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On the Reactivity of $CF_nH_{3-n}CH_2X$ (n = 0, 1, 2, and 3, and X = H or Halogen atom)

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Abstract: *Theoretical and experimental data are presented which concern the properties and reactivity of $CF_nH_{3-n}CH_2X$ (X = H, Cl, Br, and I; n = 0, 1, 2, and 3). Anomalous behavior is shown for CF_3CH_2X (X = Cl, Br, and I). This includes (i) tertiary amines do not react with CF_3CH_2X to form a quaternary salt; (ii) the ^{13}C NMR chemical shift is more than 20 ppm upfield than expected; and (iii) AM1 semi-empirical molecular orbital calculations predict C-C heterolytic bond cleavage is preferred to C-X heterolytic bond cleavage. Regarding (iii) experimental data indicate a small preference for C-X bond cleavage, but the difference may be within the error bars for some of the enthalpies.*

INTRODUCTION

We have recently encountered the problem concerning the alkylating power of $C^2F_3C^1H_2I$. As opposed to what one would expect intuitively, it is known[1] that this entity is a sluggish reagent compared to ethyl iodide, and indeed we were unable to react the anion generated from malonic ester with trifluoro ethyl iodide[2]. McBee and co-workers[1] explained this sluggishness in terms of the electron withdrawal effect of the CF_3 group, which inhibits the acceptance of a positive charge on C-1 in the transition state in S_N processes. Likewise, we met similar synthetic difficulties when attempting to force CF_3CH_2Cl, CF_3CH_2Br, and even CF_3CH_2OTs, into S_N reactions. We have found e.g. that when N- (a tertiary amine) reacts with $CF_nH_{3-n}CH_2X$ (n = 0, 1, 2, 3, and X = Cl, Br, I), in all cases the expected quaternary compounds will form, except for CF_3CH_2X (X = Cl, Br, I).

Interestingly, experimental ^{13}C NMR data show that the introduction of the three F atoms on C-2 shiftsthe δ(C-1) value more than 20 ppm upfield relative to the expected value, as estimated based on simple additivity, using a β shift increment of + 7.8 ppm[3] for the fluorine atom[4]. This point is illustrated in the Table 1.

While for CH_3CH_2X (X = Cl, Br, I, OTs) the δ(C-1) chemical shifts are in accord with the estimated values (using the relevant X increments[5]) within 2 ppm, the CF_3CH_2X compounds show a massive deviation in this regard. (Our computer-aided literature research could not locate any published ^{13}C NMR data for CF_3CH_2X). In this respect the following have to be pointed out: A breakdown in additivity for systems bearing

Table 1. Estimated and Experimental shifts for $CF_nH_{3-n}CH_2X$.

	δ(C-1)		δ(C-1) found	δ(C-1) predicted
$CH_3C^1H_2Cl$	39.9[6]	$CF_3C^1H_2Cl$	40.8	63.3
CH_3CH_2Br	28.3[6]	CF_3CH_2Br	25.6	51.7
CH_3CH_2I	-1.1	CF_3CH_2I	-5.0	22.3
CH_3CH_2OTs	66.5	CF_3CH_2OTs	64.6	89.9

halogens on adjacent carbons is a recognized phenomenon. The $YC^2H_2C^1H_2X$ (Y, X = Cl, Br, I) system e.g. exhibits, in general, up to + 8.8 ppm departure from simple additivity[6]. An outstanding case is $ClC^2H_2C^1H_2I$, where C-2 shows a + 22.5 ppm, while C-1 a - 4.4 ppm deviation[6]. Still, in each of these cases the trend that the β carbon is shifted downfield, i.e. becomes deshielded upon halogen substitution at the α position, is maintained. By contrast, in CF_3CH_2X (X = Cl, Br, I, OTs) the C-1 carbon, besides exhibiting an exceptionally large deviation from additivity, is shifted slightly upfield (with the sole exception of CF_3CH_2Cl in which δ(C-1) is practically unchanged). This shows that, as compared to CH_3CH_2X, in CF_3CH_2X C-1 is actually more shielded, which in turn suggests a somewhat exotic perturbation of the electron distribution in this system. As a first approximation these data correlate well with the observed chemical behavior of these molecules in S_N processes.

