However, the interpretation of these numbers is ambiguous due to the fact that the "lone pairs" defined in this manner include the σ bond, as in the case of the fluoromethanes discussed earlier.

A careful comparison of the three deformation density plots reveals that, in contrast to the fluoromethanes, the "leading edge" of the nitrogen lone pair changes at least as much as the "trailing edge". The "lone pair" regions for (fluoromethyl)amine and its rotated conformer are essentially superimposible except for being rotated by 6° toward the fluorine in the former.

The delocalization index of the nitrogen lone pair of (fluoromethyl)amine decreases from 0.0589 to 0.0450 upon rotation, which also suggests that the lone pair donates charge density in the anti conformation. The value of 0.0450 in the rotated structure is very close to that of the lone pair in methylamine (0.0458), as might be expected. The percentage change in the delocalization index is about the same as that between the fluorine lone pairs in fluoromethane and tetrafluoromethane, but the absolute change is almost three times as great. Table IX shows that the C–N covalent bond order in (fluoromethyl)amine undergoes a slight decrease upon rotation about the bond, concurrent with a slight increase in the C–F bond order, which is again consistent with the negative hyperconjugation hypothesis. The C–N covalent bond order in both conformers is less than that in methylamine, however, presumably because the presence of the fluorine atom increases the charge on carbon and hence the ionic character of the C–N bond in (fluoromethyl)amine. Thus there is at least some evidence that interaction of the lone pair of nitrogen with the C–F σ^* orbital stabilizes the C_s symmetric conformers of (fluoromethyl)amine, but even in this highly favorable case the effect appears to be of only a modest magnitude.

Conclusions

Internal Coulombic stabilization appears to be an important factor in stabilizing some types of organic compounds. With both strongly electron-withdrawing (F) or electron-releasing (SiH_3) groups, the charge at carbon changes linearly with the number of substituents, leading to increased Coulombic stabilization with increasing substitution. Other types of electron-withdrawing substituents such as NO_2 or CN, which have positively charged atoms as the first atom, lead to the opposite result, causing increasing Coulombic destabilization as the degree of substitution increases.

Although negative hyperconjugation does not appear to play an important role in stabilizing the perfluoroalkanes, it probably is a significant factor in other cases such as (fluoromethyl)amine, in which the substituted carbon is electron deficient and the substituent (NH_2) has a relatively high energy lone pair.

We have also observed an interesting relationship between the variation in the charges of substituents as the degree of substitution increases and the energetic consequences of this substitution. In cases where multiple substitution is thermoneutral or disfavored, a saturation effect is found which diminishes the electron-withdrawing or electron-donating ability of a substituent as a greater number of these substituents are placed around a single carbon atom. These are also the compounds (the cyanomethanes and chloromethanes) which have little Coulombic stabilization from adjacent positively and negatively charged atoms or even have strong repulsions. This sort of saturation principle agrees well with common notions regarding charge distributions in organic molecules. However, in those cases where multiple substitution is favorable (the fluoromethanes and silylmethanes), the ability of the substituent to withdraw or donate charge does *not* diminish with increasing substitution. Instead, the substituent charge remains highly constant as the number of substituents increases, and the charge on carbon changes in a linear fashion.

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Supplementary Material Available: Tables of GAPT and CHELPG atomic charges, interatomic distance matrices for fluoromethanes, and MP2/6-31G* optimized geometries in the form of Z-matrices (13 pages). Ordering information is given on any current masthead page.

Simple Electrostatic Model for Enthalpies of Formation of Singly Substituted Alkanes

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Abstract: In earlier work, Benson and Luria (*J. Am. Chem. Soc.* **1975** *97*, 704–709) showed that the greater stability of branched alkanes, compared to normal alkanes, could be explained on the basis of the electrostatic interactions between the atoms involved. This approach is extended herein to molecules containing single heteroatoms, N, O, S, Cl, Br, and I. Charges are assigned to atoms according to differences between their electronegativities and the electronegativities of atoms to which they are covalently bonded. Carbon atoms partially share the charges so established. Electrostatic energies are calculated for all pairs of atoms in the molecules. Covalent bonds are assigned energies in a simple scheme of bond additivity. Enthalpies of formation of 23 alkyl derivatives, estimated in this way, agree with experimental values within 1.4 kJ mol^{-1} on average, a difference which is close to the average quoted experimental uncertainty.

I. Introduction

Why is the C–O bond in ethanol 5 kJ mol^{-1} stronger than that in methanol, when the C–H bond in ethane is 19 kJ mol^{-1} weaker than that in methane?[1] This reversal cannot be attributed to differing stabilities of the radicals formed but must involve the molecules themselves. The question could be rephrased: what is the source of the extra stability of methane and ethanol or of the relative instability of ethane and methanol?

The principle of bond additivity,[2] while conceptually attractive, would predict that both the differences above would be zero. Empirical group additivity methods[2] could reproduce the differences, but at the expense of adding more parameters without providing an explanation. Quantum mechanical methods[3] do not add parameters and do provide an explanation at a sophisticated level, but the explanation can be difficult to express in simple terms.

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There is a clear trend in the difference in bond dissociation energies between C_2H_5–X and CH_3–X with the electronegativity of the substituent, X.[1] This suggests that the trend may be related to partial charges on the atoms and to electrostatic interactions between the atoms. It is the purpose of this article to develop a simple scheme for assigning charges to atoms in molecules, calculating electrostatic energies and relating these to the relative stability of singly substituted alkanes.

