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Energetics of Hydrate and Hemiketal Formation for Highly Fluorinated Ketones

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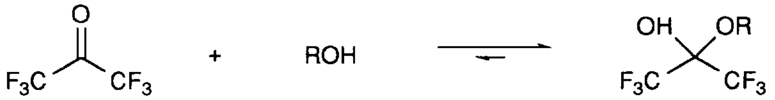
Abstract: Heats of hydration for a series of fluoroketones have been calculated at the HF/6-31G**//6-31G** level, and equilibrium constants for hemiketal formation with trifluoroethanol have been measured for a related series. These reactions were found to be considerably more favorable in cyclic than in corresponding acyclic systems. Quantum mechanical calculations indicate that this difference can be traced to steric hindrance in the acyclic adducts. Copyright © 1996 Elsevier Science Ltd

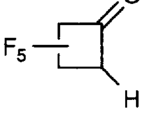
It is well known that highly fluorinated ketones, in contrast to their hydrocarbon counterparts, react with water and alcohols to form stable adducts.[1] Hexafluoroacetone, for example, adds water and methanol to form solid hydrate **A** (mp 43-45 °C)[2] and hemiketal **B** (bp 95 °C),[3] respectively.



A: R = H

B: R = CH_3

Cyclic fluoroketones[4] also add water very easily, but little is known about how they compare with acyclic analogs. In the course of investigating highly fluorinated keto-enol systems,[5] we had occasion to calculate the energies of hydration for ketones **1**, **2** and **3**. At the HF/6-31G**//6-31G** level of theory, the



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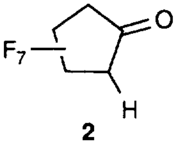

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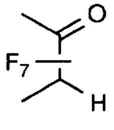

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values are -20.3, -18.6 and -13.2 kcal/mol, respectively.[6] The similar values for ketones **1** and **2** suggest that ring strain does not have a profound effect on the heat of hydration. It is therefore quite interesting that acyclic ketone **3** hydrates much less exothermically than the cyclic ketones. Is this attributable to differences in the ketones, or in the hydrates?

The question has been addressed with isodesmic group transfer reactions.[7] Figure 1 gives the energy changes for transferring a carbonyl group from formaldehyde to different methylene groups. The nearly equal energies of reaction reveal that, referenced to saturated compounds, all three ketones are destabilized to about the same extent relative to formaldehyde. The less exothermic heat of hydration for ketone **3** must therefore arise from differences in the hydrates. This is shown clearly in Figure 2, as *gem*-diol **3h** gives a slightly endothermic transfer reaction as opposed to significantly exothermic reactions for **1h** and **2h**.

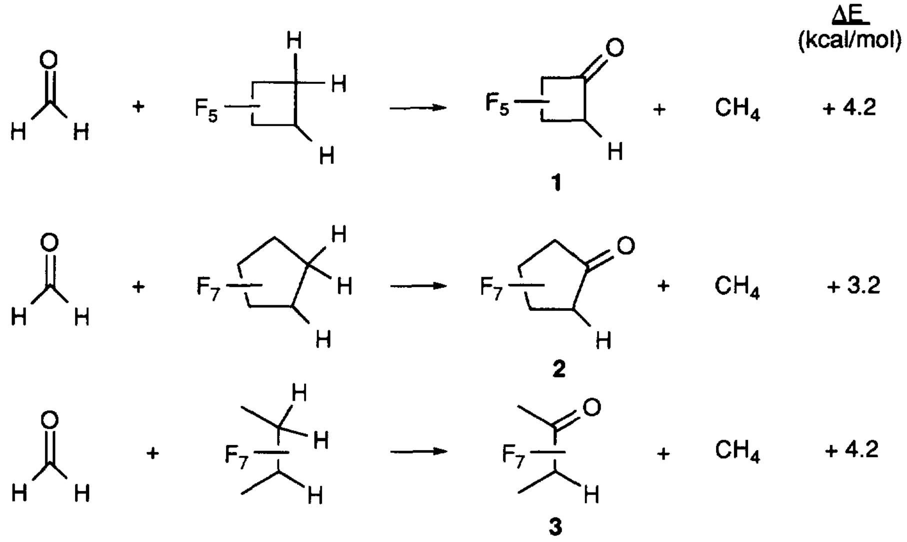


Figure 1. Carbonyl group transfer reactions (HF/6-31G**//6-31G**).

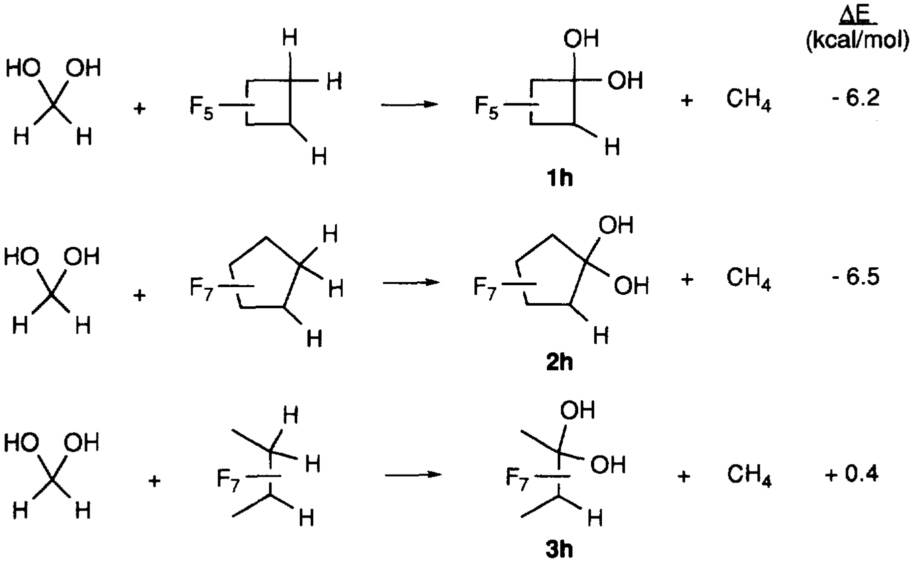
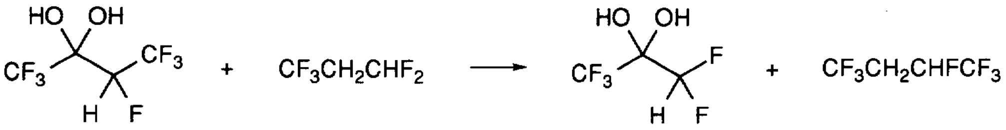


