resonance structures are more constrained and have a higher electron repulsion than those in the π-bond. Therefore, some charge density in the lone pair may be delocalized into the π^* orbital of the double bond, leading to some stabilization. The calculated rotational barrier of 20 kcal/mol for allyl anion is reduced to 17 kcal/mol in a medium of high dielectric constant. The calculated rotational barrier for the tetramethylallyl anion in the gas phase is 9.8 kcal/mol; in a polar medium it is reduced to 7.6 kcal/mol, less than half the value for the corresponding cation. In general, delocalization of electrons into empty *p* orbitals leads to relatively large stabilization, as is found, for example, in the stabilization of carbocations by alkyl substituents (*31*). Delocalization into double bonds, is less effective as might be expected.

Vinyl derivatives (e.g., vinylamine, vinyl alcohol, vinylthiol) are related to allyl anions. Each has a lone pair of electrons that may be delocalized into the adjacent π orbital, and they have rotational barriers of 4–6 kcal/mol—much smaller than those of acetyl derivatives. Again, it is possible to gain information about the rotational barriers by comparing the charge density distribution for the planar and 90° rotated forms (*32*). Figure 2 shows 3D plots of the difference in charge density (planar–rotated). Dashed contours indicate regions having extra charge density in the planar forms; solid contours indicate regions of excess density in the rotated forms.

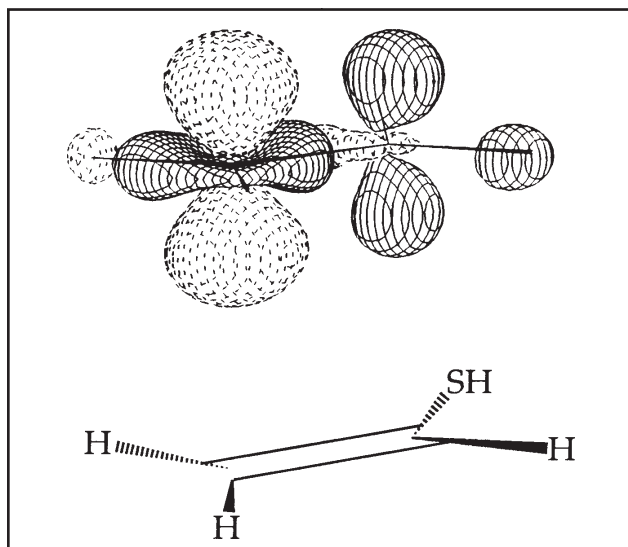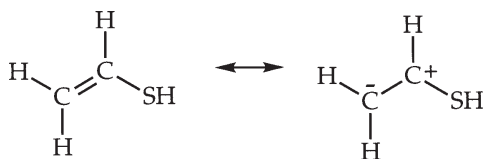It can be seen that the planar forms have some charge density that appears to be π-type, and that the

Figure 3. Charge density difference map for the rotation about the C–S bond of vinylthiol. Note that the carbon bearing the SH group is polarized in the opposite sense to the terminal carbon.

Figure 4. Structure of $C_4H_6Li_2$.

rotated forms have σ-type charge density. In this way, they are quite similar to the acetyl compounds discussed above. The σ/π shift is a common phenomenon known as σ/π polarization. The σ and π electrons repel each other, so that if π density moves toward a given atom, σ density will tend to move away from it. In any case, the changes are small, and the largest net charge is only 0.07e (Table 4). Note that the charge shift for vinylamine is somewhat greater than that for acetamide, even though the amide barrier is about three times larger than the vinylamine barrier. This again indicates that charge transfer from nitrogen to oxygen is not the main stabilizing effect in amides.

It is often difficult to see what happens at the CH carbon bearing the substituent because of the large change in charge density associated with the hydrogens of the group that is being rotated. However, the C–S bond is long enough that both carbons of vinylthiol may be examined (Fig. 3). It can be seen that the π-density is polarized in the opposite sense at the two carbons. This indicates that the role of the lone pairs at sulfur is largely to repel the π-electrons at the adjacent carbon, leading to a polarized C=C bond. Therefore the appropriate resonance structures are

The positive charge next to the sulfur will lead to an attractive interaction with the lone pair electrons, giving stabilization.