Our approach will be based on an earlier scheme applied to unsubstituted alkanes by Benson and Luria.[4] (Similar schemes had been used earlier by Lifson and Warshel[5] and Palm and Palm[6] and other schemes also exist.[7–14]) In the next section we will extend Benson and Luria's scheme to include heteroatoms. It will be seen that simple electrostatic effects are capable of quantitatively explaining the differences in stabilities of methyl and ethyl derivatives. To incorporate tertiary butyl derivatives in the same scheme, it is necessary to introduce an inductive or charge-sharing effect. This is done in section III. Residual covalent bonding terms are worked out in section IV, so that heats of formation may be compared to experimental values.

II. Simple Electrostatic Model

Benson and Luria's model[4] for hydrocarbons assumed that each bond between a hydrogen atom and an sp^3 hybridized carbon atom generated a certain separation of charge. A fraction, y, of an electron would shift from H to C or vice versa; it was not necessary to specify the sign of the charge transfer. If a carbon atom was bonded to n hydrogen atoms, each with a charge of $+y$, the charge on the carbon atom would be $-ny$.

They then calculated the electrostatic energy, E_{el}, of the molecule by summing the Coulombic interactions between all pairs of atoms, both bonded and nonbonded. Here q_i is the charge on

$$E_{el} = \sum_{i \neq j} q_i q_j / r_{ij} \tag{1}$$

atom i and r_{ij} is the internuclear distance. They found that this model was capable of explaining the greater stability of branched alkanes compared to linear alkanes. Provided the charge transferred, y, was chosen as 0.0581 of the charge of an electron, the agreement with experimental heats of formation of alkanes was quantitative.

The model was simple but effective. They did consider the second-order effects due to atomic polarizability, but found these only affected energies by 0.4 kJ mol^{-1}, although they had a larger effect on net dipole moments. All atom–atom interactions had a significant effect on the energy, but the greatest effect was caused by pairs of atoms covalently bonded to each other. The trends could be qualitatively understood in terms of these interactions. Thus in *n*-pentane, the largest interactions involved two bonds between secondary carbon atoms ($E_{el} = (2y)^2/r_{cc}$) and two bonds between primary and secondary carbons ($E_{el} = 2y \cdot 3y/r_{cc}$) for a total repulsion of $20y^2/r_{cc}$. In neopentane, on the other hand, the central carbon atom would have no charge, and there would be no repulsive interaction between covalently bonded carbons, explaining the greater stability of the molecule.

We now seek to extend this method to molecules containing elements other than hydrogen and carbon, with bond polarities differing depending on the nature of the bonded atoms. There have been earlier attempts to incorporate heteroatoms. Benson[15] considered the question but foresaw difficulty with dipole moments. Palm[6] inferred charges on F and O atoms from experimental dipole moments. Davidson, O'Neal, and Ring[16] applied similar schemes to silane and alkylsilanes. Buckley and Rodgers[11] added terms for induced charges, fit 11 parameters to the heats of formation and dipole moments of 21 straight-chain alkanes, fluoroalkanes, and chloroalkanes, and applied the results to 19 more fluoro- and chloroalkanes.

It is reasonable to suppose that the bond polarity will depend on the electronegativities of the two bonded atoms, so we need to choose a scale of electronegativity and a relationship between electronegativity and charge.

In this search we can be guided by the work of Luo and Benson.[17] They correlated heats of formation of alkyl derivatives with various scales of electronegativity. They found the best correlation occurred for a new scale of electronegativity, the covalent potential, V_x. Here n_x is the number of valence electrons

$$V_x = n_x / r_x \tag{2}$$

in the neutral atom X and r_x is the covalent radius of X. Thus V_x is the energy of attraction between an electron at the covalent radius and the nucleus, shielded by the core electrons. The scale was proposed by Yuan[18] and is similar to an earlier scale by Gordy.[19] This scale also correlates well with other molecular properties, including homolytic and heterolytic bond dissociation energies.[17] It agrees well with Mulliken electronegativities of ground and valence state atoms. We have therefore adopted this scale of electronegativity for our model.

Luo and Benson[17] found the correlation between V_x and $\Delta_f H(C_2H_5X) - \Delta_f H(CH_3X)$ was linear. We have accordingly started with the assumption that the charge transferred along a bond, q(bond), is a linear function of the difference in electronegativities between the bonded atoms. By analogy with Benson and Luria,[4]

$$q(\text{bond}) = y(V_x(\text{atom A}) - V_x(\text{atom B})) \tag{3}$$

the charge on a polyvalent atom will be the sum of the charges contributed by the various bonds it forms.

$$q(\text{atom}) = \sum_{\text{bonds}} q(\text{bonds}) = \sum_{\text{bonds}} y[V_x(\text{attached atoms}) - V_x(\text{atom})] \tag{4}$$

There have been a number of more sophisticated models for assigning atomic charges.[6–14] Here we are making use of Ockham's razor, keeping the model as simple as possible, only introducing additional complexity if it is needed to explain experimental facts.

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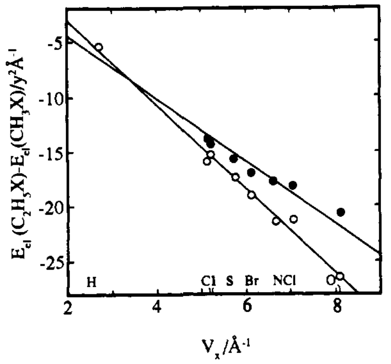

Figure 1. Differences in electrostatic energies between C_2H_5X and CH_3X as a function of the covalent potential, V_x: (○) simple model of section II and (●) model of section III with partial charge sharing by carbon atoms.