In view of the above observations, we decided to carry out a computational study of $CF_nH_{3-n}CH_2X$ (n = 0, 1, 2, 3, and X = H, Cl, Br, I), using the most advanced semiempirical method, the AM1 model[7]. Here we report the results of our calculations on these molecules and their S_N1 type reactions, involving different leaving groups. The various reaction products (ions) were independently optimized with respect to structural variables. The difference in their respective heats of formations yields the reaction heat, which can then serve as a basis for the comparison of the various potential reaction paths.

MATERIALS AND METHODS

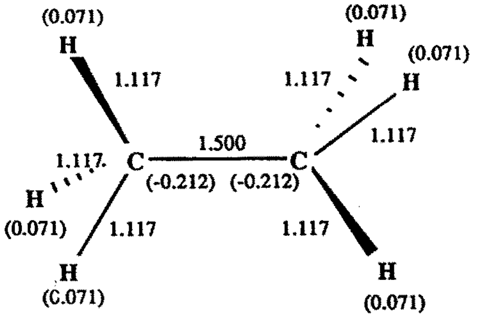
The calculations were carried out in the framework of the AM1 molecular orbital approximation on the Tektronix Computer-Aided Chemistry (CAChe) Worksystem, a reactivity modeling system designed around the Apple Macintosh. AM1 molecular orbital calculations were carried out using the MOPAC program (version 5.10) running on the Tektronix CAChe worksystem. In all cases, the default Broyden-Fletcher-Goldfarb-Shanno[8] (BFGS) Method was employed for full geometry optimization, the default SHIFT = 15 eV option was used to allow 15 eV of damping of the SCF iterations to be determined by the rate of convergence[9] and the PRECISE option was used to tighten the convergence criteria for the self-consistent field iterations and for the geometry optimization. All geometrical variables were optimized.

^{13}C NMR spectra were recorded on a JEOL FX-100 instrument in $CDCl_3$ at ambient temperature (δ_{TMS} = 0.0 ppm). The CF_3CH_2X compounds were prepared according Tiers et al[10].

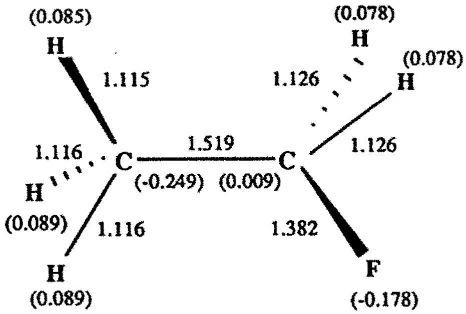
RESULTS AND DISCUSSION

First, the simple C_2H_5X was studied (X = H or halogen atom). The bond lengths, charge distributions, and heats of formation from AM1 calculation for C_2H_6, C_2H_5F, C_2H_5Cl, C_2H_5Br, and C_2H_5I molecules are collected in Figure 1. The bond angles informations are given in Table 2. It can be seen that in the C_2H_5F molecule, the C_1-C_2 bond distance is longer than in the other molecules, C_1 has a larger negative charge, C_2 has a positive charge, while in the other molecules it has a negative charge. Since the fluorine is the most electronegative atom, when one of hydrogens is substituted by fluorine, the C_1-C_2 bond is longer than when hydrogen is substituted by other halogen atoms.

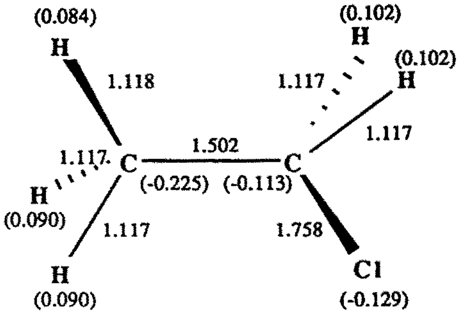
Figure 1. Bond Lengths (Å), Distribution of Formal Charges (e) and Heats of Formation in C_2H_5X (X = H or Halogen)