Figure 2. *gem*-Diol group transfer reactions (HF/6-31G**//6-31G**).

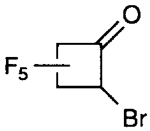
The difference probably arises from steric repulsions between the trifluoromethyl and hydroxyl groups in **3h** that are relieved in the cyclic hydrates. This conclusion is supported by the isodesmic reaction shown below, which suggests that replacing the trifluoromethyl group at C_3 of **3h** with the smaller fluorine atom also leads to substantial stabilization of the hydrate.[8] Since ketone **3** is the simplest acyclic analog of **1** and **2**, even greater contrasts with the cyclic ketones can be anticipated for higher homologs of **3**.



3h

$\Delta E = -6.5$ kcal/mol (HF/6-31G**//6-31G**)

Experimental support was sought for the large differences in the calculated heats of hydration. Since the hydration equilibria lie so far toward the hydrate, accurate measurements in solution would be very difficult. We therefore examined the addition of trifluoroethanol to the ketones with the hope that equilibrium positions would fall in an accessible range. Unfortunately, enolization[9] of ketones **1** and **2** competed with addition of the alcohol, so α-bromo ketones **4**-**7** were used instead. These were chosen primarily because of their ease of preparation, as shown below for ketone **4**. The other ketones were synthesized in similar fashion.[10]



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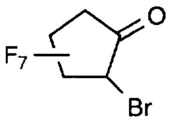

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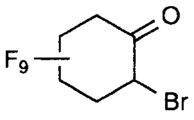

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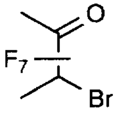

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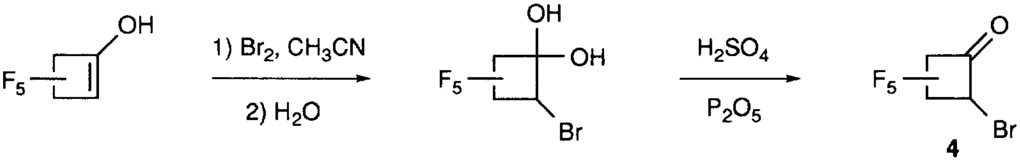

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Trifluoroethanol added smoothly to all four ketones in methylene chloride containing a catalytic amount of N-methylpyrrolidone, with the results reported in Table 1.[11] Hemiketal formation for ketone **4** was so favorable that an equilibrium constant could not be measured reliably, so a lower limit was assigned based on our detection capability using ^{19}F NMR spectroscopy. Clearly, the addition of trifluoroethanol to ketones **4**-**7** follows the same trend as the addition of water to ketones **1**-**3**.

In summary, cyclic fluoroketones add nucleophiles more exothermically than their acyclic counterparts. A study of isodesmic reactions indicates that steric interactions in the adducts are the principal reason for the contrast.

Table 1. Hemiketal Formation with Trifluoroethanol.

Ketone	K_{eq} (22 °C)	ΔG° (kcal/mol)
4	$>10^3$	<-4.0
5	390 ± 20	-3.5
6	150 ± 20	-2.9
7	0.20 ± 0.02	+0.94

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4. Perfluorocyclobutanone, for example, forms a stable hydrate (mp 52 °C). England, D. C. *J. Am. Chem. Soc.* **1961**, *83*, 2205.
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6. The values are corrected for zero point vibrational energies and 298 K. The corrections are based on HF/6-31G** calculations with frequencies larger than 500 cm^{-1} scaled by 0.893. Hehre, W.J.; Radom, L.; Schleyer, P.v.R.; Pople, J.S. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
7. This follows the lead of Wiberg, *et al.* who used the same approach while examining the hydration of hydrocarbon-derived ketones. Wiberg, K.B.; Morgan, K.M.; Maltz, H. *J. Am. Chem. Soc.* **1994**, *116*, 11067.
8. ΔH_{hyd}(298K) or pentafluoroacetone is -18.6 kcal/mol at the HF/6-31G**//6-31G** level of theory.
9. For a full discussion of the enolization of ketones **1** and **2**, see reference 5.
10. The synthesis of ketone **5** has been reported previously (reference 5c).
11. The ratio of diastereomeric ketals was 1:1 for **7** but 7:1 for **5**, and only a single isomer was found for **4**. Presumably the diastereomers with hydroxyl cis to bromine are favored for steric reasons. Because of signal overlap, the ratio was not determined for **6**.

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