Readers will recognize that, for diatomics, eq 3 is similar to Pauling's original approach.[20] We are, however, using a different definition of electronegativity than Pauling.

In this model, the transfer of charge between C and O will be in the opposite direction to that between C and H. We can anticipate that this may be related to the reversal in bond strengths noted in the opening paragraph.

A computer program has been written to implement this model. The molecules chosen were the methyl, ethyl, and *tert*-butyl alcohols, chlorides, amines, bromides, thiols, and iodides and corresponding alkanes, 23 molecules in all. Molecular geometries and internuclear distances were generated with the Chem-X molecular mechanics program.[21] Covalent potentials and valences were calculated. The charges on atoms (in units of y) were calculated by summation over the covalent bonds as in eq 4. The electrostatic energy (in units of $y^2/Å$) was calculated by summing over all interactions as in eq 1.

It has been suggested[15] that the virial theorem may require the introduction of a numerical factor in eq 1 when the total energy is considered. However, on substituting eq 1, or any other expression with an inverse dependence on r_{ij}, into the virial theorem for polyatomic systems[22] and differentiating with respect to r_{ij}, one finds that both the potential energy and the total electronic energy have the same dependence on r_{ij}, as given by eq 1. This equation could be divided by a dielectric constant,[8b,9] but use of a constant dielectric constant would have the same effect on all molecules. A variable dielectric constant would have more subtle effects, but it would be difficult to decide how the dielectric constant should vary.

Luo and Benson[17] found a strong correlation between the experimental difference, $\Delta_fH(C_2H_5X) - \Delta_fH(CH_3X)$, and V_X. Similarly, we have plotted $E_{el}(C_2H_5X) - E_{el}(CH_3X)$ as a function of V_X as the open points in Figure 1. The units of E_{el} are $y^2/Å$ and those of V_x are $Å^{-1}$. There is a strong linear relationship with a correlation coefficient of 0.995. Thus the linear relationship between electronegativity and charge, eq 3, leads to a linear relationship between electronegativity and energy in Figure 1.

Since $\Delta_fH(C_2H_5X) - \Delta_fH(CH_3X)$ and $E_{el}(C_2H_5X) - E_{el}(CH_3X)$ are both linearly related to V_X, they must be linearly related to each other, as shown in Figure 2.

The trends can be explained quantitatively again in terms of the strongest interaction between covalently bonded atoms. In ethane, corresponding to the highest points on Figures 1 and 2, the two carbon atoms each have a charge of $3\cdot2.49y$ and repel each other with an energy of $55.8y^2/r_{cc}$. In ethanol, corresponding to the lowest points in Figures 1 and 2, one carbon atom has a charge of $(2\cdot2.49 - 2.92)y$ and the two carbons repel each other with an energy of only $15.4y^2/r_{cc}$. There are no C–C repulsions in methane and methanol. The smaller C–C repulsion accounts

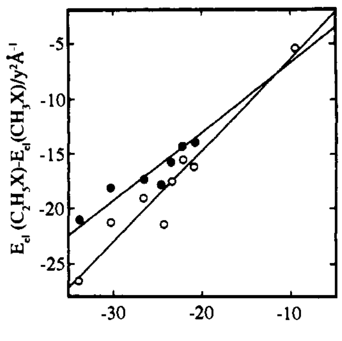

Figure 2. Differences in electrostatic energies between C_2H_5X and CH_3X as a function of differences in their experimental standard enthalpies of formation:[23] (○) simple model of section II and (●) model of section III.

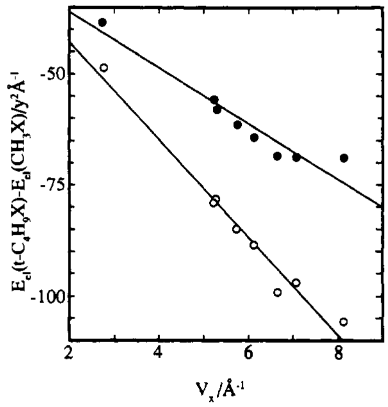

Figure 3. Differences in electrostatic energies between t-C_4H_9X and CH_3X as a function of V_x: (○) model of section II and (●) model of section III.

for the greater stability of ethanol compared to ethane, with respect to their methyl analogues.

Similarly, the calculated differences in electrostatic energies between *tert*-butyl derivatives and methyl derivatives were found to be linear in V_x, as shown in Figure 3. The correlation coefficient was 0.989. The ratio of the slopes in Figures 3 and 1 is 2.86. This is close to the ratio of 3:1 for the number of methyl groups attached to the central carbon atom in *tert*-butyl groups as opposed to ethyl groups.

This pattern may be understood algebraically by considering the strongest interactions, normally those between bonded carbon atoms. The charge on the central carbon atom, according to eq 4 is

$$q_c = [V_x - V_c - (3 - m)(V_c - V_H)]y \qquad (5)$$

Taking $q_{c,me}$ as the charge on the m neighboring carbon atoms in methyl groups, the electrostatic repulsion between the bonded carbon atoms is

$$E_{cc} = -q_{c,me}ym[V_c + (3 - m)(V_c - V_H)]/r_{cc} + q_{c,me}ymV_x/r_{cc} \qquad (6)$$

From the last term we see that, as $q_{c,me}$ is negative, the electrostatic repulsion declines as a linear function of V_X and that the slope of a plot of E_{cc} vs V_x would be proportional to m. (The slope would be $3q_{c,me}y/r_{cc}$ for *tert*-butyl and $1q_{c,me}y/r_{cc}$ for ethyl.)