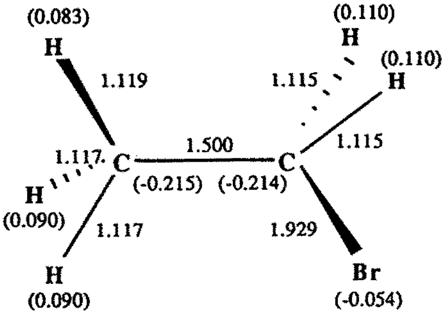
(1a) ΔH_f = -17.41 Kcal/mol



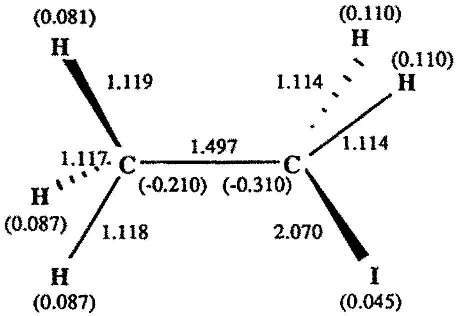
(1b) ΔH_f = -66.30 Kcal/mol



(1c) ΔH_f = -26.16 Kcal/mol



(1d) ΔH_f = -13.12 Kcal/mol



(1e) ΔH_f = -1.07 Kcal/mol

Figure 2. Bond Lengths (Å), Distribution of Formal Charges (e) and Heats of Formation in CH_2FCH_2I, CHF_2CH_2I and CF_3CH_2I.

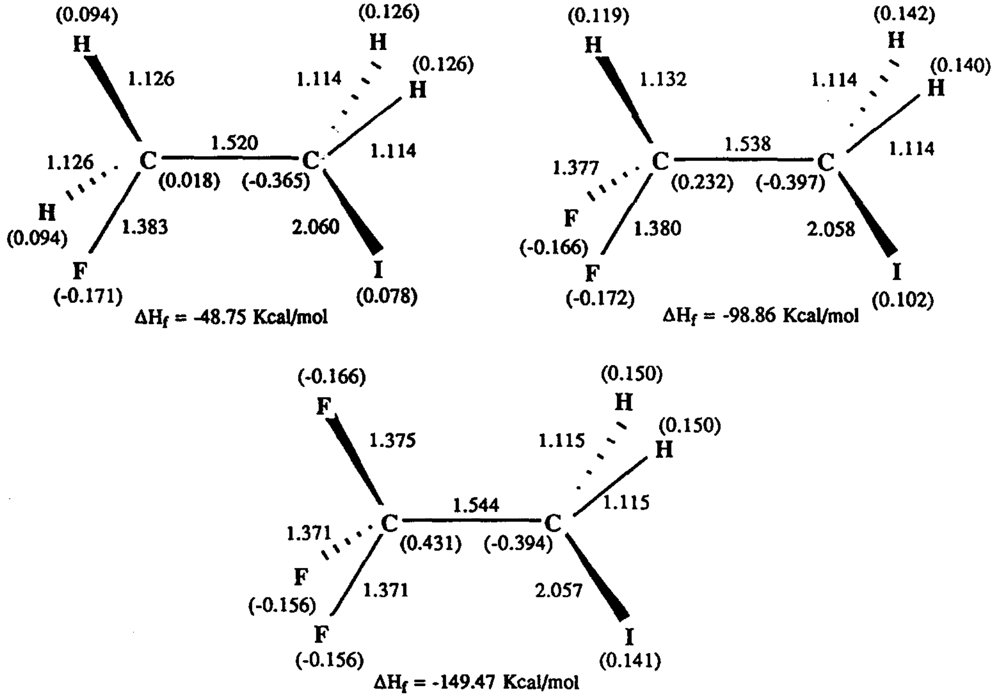


Table 2. Comparative Bond Angles/Degrees from AM1 Calculations.

