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Comparative Stability of Fluoroketone Hemi-thio Acetals, Ketals and Hydrates

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Abstract The relative thermodynamic stability of hemi-thio acetals, ketals and hydrates of fluoroketones have been determined by AM1 and MNDO calculations of isodesmic reactions.

Fluoroketones possess unique properties in relation to the corresponding aliphatic or aryl ketone derivatives in that fluoroketones readily form very stable hydrates. [1] X-ray crystal structures have been obtained for the hydrates of several trifluoromethyl ketones. [2] The addition of a nucleophile to a fluoroketone also occurs at a much lower cost in energy than the same addition reaction to an aliphatic ketone. [3] These novel physical properties have led to the application of fluoroketones as inhibitors of a wide variety of hydrolytic and proteolytic enzymes. [4] Indeed, fluoroketones are extremely efficient inhibitors of serine esterases such as acetylcholinesterase and chymotrypsin. Fluoroketones are also of considerable interest to the pharmaceutical industry as potent inhibitors of clinically relevant proteases such as elastase and renin. In these examples, the fluoroketone establishes a stable hemi-ketal with the nucleophilic serine residue within the active site of the enzyme. Verification of covalent bond formation between the enzyme and the fluoroketone as the actual inhibitory species has been determined by a number of NMR studies of chymotrypsin and acetylcholinesterase. [5] An X-ray crystal structure has been solved for a porcine pancreatic elastase - fluoroketone inhibitor complex which clearly shows the covalently bound hemi-ketal of the inhibitor within the active site. [6] Interestingly, fluoroketones are much less efficient inhibitors of cysteine proteases such as cathepsin. [7] Indeed, studies of a series of fluoroketone inhibitors of acetylcholinesterase have shown that systematically increasing the number of fluorine substituents alpha to the carbonyl provide a concomitant increase in the inhibitory potency of the compound. [8] As fluorine substitution was increased from the mono alpha-fluoromethylketone to the trifluoromethylketone derivative of an inhibitor of cathepsin, the opposite result was obtained. [7d] For cathepsin inhibition, the trifluoromethylketone was even less effective than the simple methylketone derivative.

As part of our continuing interest in fluoroketone inhibitors of hydrolytic enzymes, [9] we have undertaken a study to assess the relative stability of hemi-thio acetals, ketals, and hydrates of fluoroaldehydes and ketones. Isodesmic reactions have frequently been used for the determination of relative thermochemical stability. Isodesmic reactions are transformations in which the number of bonds of each formal type are

conserved and only the relationships among the bonds are altered. [10] An advantage of using isodesmic reactions is that the calculations can be accomplished using relatively low level basis sets since the inherent errors possible for the individual reactant and product molecules are largely canceled out by this method.

The heat of formation was determined for a series of isodesmic reactions shown in Figure 1 using

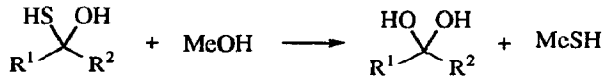

Figure 1. Isodesmic reaction for the conversion of hemi-thio acetals and ketals to the corresponding hydrate.

AM1 and MNDO semi-empirical methods. [11] The results of the calculations are presented in the Table. The data indicate that the hydrate is more stable than the hemi-thio ketal in all cases examined; however, the stability of the hydrate relative to the hemi-thio ketal is substantially enhanced for the fluorinated compounds. The ΔH value for the conversion of the hemi-thio ketal to the hydrate of acetone is -5.25 kcal/mol, while the same reaction for trifluoroacetone is -17.69 kcal/mol, Table entries 1 and 3, respectively. Hexafluoroacetone is not significantly different than trifluoroacetone in this hypothetical reaction, compare Table entries 2 and 3. Nevertheless, the degree of fluorine substitution does enhance the exothermicity of the process. Monofluoroacetone provides a value of -11.41 kcal/mol while difluoro- and trifluoroacetone are progressively more negative, compare Table entries 3 - 5. Electron donating and electron withdrawing aryl trifluoromethyl ketones were also compared, Table entries 8 - 10. In these cases, the electron donating substituent was deleterious to the overall reaction while the electron withdrawing group accentuated the stability of the hydrate over the hemi-thio ketal relative to the unsubstituted phenyl ketone. In all of the ketone cases examined, the AM1 and MNDO data provided the same trend; however, the calculated values of ΔH were not the same.The results for comparison of the aldehyde derivatives, acetaldehyde vs trifluoroacetaldehyde, are interesting in that the non-fluorinated aldehyde isodesmic reaction is slightly more favorable by AM1 calculations, while the MNDO data indicate the opposite result. These comparative data for the aldehyde/fluoroaldehyde reactions are the only exception to the observed trends noted above for the AM1 and MNDO data sets. [12]