Similar arguments may be applied to the strength of the C–X bond. The electrostatic interaction between the bonded atoms is

$$E_{cx} = q_xy[(m - 3)(V_c - V_H) + V_x - V_c]/r_{xc} \qquad (7)$$

When q_x is positive, as for H, increasing m makes E_{cx} more positive or repulsive, and the C–H bond in ethane is weaker than that in methane. When q_x is negative, as for O, increasing m makes E_{cx} more attractive and the C–O bond in ethanol is stronger than that in methanol. Other interactions in the molecules and the product

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Table I. Net Charges Assigned to Atoms

molecule	atom	this work[a]	Mullay[12]	FEOE[13]	MM[9]	OPLS[27]	WB[29]	GAPT[30]
CH_4	H	0.083	0.037	0.005	0.007	0.0	−0.061	−0.018
	C	−0.33	−0.148	−0.021	−0.028	0.0	0.24	0.073
C_2H_6	H	0.083	0.042	0.006	0.007	0.0	−0.079	−0.048
	C	−0.25	−0.126	−0.018	−0.021	0.0	0.24	0.145
CH_3OH^1	H	0.083	0.065		−0.003	0.0	−0.044	
	C	−0.15	−0.021	0.025	0.232	0.265	0.85	
	O	−0.28	−0.381		−0.578	−0.7	−1.26	
	H^1	0.18	0.207		0.356	0.435	0.61	
$CH_3C^1H_2OH^1$	H	0.083				0.0		
	C	−0.21				0.0		
	C^1	−0.10				0.265		
	O	−0.28				−0.7		
	H^1	0.18				0.435		

[a] Dielectric constant was assumed to be unity.

radicals are also significant, but eq 7 is capable of explaining the paradox in the opening sentence of section I.

However, the ratio of slopes for the open points in Figures 3 and 1 is not the same as that observed experimentally. Luo and Benson[17] found the slope of a plot of $\Delta_f H°(t\text{-}C_4H_9X) - \Delta_f H°(CH_3X)$ against V_x to be only 2.03 times greater than the slope for $\Delta_f H°(C_2H_5X) - \Delta_f H°(CH_3X)$ against V_x. Another method of comparing our results to experiment is to examine the isodesmic reactions:

$$i\text{-}C_4H_{10} + CH_3OH \rightarrow CH_4 + t\text{-}C_4H_9OH \qquad (8)$$

$$C_2H_6 + CH_3OH \rightarrow CH_4 + C_2H_5OH \qquad (9)$$

From experimental data,[23] the ratio of the enthalpies of reaction, $\Delta H°(8)/\Delta H°(9)$, is 2.11. From the present model, the ratio $\Delta E_{el}(8)/\Delta E_{el}(9)$ is 2.75.

In the next section we will introduce a model which is capable of harmonizing the results for ethyl and *tert*-butyl derivatives.

III. Model with Charge Shared between Carbon Atoms

To try to understand the different effects of electronegativity of the substituent, X, on the heats of formation of ethyl and *tert*-butyl derivatives, we return to the semiempirical fits of Luo and Benson.[17] They examined methyl, ethyl, isopropyl, and *tert*-butyl derivatives and found the following expression gave the best fit to the experimental data:

$$\Delta_f H°(C(CH_3)_m H_{3-m}X) - \Delta_f H°(CH_3X) = [3.8 - 6.3m(m-1)] - mV_x/(0.16 + 0.050m) \qquad (10)$$

The numbers are empirical constants, which have been adjusted to provide results in kJ mol^{-1}. The expression fitted the experimental data for the 23 cases considered with an average deviation of 1.2 kJ mol^{-1}.

In the last term in eq 10, the factor mV_x in the numerator, on its own, would cause a 3-fold greater slope in a plot of $\Delta_f H°(t\text{-}C_4H_9X) - \Delta_f H°(CH_3X)$ vs V_x compared to a plot of $\Delta_f H°(C_2H_5X) - \Delta_f H°(CH_3X)$ vs V_x. This is similar to the ratios we found in the previous section for $E_{el}(t\text{-}C_4H_9X) - E_{el}(CH_3X)$ compared to $E_{el}(C_2H_5X) - E_{el}(CH_3X)$. The factor mV_x also appeared in the last term of eq 6. The denominator in eq 10 acts as a damper, reducing the effect of the factor of m in the numerator. We seek a similar damping effect to reduce the effect of methyl substitution in the electrostatic model.