	C_2H_6	C_2H_5F	C_2H_5Cl	C_2H_5Br	C_2H_5I
H(3) -C(1) -C(2)	110.7	109.4	109.4	109.3	109.7
H(4) -C(1) -C(2)	110.7	110.4	111.1	111.3	111.4
H(5) -C(1) -C(2)	110.7	110.4	111.1	111.3	111.4
H(6) -C(2) -C(1)	110.7	109.9	111.3	110.9	110.7
H(7) -C(2) -C(1)	110.7	109.9	111.3	110.9	110.7
X(8) -C(2) -C(1)	110.7	112.0	111.9	113.5	113.5

	CH_2FCH_2I	CHF_2CH_2I	CF_3CH_2I
F(3) -C(1) -C(2)	111.1	111.2	111.8
F(4) -C(1) -C(2)		112.6	115.1
H(4) -C(1) -C(2)	110.2		
F(5) -C(1) -C(2)			115.2
H(5) -C(1) -C(2)	110.2	111.0	
H(6) -C(2) -C(1)	110.2	109.8	107.5
H(7) -C(2) -C(1)	110.2	108.7	107.6
I(8) -C(2) -C(1)	112.4	113.8	117.6

For the CH_2FCH_2I, CHF_2CH_2I, and CF_3CH_2I molecules, the bond lengths, charge distributions, and heats of formation from AM1 calculations are shown in Figure 2. The bond angles are given in Table 2. The calculated C_1-C_2 bond length increases with the number of fluorine substituents. Parallel with this, the positive charges on C_1 and I atoms increase. Since the fluorine is the most electronegative atom, the more fluorine atoms are added to C_1, the weaker the C_1-C_2 bond and the longer the C_1-C_2 bond. On the other hand, no effect on the C_2-I bond length by the number of fluorine substituents on C_1, could be seen.

The heats of formation calculated for the various S_N1 products are listed in Table 3. It was found that for the CF_3 substituted molecules, CF_3CH_2Cl, CF_3CH_2Br, and CF_3CH_2I it is thermodynamically easier to have $CF_3^{\cdot}$ as a leaving group than $X^{\cdot}$. In other words, it is easier to break the C_1-C_2 bond than to break the C_2-X bond. For all the other molecules, however, it seems to be easier to have X^- as a leaving group than CH_2X^- or CH_2F^- or $CHF_2^{\cdot}$. That is, it is easier to break the C_2-X bond than the C_1-C_2 bond, reactions with tertiary amines should lead to formation of quaternary salts. We can plot the difference of the energies to break the C_1-C_2 bond and the C_2-X bond vs. the number of fluorine substituents on C_1 as shown in Figure 3. It can be seen that when the number of fluorine substituents is zero, the order of leaving groups are $Cl^->Br^->I^-$, while when the number of fluorine substituents is equal to three, the leaving groups are $CH_2Cl^+>CH_2Br^+>CH_2I^+$. If the number of fluorine substituents could be 2.5, the energy difference would be zero. At this point the energy required to break the C_1-C_2 bond is about the same as the energy to break the C_2-X bond. Since this hypothesis obviously can not be checked, it can be concluded that there is a qualitative jump from CF_2H- to CF_3-, and the reactivity of the corresponding molecules dramatically changes. The energy differences are quite large, supporting these conclusions.

Figure 3. The Difference of the Energies to Break the C_1-C_2 Bond and the C_2-X Bond *vs.* the Number of Fluorine Substituents on C_1.

