THE STERIC EFFECT OF A TRIFLUOROMETHYL GROUP

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In the study of ene reaction of trifluoromethyl ketones, a trifluoromethyl group was found to behave as a much larger substituent than commonly believed. Similar results were obtained in the dehydration of trifluoromethyl homoallyl alcohols.

KEYWORDS trifluoromethyl; ketone; steric effect; ene reaction; dehydration; alcohol; cyclohexene; transition state

There are many biologically active organofluorine compounds and their activities are attributed to the fact that the steric requirement of a fluorine atom is nearly as small as a hydrogen atom, while a carbon-fluorine bond is much stronger than a carbon-hydrogen bond. Therefore, an organism cannot distinguish a fluorine derivative of a biologically active compound from the unfluorinated one and the fluoride compound is taken up in the metabolic path of the original compound. This is called the "mimic effect" of fluoride compounds. Similar examples are known where a methyl group is replaced by a trifluoromethyl group. Thus, trifluoromethyldeoxyuridine derivatives show antiviral activity, since they are taken up in the place of thymidine due to the similarity of the shapes of the two compounds.

In the course of our study of the ene reaction of trifluoromethyl ketones, we noticed that a trifluoromethyl group behaves as a much larger substituent than the above generalization indicates. Thus, the reaction of trifluorocacetone with 2-octene gave an l-isomer regio- and stereoselectively, based on Prelog-Seebach's notation. This result is explained by comparison of the transition states (A) and (B). Namely, the steric repulsion between the trifluoromethyl group and the alkenyl part of 2-octene in B is much larger than that between the methyl and the alkenyl part in A and the l-isomer is formed through A.

Interestingly, other trifluoromethyl ketones, 1,1,1-trifluoro-2-hexanone and a,a,a-trifluoroacetophenone, gave products of the same stereochemistry as trifluorocacetone did. (Chart 1) These results suggest that a trifluoromethyl group behaves as a larger substituent than an n-butyl or a phenyl group in this reaction. This is far from the above idea concerning the steric effect of a trifluoromethyl group.

On the other hand, concerning the steric effect of a trifluoromethyl group, there have been a few reports. Taft has proposed a scale of the steric effect, Es. Dubois' Group critically revised the Es and proposed Es' scale. The Es value of a phenyl group is not mentioned, but Es' value of a phenyl group is much larger than that of a trifluoromethyl group. This is far from our results. Sternhell et al. reported effective van der Waals' radii based on the rotational barrier of biphenyl derivatives. Here, a trifluoromethyl group shows a value, 2.2 Å, similar to a sec-butyl group does. This seems to be consistent with our results. However, unbelievably, in their scale a trimethylsilyl group is smaller than a tert-butyl group and an amino group is larger than a dimethylamino group. Therefore, we studied the steric effect of a trifluoromethyl group more extensively. We synthesized a number of trifluoromethyl ketones and investigated their ene reaction with cyclohexene, 1,2-disubstituted alkene of the

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least steric requirement. The results are summarized in Chart 2.9)

\[
\text{Cyclohexene} + \text{CF}_3\text{COR} \xrightarrow{\text{AlCl}_3, -78^\circ C} \text{CF}_3\text{OH} \]

\[\text{R} : \text{H, Me, n-Bu, Ph, iso-Bu, c-Hex, sec-Bu, CF}_3\text{thexyl}\]

Yield (%) 43 53 41 21 9 6 6.7 7 0

Chart 2

Trifluoroacetaldehyde and the ketones to cyclohexyl trifluoromethyl ketone reacted with an equimolar amount of cyclohexene at -78°C to give ene reaction products of the same stereochemistry. Only when the four equivalents of cyclohexene were used did sec-butyl trifluoromethyl ketone give a small amount of the product. The thexyl ketone did not react at all, even when ten equivalents of cyclohexene was used. Hexafluoroacetone reacted without a catalyst at 150°C to afford a small amount of the product. Therefore, a thexyl group is much larger than a trifluoromethyl group. The fact that sec-butyl trifluoromethyl ketone gave the product of the same stereochemistry as trifluoroacetone did shows that a sec-butyl group is slightly smaller than a trifluoromethyl group.

If the steric effect of the alkyl groups could be estimated from the yields of the ene reaction,10) the order of the steric effect is as shown in Chart 2 and a trifluoromethyl group has slightly larger steric effect than a sec-butyl group in the transition state of this reaction. This suggests that not the total volume, but the shape of a substituent near the reaction center affects the reaction. Thus, a thin n-butyl group had a smaller steric effect than a β-branched isobutyl group, the steric effect of which was smaller in turn than that of an α-branched sec-butyl group. A flat phenyl group had a smaller effect than an isobutyl group. A sec-butyl group acts as a slightly smaller substituent than a trifluoromethyl group, if the C-H part of the former is directed to the reaction center in the transition state of the slow reaction.