In section II we noted that the largest electrostatic forces in the molecules were the forces between covalently bonded carbon atoms. Carbon has the highest valence of the atoms considered; since eq 4 involves a summation over the bonds to an atom, the carbon atom, with the most bonds, is capable of achieving the highest charge. Each bond to a hydrogen atom gives the carbon a charge of $-2.49y$. Replacement of a hydrogen atom by a more electronegative group reduces the charge. Thus, among the *tert*-butyl derivatives, in isobutane the central carbon has a charge of $-2.49y$, in neopentane it has a charge of zero, and in *tert*-butyl alcohol, a charge of $+2.92y$. The carbon atoms in the methyl groups in all cases would have charges of $-3\cdot 2.49y$. This change, from repulsive C–C electrostatic interactions in isobutane to attractive interactions in *tert*-butyl alcohol, accounts for the extra stability of *tert*-butyl alcohol. However, these carbon atoms all start with the same intrinsic electronegativity. In our model we have transferred charge between atoms of differing electronegativity but not between carbon atoms of equal electronegativity. It would appear to be logical to allow carbon atoms to share charge among themselves. This would reduce the attraction between bonded carbon atoms in *tert*-butyl alcohol, thus damping the electrostatic forces, which is the effect we seek.

This became our second model. We performed the calculations described in section II and then obtained an average charge, $\bar{q}_c$, for carbon atoms. If we replaced each carbon atom charge by the average, that is, assuming total charge sharing among the carbon atoms, the ratio, $\Delta E_{el}(8)/\Delta E_{el}(9)$, dropped to 0.554, beyond the experimental value. Considerably greater scatter was introduced into plots like Figures 1 and 3.

Accordingly, we introduced a model in which carbon atoms were permitted to partially share charge among themselves.

$$q^*_c = p\bar{q}_c + (1-p)q_c \qquad (11)$$

Here q_c is the charge on a carbon atom according to the model of section II, q^*_c is the charge according to the new model and p is the fraction of the charge shared. Readers will note that the sharing of charge is like an inductive effect and that p is similar to the propagator of the inductive effect.

This model was applied as before, with q^*_c replacing q_i or q_j for carbon atoms in eq 1. The propagator, p, was varied in steps of 0.1 from 0.0 to 1.0. The value of 0.4 for p gave a ratio, $\Delta E_{el}(8)/\Delta E_{el}(9)$, of 2.0, close to the experimental ratio of heats of reaction of 2.11. This value of p will be selected for all subsequent discussion. It is similar to values of the attenuator of the inductive effect used by others.[24]

Plots in Figures 1 and 3 of $E_{el}(C_2H_5X) - E_{el}(CH_3X)$ and of $E_{el}(t\text{-}C_4H_9X) - E_{el}(CH_3X)$ vs V_x remain linear, with correlation coefficients of 0.986 and 0.964, respectively. Plots of the same theoretical differences against the experimental differences, $\Delta_f H(C_2H_5X) - \Delta_f H(CH_3X)$ and $\Delta_f H(t\text{-}C_4H_9X) - \Delta_f H(CH_3X)$, are shown in Figures 2 and 4. The correlation coefficients are 0.973 and 0.964, respectively. The slopes are similar, 0.626 and $0.651y^2$ mol/kJ Å, respectively.

Using the average slope from Figures 2 and 4 and applying the permittivity of a vacuum and appropriate unit conversion factors, y is found to be 0.033 times the charge on an electron. With this value of y, the charge on each atom was calculated. Representative values are given in Table I. These charges would increase in proportion to the square root of the dielectric constant, if one were included.

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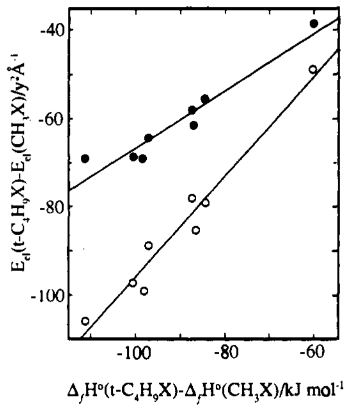

Figure 4. Differences in electrostatic energies between *t*-C_4H_9X and CH_3X as a function of differences in standard enthalpies of formation: (○) model of section II and (●) model of section III.

Hydrogen atoms bonded to carbon have a charge of +0.083, indicating they have lost about 8% of the possession of an electron, compared to a neutral atom. Because of the greater electronegativity of O compared to C, hydrogen atoms bonded to oxygen have lost possession of about 18% of an electron. Oxygen atoms have gained possession of about 28% of an electron from their two bonding partners. Charges on the carbon atoms vary because of the partial charge sharing.

The pattern of charges provides a more detailed answer to the questions posed in the opening paragraph of the article.

Methane involves four bonds, all between carbon and hydrogen atoms of opposite charges. All these interactions are attractive, accounting for the relative stability of this molecule and the great strength of the C–H bonds. The electrostatic energy, including bonded and nonbonded interactions, is −107.5 kJ mol^{-1}. This is actually larger than the heat of formation of this molecule, −74.5 kJ mol^{-1}, although it is a small fraction of the heat of atomization, 1663.1 kJ mol^{-1}.

In ethane, in addition to the attractive C–H interactions, there is also a direct, repulsive interaction between the two carbon atoms. This accounts for the relative instability of this molecule. The C–C repulsion effectively cancels out three C–H attractions. The replacement of an H in methane by a CH_3 reduces the charge on the other C, reducing the C–H electrostatic attraction and weakening the C–H bond. The total electrostatic energy is −115.6 kJ mol^{-1}. This is 8% greater than the electrostatic energy in methane, but the increase is small considering ethane has 60% more atoms than methane.

Similarly, the model predicts that in methanol there is repulsion between the carbon atom, with an extra 15% of an electron, and the oxygen, with an extra 28%. This repulsion is only about two-thirds as great as that between the carbon atoms in ethane. The total electrostatic energy is −103.3 kJ mol^{-1}.