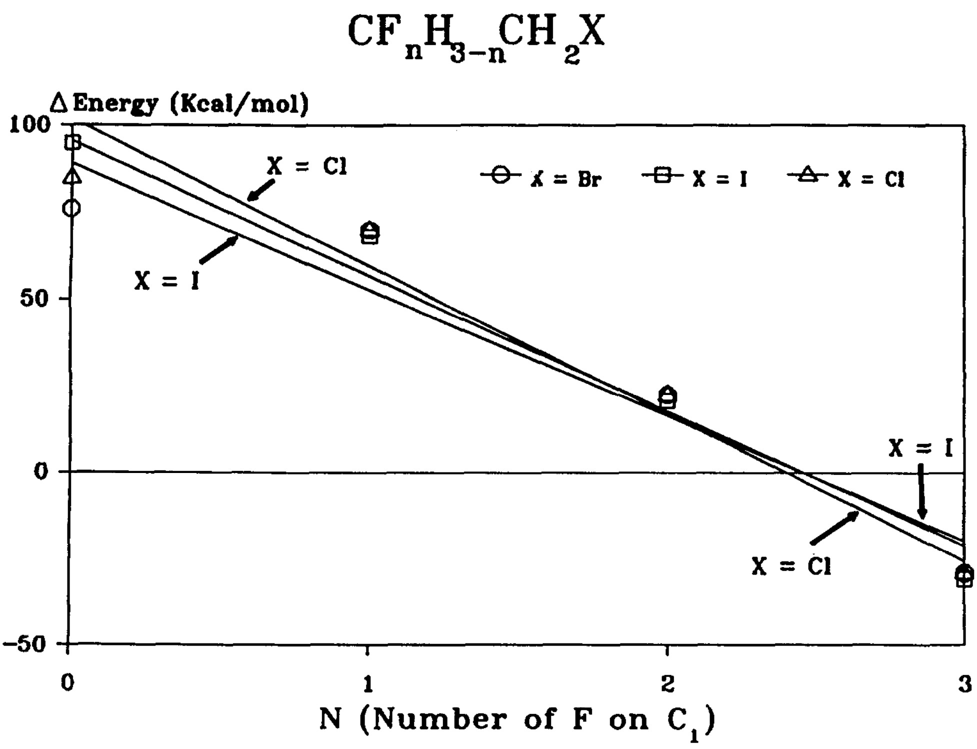


Table 3. Heats of formation (Kcal/mole) of the various S_N1 reactions of $CF_nH_{3-n}CH_2X$ (n = 0, 1, 2, and 3, and X = H or halogen atom) from AM1 calculations and experimental data[a].

reactant	products	heat of formation of products(AM1)	enthalpy difference	experimental data	enthalpy difference
CH_3CH_2I	$I^- + C_2H_5^+$	-2.2+216.8=214.6		-44.9+215.6=170.7	
	$CH_2I^- + CH_3^+$	37.8+252.4=290.2	75.6	24.4+261.3=285.7	115.0
CH_2FCH_2I	$I^- + CH_2FCH_2^+$	-2.2+180.6=178.4		-44.9+187[b]=142.1	
	$CH_2F^- + CH_2I^+$	-13.9+261.9=248.0	69.6	-12.4[c]+245[d]=232.6	90.5
CHF_2CH_2I	$I^- + CHF_2CH_2^+$	-2.2+148.7=146.5		-44.9+149.9[e]=105	
	$CHF_2^- + CH_2I^+$	-93.2+261.9=168.7	22.3	-87.0+245=158	53
CF_3CH_2I	$I^- + CF_3CH_2^+$	-2.2+114.4=112.2		-44.9+120=75.1	
	$CF_3^- + CH_2I^+$	-178.8+261.9=83.1	-29.0	-154.9+245=90.1	15
CH_3CH_2Cl	$Cl^- + C_2H_5^+$	-37.7+216.8=179.1		-54.3+215.6=161.3	
	$CH_2Cl^- + CH_3^+$	21.6+252.4=274.0	94.8	10.8+261.3=272.1	110.8
CH_2FCH_2Cl	$Cl^- + CH_2FCH_2^+$	-37.7+180.6=142.9		-54.3+187=132.7	
	$CH_2F^- + CH_2Cl^+$	-13.9+224.9=211.0	68.0	-12.4+227[d]=214.6	81.9
CHF_2CH_2Cl	$Cl^- + CHF_2CH_2^+$	-37.7+148.7=111.0		-37.7+149.9=112.2	
	$CHF_2^- + CH_2Cl^+$	-93.2+224.9=131.7	20.6	-87.0+227=140	27.8
CF_3CH_2Cl	$Cl^- + CF_3CH_2^+$	-37.7+114.4=76.7		-54.3+120=65.7	
	$CF_3^- + CH_2Cl^+$	-178.8+224.9=46.1	-30.7	-154.9+227=72.1	6.4
CH_3CH_2Br	$Br^- + C_2H_5^+$	-20.4+216.8=196.4		-50.9+215.6=164.7	
	$CH_2Br^- + CH_3^+$	28.7+252.4=281.1	84.6	17.9+261.3=279.2	114.5
CH_2FCH_2Br	$Br^- + CH_2FCH_2^+$	-20.4+180.6=160.2		-50.9+187=136.1	
	$CH_2F^- + CH_2Br^+$	-13.9+243.9=230.0	69.8	-12.4+234[d]=221.6	85.5
CHF_2CH_2Br	$Br^- + CHF_2CH_2^+$	-20.4+148.7=128.3		-50.9+149.9=99	
	$CHF_2^- + CH_2Br^+$	-93.2+243.9=150.7	22.4	-87.0+234=147	48
CF_3CH_2Br	$Br^- + CF_3CH_2^+$	-20.4+114.4=94.0		-50.9+120=69.1	
	$CF_3^- + CH_2Br^+$	-178.8+243.9=65.1	-28.9	-154.9+234=79.1	10

[a] Ref. 11, unless otherwise stated. [b] Refs. 11 and 12. [c] Refs. 11, 13, and 14. [d] Ref. 15. [e] Ref. 16.