It was not possible to examine vinylamine and vinyl alcohol in the same fashion because of the shorter C–N and C–O bonds, but it is possible that π-polarization is also an important contributor to the development of some extra π-density at the terminal CH_2 of these compounds.
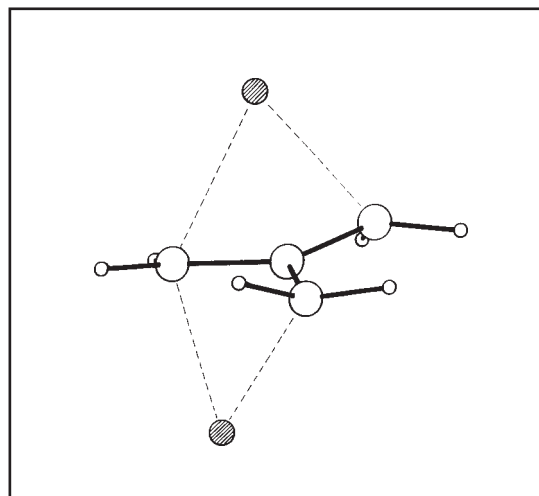
Y-Aromaticity

Two interesting observations have led to the concept of "Y-aromaticity" (*33*). The first is that isobutene will react with two equivalents of butyllithium to give a dianion. The second is that guanidine is more basic than normal amines. In each case, a species is formed that has six π-electrons, and for which three equivalent resonance structures may be written.
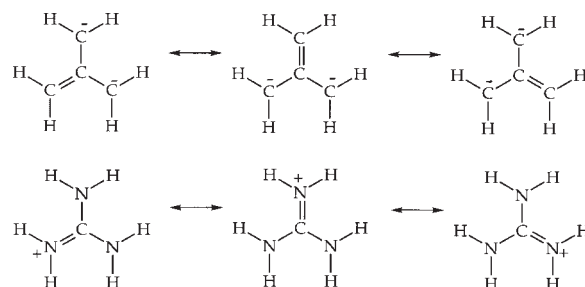
The 6 π electrons were assumed to lead to stabilization in the manner seen with benzene. But there is an important difference. In benzene the 6 π electrons may be spread over 6 C–C σ bonds, giving a net 1 π electron per σ bond (*36*). This is important in the stabilization of benzene (*37*). In the above ions, the 6 π electrons can only be spread over 3 σ bonds, giving 2 π electrons per σ bond as is found for ordinary double bonds. As a result, little stabilization would be expected.

A calculation for the isobutene dianion revealed that its gas phase energy is quite large, with no indication of any special stabilization (*38*). In addition, it is nonplanar, whereas a planar structure would have been expected if it were an "aromatic" system (*39*). The origin of the stability of the dianion arises from the associated lithium cations. The structure is shown in Figure 4 (*38*). Each lithium cation is strongly associated with two anionic carbons. The strong interaction of the lithium cation results from its small size, which enables it to come rela-

tively close to the carbons, leading to a strong coulombic interaction (*40*). There is no reason to believe that the dianion itself has any special stabilization.

Guanidine is somewhat more basic than most amines. This could be attributed to resonance stabilization of the guanidinium ion. However, there is another factor to consider. Hydroxyl ion in water is a relatively weak base. In the gas phase, hydroxyl ion can abstract protons from toluene (*41*), whereas in solution it can barely abstract a proton from a much stronger acid, acetone. The low basicity of hydroxyl ion in water results from strong hydrogen bonding, which must be lost when it accepts a proton. In guanidinium ion, the positive charge is at the amino protons. This is generally the case, for even in ammonium ion the nitrogen has a partial negative charge, and all of the positive charge is held by the protons. The positively charged hydrogens will be strongly hydrogen bonded in water, stabilizing the guanidinium ion (*38, 42*). As a result, guanidine is more readily protonated than ordinary amines that cannot spread the charge over three NH_2 groups. Additional evidence that there is no special stabilization of guanidine comes from the observation that the imine of acetone ($Me_2C=NH$) is not much less basic than guanidine in the gas phase (*38*).

Conclusion

I have presented just a few examples of how changes in charge distribution caused by substituents can modify the properties and reactions of organic compounds. Hydrogen bonding, is of course, one of the more familiar of the electrostatic interactions. There are many other recent examples, such as in the control of the stereochemistry of additions to double or triple bonds (*43*), in the control of reactivity (*44*), in antibiotic binding to DNA (*45*), in controlling the properties of polypeptides (*46*), and in explaining the unusual acidity of carbon acids in enzyme-catalyzed reactions (*47*). These are just a few examples. In fact, much of chemistry is at least partially controlled by electrostatic interactions (*48*).

Acknowledgments

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