In ethanol, the charge on the carbon atom bonded to oxygen drops to 10% of an electronic charge. There is less C–O electrostatic repulsion than in methanol, explaining the greater stability of ethanol compared to methanol and the greater strength of the C–O bond. On the two carbon atoms, there are charges of 10% and 21% of an electronic charge. The repulsion between these atoms is only 36% as great as the repulsion between the carbon atoms in ethane. The withdrawal of charge from the carbon atoms by the oxygen atom explains the greater stability of ethanol compared to ethane.

For the isodesmic reaction, eq 9, the change in electrostatic energy is calculated to be −23.5 kJ mol^{-1}. The experimental enthalpy of reaction is −24.7 ± 0.8 kJ mol^{-1}.

A referee has suggested this method might be used to estimate parameters for an additivity scheme. We can consider the prospects for this by taking ethanol as an example. The electrostatic interactions between bonded atoms equal −131 kJ mol^{-1}. At first glance, this might appear to be a bond additivity term,[2] but the charges on the atoms are affected by all their neighbors. Thus this quantity already incorporates some indirect next next nearest neighbor effects, which are at a level higher than group additivity,[2] which includes only next nearest neighbor effects. The direct electrostatic interactions between nonbonded atoms in ethanol are as follows: next nearest neighbors, −16 kJ mol^{-1}; next next, −13 kJ mol^{-1}; next next next, +17 kJ mol^{-1}. This series attenuates slowly, indicating that the success of group additivity is due to a partial cancellation of these terms. A similar conclusion was reached for alkanes in ref 4. This method may be useful for predicting weaknesses of group additivity or extending the scheme.

The charges in the model of Benson and Luria[4] for alkanes were 30% less than in our model. This similarity offers promise that the present model could, like that of Benson and Luria,[4] also be extended to longer linear alkanes, to radicals, and to unsaturated compounds.

Benson and Luria[4] also calculated dipole moments from their charges. When they considered only the point charges, they found calculated dipole moments were less than the experimental values. Inclusion of induced dipoles increased the calculated values to give reasonable agreement with experiment. Similarly, from the present point charges for methanol we calculate a dipole moment of 1.1 Debye, somewhat less than the experimental value of 1.7 Debye.[9] We have not taken induced dipoles into account.

Buckley and Rodgers[11] did take induced dipoles into account and obtained good agreement with experimental dipole moments. Before the induced dipoles were applied, their basic charge on a hydrogen atom was +0.065, a little less than our value, and their charge on a chlorine atom was −0.181, larger than our value of −0.061. However, about half their charge on a chlorine atom was removed by the induced dipole of a C–Cl bond. They allowed the bond polarizability to be an adjustable parameter and added the polarization work to the enthalpy of formation. For several molecules the calculated polarization work exceeded the energy available from eq 1, so that the net electrostatic contribution was repulsive.

Palm[6] inferred atomic charges from experimental dipole moments. For H bonded to C the charges varied from −0.040 to −0.067, for H bonded to O, +0.33, and for O, −0.58.

James and Keenan[25] inferred a charge of 0.13 on hydrogen from a study of the thermal properties of solid methane and Gussoni et al.[26] a value of 0.065 from infrared intensities of the same molecule.

The next four columns in Table I show the results of other semiempirical methods of assigning charges to atoms. Mullay[12] obtained charges on H atoms in alkanes about half of the present values and charges on O about 30% greater. The full equalization of orbital electronegativity[13] (FEOE) and molecular mechanics[9] methods gives charges on hydrogen atoms an order of magnitude less than the present work. To model the properties of liquids, Jorgensen[27] placed no charges in alkyl groups but larger charges in hydroxyl groups. The CHARMM molecular mechanics program,[28] on the other hand, assigns a charge of +0.09 atomic units to H bonded to C, very similar to the present model.

Results of ab initio calculations[29,30] are listed in the final two columns of the table. The polarities of the C–H bonds are reversed in these results. There is considerable controversy regarding the best way to calculate atomic charges from ab initio calculations.[31] Depending on the basis set and the method of apportioning electron density to atoms, the charges on carbon atoms and alkyl hydrogen atoms in alkanes and methanol have all been calculated to have both positive and negative signs and a variety of magnitudes.[31]

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In summary the charges inferred in this work imply more polar C–H bonds and less polar C–O bonds than in most other models, but the charges are not unreasonable given the wide range of values in the literature.

IV. Covalent Contributions and Enthalpies of Formation

In the previous section we saw that electrostatic forces can explain the trends in differences between heats of formation, $\Delta_fH(C_2H_5X) - \Delta_fH(CH_3X)$ and $\Delta_fH(t\text{-}C_4H_9X) - \Delta_fH(CH_3X)$. In this section we wish to relate the model of section III to individual heats of formation.

In section III we saw that the electrostatic forces in methane account for only 6% of the heat of atomization of the molecule. The remaining forces must be covalent bonding and nonbonding, nonelectrostatic interactions. The nonbonding interactions are likely to be weaker than covalent bonds and will tend to cancel between similar molecules. For example, in the isodesmic reaction 9, there are 27 such interactions in the reactants and 27 in the products and only four of these change. Just as we have grouped electrostatic interactions between bonded and nonbonded atoms together as E_{el}, we will group the remaining interactions together as E_{cov}. The heat of formation of a molecule is then given by

$$\Delta_fH^\circ = E_{el} + E_{cov} \qquad (12)$$

This takes a form similar to Pauling's expression for diatomic molecules.[20]

We next assume that the principle of bond additivity may be applied to E_{cov}. Bond additivity, without electrostatic corrections,

$$E_{cov} = \sum_{\text{bonds}} \Delta_fH_{cov}(\text{bond}) \qquad (13)$$

gives a good first approximation to thermochemical properties.[2] According to bond additivity, the enthalpies of reaction for isodesmic processes like (8) and (9) would be zero. Since our electrostatic model is designed to explain the differences, the sums in eqs 12 and 13 should be capable of correlating the absolute heats of formation.