In order to investigate the suitability of the AM1 method for this study, we have compared the calculated heats of formation with experiment and, in one case ($CH_2FCH_2^+$), a combination of theory and experiment. Most of the data have been taken from the compilation of Lias et al[11]. For $CH_2FCH_2^+$ a heat of formation of 187 kcal/mol was deduced from the calculated energy difference of $CH_2FCH_2^+$ and CH_3CHF^+ [12] and the experimental heat of formation of CH_3CHF^+ [11]. The heat of formation of CH_2F^- was deduced from the deprotonation enthalpy of CH_3F[14] and H^+ [11]. For CH_2X^+ (X = Cl, Br, and I) the heats of formation were taken from the work of Holmes et al[15] (it ought to be mentioned that these differ from the values given by Lias et al by 10 kcal/mol). Finally, the heat of formation of $CHF_2CH_2^+$ was taken from the work of Heinis et al[16]. While the calculated results for the halide ions are not satisfactory (too unstable), for the other species (both cations and anions) the agreement with experiment is reasonable. More important for present purposes are the sums of the heats of formation of the pairs of decomposition products corresponding to the two distinct pathways. For the halide ion route, the AM1 heat of formation is systematically higher than experiment (because of the halide ion error), while for the other route the agreement is excellent. The AM1 data reproduce the experimental trends well. Thus, when the number of fluorines in $CH_{3-n}F_nCH_2Br$ increases, the differences between the two pathways becomes smaller. Although the experimental data indicate that C-C cleavage pathway is never favored over C-X cleavage, the enthalpy differences are very small, and may be within the experimental error. Thus, it may be noted that if one uses the heat of formation for CH_2Br^+ from Lias et al, rather than the one from Holmes et al, the two decomposition pathways for CF_3CH_2Br have equal enthalpy changes. Most interesting is the fact that the experimental heats of formation cannot differentiate the two sets of products resulting from ionic decomposition of CF_3CH_2Br, lending credence to the suggestion that the CF_3^- pathway is certainly possible and explain the lack of success in the synthetic efforts to produce CF_3CH_2-$N^+\lessgtr$ quaternary salts.

In conclusion, these results offer a subtle but fundamental alteration in our view of the chemical behavior of the CF_3CH_2X (X = Cl, Br, I) system: by introducing the three fluorine atoms in the β position, X entirely looses its "leaving-group" character. Thus as opposed to the intuitively plausible explanation for the diminished reactivity of this system put forward by McBee et al. (see introduction), the $CF_3CH_2^+$ ion as such can no longer be conceived as an entity of potential existence in S_N reactions. The CF_3CH_2OTs molecule was not included in our calculations due to increased difficulties in dealing with this system. Nevertheless, given its similarity to the X = Cl, Br and I cases both in terms of reactivity and ^{13}C chemical shifts (see introduction), we can safely assume that the above conclusions apply to CF_3CH_2OTs, and very likely to a range of other CF_3CH_2X derivatives as well.

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(4) We note that using simple additivity in this sense can be expected to give only a relatively rough estimated of δ(C-1). For CH_3CX_3 (X = Cl, Br) the deshielding of the β carbon is known to be greater by ~ + 7 ppm than that predicted by simple additivity. On the other hand in $C^1D_3CF_3$ δ(C-1) was reported[5] to be 20.5 ppm (in acetone-d_6 at 233K); this corresponds with a ~ + 15.2 ppm combined β effect for the three F atoms, which is smaller than that expected from additivity. When using this value for the prediction of δ(C-1) in the CF_3CH_2X system, the calculated values listed above will all be shifted by - 8.2 ppm, thereby giving a smaller but still spectacular difference with respect to the experimental data.

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