The stability of geminal diols or hydrates has been explained by the anomeric effect. [13] First row elements such as hydroxyl groups serve as σ-acceptors and π-donors. For $R^1R^2C(OH)_2$, one hydroxyl group can serve as the π-donor and the other as the σ-acceptor, and therefore stabilize the molecule. Although thiols can act as a σ-acceptor which can stabilize a strong π-donor, the second row element (S) is not as effective as the first row element (O). The anomeric effect is not noted for $R^1R^2C(SH)_2$. [14] Therefore, hemi-thio ketals would not be expected to be as stable as the corresponding hydrates since the degree of anomeric stabilization of the molecule should not be as high.

The enhanced stability of the fluoroketone hydrate over the hemi-thio ketal, relative to the non-fluorinated analog, can then also be rationalized by a consideration of the effect of the fluoroalkyl substituent on the anomeric effect. The energy of the π–acceptor orbital of the heteroatom substituent (O) will be lowered in response to substitution of an alkyl group with an electron withdrawing fluoroalkyl group. [11] The substitution of fluorine for hydrogen results in an increased interaction with the π-donor substituent on the same carbon, resulting in an enhanced anomeric stabilization. [15]

Table. Heats of formation calculated for the isodesmic reaction in Figure 1

Entry	R_1[1]	R_2[1]	AM1[2]	MNDO[2]
1	CH_3	CH_3	-5.25	-1.05
2	CF_3	CF_3	-17.69	-13.40
3	CF_3	CH_3	-17.70	-12.19
4	HCF_2	CH_3	-14.35	-9.92
5	H_2CF	CH_3	-11.41	-6.86
6	CF_3	H	-10.55	-11.44
7	CH_3	H	-13.88	-7.75
8	CF_3	Ph(*p*-OMe)	-12.57	-8.96
9	CF_3	Ph	-14.63	-12.04
10	CF_3	Ph(*p*-CF_3)	-17.71	-12.69

[1] R_1 and R_2 as shown in Figure 1. [2] kcal/mol.

The relatively poor activity of fluoroketones as inhibitors of cysteine proteases compared to serine proteases may then be understood on the grounds that the formation of a covalent hemi-thio (cysteine) ketal within the active site may not be as favorable as formation of a hemi-ketal (serine). Therefore, there may be less of a driving force for the cysteine protease to ultimately displace water from the hydrated inhibitor present in an aqueous environment. [16]

In summary, the isodesmic calculations reveal that hemi-thio ketals of fluoroketones are not as stable as the corresponding hemi-ketal derivative. The results are explained by an enhancement of the anomeric effect for the fluoromethyl substituted hemi-ketal derivative. These data also provide a rationalization for the diminished activity of fluoroketones acting as inhibitors of cysteine proteases relative to the inhibitory activity of fluoroketones toward serine esterases.

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15. An alternative explanation of electrostatic stabilization of hydrates by the electronegative oxygen substituents on the hydrated carbon has also been presented, see: Henke, S. L.; Hadad, C. M.; Morgan, K. M.; Wiberg, K. B.; Wasserman, H. H. *J. Org. Chem.* **1993**, *58*, 2830-2839. Since S is less electronegative than O, this argument would also hold for the present study.

16. NMR studies (^{19}F, ^{1}H and ^{13}C) indicate that hydration of trifluoroacetone occurs much more readily than formation of a hemi-thio acetal upon reaction with thiophenol. The hemi-thio acetal (PhS) does form in d_6 DMSO: ^{19}F NMR -74.37 ppm, ^{13}C NMR 83.0 ppm (q, J_{C-F} = 119.4 Hz); trifluoroacetone (d_6 DMSO): ^{19}F NMR -75.2 ppm, ^{13}C NMR 188.9 ppm (q, J_{C-F} = 137.7 Hz). For NMR studies of the reaction of thiols with unsaturated trifluoromethyl ketones, see: Linderman, R. J.; Jamois, E. J.; Tennyson, S. D. *J. Org. Chem.* **1994**, *59*, 957-962.

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