For each molecule, the value of E_{cov} may be found by substituting the experimental value of Δ_fH° and the value of E_{el} from section III in eq 12 and solving. The sum, $\Delta_fH_{cov}(C\text{–}C) + 2\Delta_fH_{cov}(C\text{–}H)$, was determined from the increments in E_{cov} from CH_3X to C_2H_5X to $t\text{-}C_4H_9X$. The individual value of $\Delta_fH_{cov}(C\text{–}H)$ was found by subtracting the above sum, multiplied by the number of CH_2 groups, from E_{cov} for the five hydrocarbons and averaging. The other values of $\Delta_fH_{cov}(\text{bond})$ were obtained by subtracting appropriate numbers of C–H and C–C covalent bond enthalpies from E_{cov} values for the respective classes of molecules and averaging.

The values of $\Delta_fH_{cov}(\text{bond})$ obtained were as follows, in kJ mol^{-1}: C–H, 7.7; C–C, −15.0; C–Cl, −61.3; C–Br, −7.7, C–I, 52.5; C–O + O–H, −125.0; C–S + S–H, 21.7; and C–N + 2N–H, 94.2. It is not possible to obtain separate values for C–O, O–H, C–S, S–H, C–N, and N–H from the molecules considered. Extension of the present approach to ethers or water, thioethers or H_2S, secondary or tertiary amines, or ammonia would be necessary. The values obtained do not have any simple significance. All are relative to the covalent bonds in the elements in their standard states. The substituted alkanes we have considered are in the gas phase, but some of the elements concerned are liquids and solids. Hybridization of the carbon is different from the element, graphite, to the substituted alkanes. The values of Δ_fH_{cov} include not just changes in electronic energy but also in vibrational, rotational, and translational energies. We have argued recently that H–H nonbonded van der Waals repulsions in CH_4 are of comparable magnitude, but opposite sign, to the total electrostatic energies inferred here.[32] Since the present model does not allow for van der Waals forces, any such forces which do exist will be arbitrarily apportioned to the electrostatic or covalent forces. A more complete model, incorporating all three types of force, is expected to lead to different atomic charges and different values of $\Delta_fH_{cov}(\text{bond})$. Benson and Luria[4] used diamond as a reference with their smaller electrostatic energies, to find $\Delta_fH_{cov}(C\text{–}C)$ to be −1 kJ mol^{-1}. Buckley and Rodgers[11] obtained values of −7.2 kJ/mol for C–H, +4.9, C–C, and −52.6, for C–Cl. One trend which is evident in the list above is the steady increase in $\Delta_fH_{cov}(\text{bond})$ between C–Cl, C–Br, and C–I.

Table II. Experimental and Predicted Enthalpies of Formation of Alkyl Derivatives, kJ mol^{-1} [a]

X	CH_3X	C_2H_5X	$t\text{-}C_4H_9X$
OH	−201.5 ± 0.3 [−205.1]	−235.2 ± 0.4 [−236.1]	−312.5 ± 0.8 [−308.5]
Cl	−81.9 ± 0.5 [−82.5]	−112.1 ± 1.1 [−109.6]	−182.2 ± 2.3 [−184.4]
NH_2	−23.0 ± 0.5 [−20.7]	−47.4 ± 0.7 [−47.4]	−120.9 ± 0.7 [−123.2]
Br	−35.5 ± 1.1 [−36.1]	−61.9 ± 1.7 [−61.6]	−132.4 ± 1.8 [−132.0]
SH	−22.9 ± 0.7 [−21.3]	−46.3 ± 0.6 [−44.6]	−109.6 ± 0.9 [−113.1]
I	14.7 ± 1.3 [−14.3]	−7.5 ± 1.7 [−6.9]	−72.0 ± 3.3 [−72.2]
CH_3	−83.7 ± 0.4 [−84.2]	−104.7 ± 0.5 [−104.8]	−168.1 ± 0.8 [−166.7]
H	−74.4 ± 0.4 [−76.5]	−83.8 ± 0.4 [−84.2]	−134.2 ± 0.7 [−133.1]

[a] Predicted values are in square brackets below the experimental results.[23]

Equations 13 and 12 can now be applied in the reverse direction to calculate heats of formation of the molecules for comparison with experiment. The results are shown in square brackets in Table II. Experimental values are also listed, with the quoted uncertainties. The total range of values is from +14.7 to −312.5 kJ mol^{-1}. The largest deviation observed is 4.0 kJ mol^{-1}, for *tert*-butyl alcohol. The average absolute difference between experimental values and those obtained from eq 12 is 1.4 kJ mol^{-1}. This is similar to the average quoted uncertainty in the experimental values, which is 1.0 kJ mol^{-1}. To achieve this fit, 10 parameters (p, y, and the eight values of $\Delta_fH_{cov}(\text{bond})$) have been adjusted. This is two fewer parameters than needed in the semiempirical expressions of Luo and Benson[17] for an average deviation of 1.2 kJ mol^{-1} and maximum deviation of 8 kJ mol^{-1}. In the group additivity scheme,[2] 26 parameters would be needed to calculate these quantities. Benson and Luria[4] obtained an average difference of 0.8 kJ mol^{-1} with three parameters for ten alkanes. Buckley and Rodgers[11] with 11 parameters, differed from experiment by an average of 3.7 kJ mol^{-1} for 38 haloalkanes. Palm and Palm[6] had average deviations of 3.2 kJ mol^{-1} for 21 alkanes and of 8.5 kJ mol^{-1} for eight substituted compounds. Of more significance than the absolute values are the trends across the table, which involve only the parameters p and y. For the alcohols the predicted difference between $t\text{-}C_4H_9OH$ and CH_3OH is −103.4 kJ mol^{-1}, compared to an experimental difference of −110.8 kJ mol^{-1}. All the rest of the comparisons are closer, ranging from a difference of −100.4 kJ mol^{-1} from experiment vs −101.9 kJ mol^{-1} from eq 12 for the chlorides to −59.8 kJ mol^{-1} from experiment vs −56.6 kJ mol^{-1} from eq 12 for isobutane compared to methane.

V. Conclusion

On the basis of the good agreement obtained between calculated and observed values, we conclude that electrostatic forces play a significant role in the thermochemical properties of substituted alkanes. The simple model employed herein may not be the only one which would give such agreement, however. A number of authors[8,12,13] have proposed more sophisticated relationships between electronegativity and charge than the simple eq 4. An important point is that C and H must have substantially different charges so that the trends in the bottom two rows of Table II will be sufficiently different.

The charge sharing scheme of eq 11 is not unique either.[8,11,12] It constitutes a partial second iteration in establishing the charge distribution, with eq 4 as the first iteration. The second iteration could be extended to include partial charge sharing among all the

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atoms in a molecule or among all nearest neighbors. Further iterations could be added.

Options other than eqs 12 and 13 could also be considered for combining electrostatic and covalent forces. Some authors[8,10] have proposed that covalent bonding weakens as charge separation occurs. Van der Waals interactions between nonbonded atoms could be considered explicitly, as is done in molecular mechanics programs.[14,21,28] Jackson[33] has interpreted the changes in bond dissociation energies from methane to isobutane in terms of hybridization and van der Waals interactions. Such refinements are not yet necessary for the 23 molecules considered here.

The method could be extended in several ways. Isopropyl derivatives agreed well with the expression of Luo and Benson[17] and should work well with the present model. Indeed, propane and isobutane already appear in Table II. The method could be extended to ethers, thioethers, secondary and tertiary amines, larger alkyl groups, and other substituents, X. It could be extended to di-, tri-, and polysubstituted alkanes if induced dipoles or van der Waals forces are included.[11,15] Following Benson and Luria[4] it could be extended to radicals and alkenes. Once it has been refined, it could be made accessible in molecular mechanics programs, where it might reduce the number of input parameters required or provide better understanding of the forces involved. With the inclusion of appropriate induced dipoles, it could be used to calculate molecular dipole moments and intermolecular forces.

As it stands, the method does provide a simple, quantitative explanation for the interesting effects of methyl groups on molecular stability in Table II; an explanation which has been lacking for more than 20 years.[1]

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Computer Simulation of the CO_2/HCO_3^- Interconversion Step in Human Carbonic Anhydrase I

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Abstract: The CO_2/HCO_3^- interconversion step in human carbonic anhydrase I is simulated using the empirical valence bond (EVB) method in combination with free energy perturbation molecular dynamics calculations. The calculated free energy profile for the enzyme reaction is found to be in reasonable agreement with experimental kinetic data. The simulations show that the enzyme is able to reduce both the activation barrier as well as the exothermicity of the interconversion step (compared to the water reaction). The catalytic zinc ion appears to be important for both of these effects, its strong interaction with the reacting hydroxide ion being a key element of the catalytic effect. The predicted conformation of the HCO_3^- complex with the enzyme is similar to that observed experimentally for a mutant version of isozyme II. The geometry of the transition state generated by the EVB simulations is compared to ab initio studies of model systems and also to some relevant experimental inhibitor complexes. The simulated energetics of the uncatalyzed solution reaction is used to estimate the reaction free energy in vacuo, and the results are found to be in good agreement with high-level basis set ab initio calculations.

Introduction

One the most interesting challenges facing computational chemistry today is to be able to model catalytic reactions in enzymes in a quantitative way. The prospects for this type of "computational enzymology" approach to be successful are beginning to look rather promising, owing to both theoretical advances as well as increased computer power.[1,2] In this paper we report simulations of the CO_2/HCO_3^- interconversion step in human carbonic anhydrase I (HCAI). The empirical valence bond (EVB) method[1] is used for constructing the reaction potential energy surface, and the free energy perturbation (FEP) technique combined with molecular dynamics (MD) simulation is employed to evaluate reaction free energy profiles. The results from the simulations are found to be in reasonable agreement with experimental estimates of the reaction energetics,[3f,g] and they emphasize the important multiple functions of the active site metal during the catalytic process.

Carbonic anhydrase (CA) is an example of a metalloenzyme that serves as a useful test case for theoretical studies of the role of metal ions in enzyme catalysis, since it has been subjected to extensive experimental investigations, both with respect to structure and function.[3]

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