Next, dehydration of the homoallyl alcohols was investigated to compare the steric effect of a trifluoromethyl group with those of other alkyl groups. This dehydration was established to proceed through an anti-elimination mechanism.11) Thus, if an alkyl group (R) is smaller than a trifluoromethyl group, this reaction will give an E-isomer preferably. If larger, a Z-isomer will be formed. The results of dehydration summarized in Chart 3 show that the E/Z ratio decreases with the increase of the steric effect of the alkyl groups.12)

\[
\text{R} = \text{H, Me, Ph, n-Bu, iso-Bu, c-Hex, sec-Bu, thexyl}\]

\[E/Z = \frac{13}{2} \quad \frac{9}{2} \quad \frac{3}{1} \quad \frac{2}{1} \quad \frac{5}{2} \quad \frac{7}{8} \quad \frac{2}{3} \quad \frac{1}{10}\]

Chart 3

This order is slightly different from that observed in the ene reaction. A cyclohexyl group is about the same as a trifluoromethyl group, a sec-butyl group is a little larger than a trifluoromethyl
group. This difference may be due to the difference in the reaction temperatures, -78°C in the ene reaction and 110°C in the dehydration. Thus, a rapid rotation around the C=C bond at 110°C makes the difference between the n-butyl and isobutyl groups much smaller than at -78°C. The C-H part of the sec-butyl group is nearly fixed to the reaction center at -78°C and it behaves as a smaller substituent than a trifluoromethyl group, but at 110°C, rotation around the C=C bond becomes faster and the sec-butyl group behaves as a larger substituent than a trifluoromethyl group.

In conclusion, a trifluoromethyl group behaves as a much larger substituent in the transition states of some reactions than formerly believed, even though the total volume of a trifluoromethyl group may be similar to that of a methyl group in an interaction mimicking a methyl analog of a biologically active compound. Therefore, a round and hard trifluoromethyl group has a larger steric effect than a thin and flexible n-butyl group or a flat phenyl group, even though its total volume is much smaller than the latter.

REFERENCES AND NOTES

1) a) E. J. Ariens, "Drug Design." Vol. 5, Academic Press (1975);  
5) The reaction of 1,1,1-trifluoro-2-hexanone gave 6-methyl-5-(trifluoromethyl)-7-dodecen-5-ol (1), colorless oil, 63 %, 19F-NMR: 11.97 ppm (from TBF) with two cyclized products 10 % yield (in total), but any stereo isomer of 1 was not observed. This was dehydrated to (5Z,7E)-6-methyl-5-(trifluoromethyl)-5,7-dodecadiene with smaller amounts of (4Z,7E)- and (4E,7E)-4,7-dienes, but (5E,7E)-diene was not obtained.11) The structure of the ene product from trifluoroacetophenone was similarly determined.
9) A typical experiment is as follows. Reaction of equimolar amounts of cyclohexene, isobutyl trifluoromethyl ketone and AlCl3 in anhydrous CH2Cl2 at -78°C for 2.5 h gave 1-3-[1-hydroxy-3-methyl-1-(trifluoromethyl)butyl]cyclohexene (9 %). Colorless oil, HRMS Calcld. for C19H19F6O: 326.139. Found: 236.139.
10H-NMR (CDCl3) : 0.97 (3H, d, J=6.7 Hz), 1.00 (3H, d, J=6.7 Hz), 1.31-1.43 (1H, m), 1.45-1.64 (3H, m), 1.78-2.03 (5H, m), 2.09 (1H, bs), 2.58-2.66 (1H, m), 5.74 (1H, bd, J=10.4 Hz), 5.84-5.90 (1H, m). 19F-NMR (CDCl3) ppm: 12.89 (s). No other products were isolated besides the starting materials. A mixture of the 1 and the y-isomers (4:1) was obtained by the Grignard reaction of 3-bromocyclohexene and CF3CO-iso-Bu with Mg. The isomers were separated by a preparative glc and showed well separated 19F-NMR. The 1-isomer was dehydrated by pyridine and phosphoryl chloride to 3-[2-methylpropyl(trifluoromethyl)methylene]cyclohexene; colorless oil. There was no correlation observed between the 2-H and methane-H of the isobutyl group in 2D-NMR. The low chemical shift on 19F-NMR (-7.78 ppm, s) shows that the trifluoromethyl group is cis to the double bond. The other reaction products gave satisfactory spectral data. Their structures were determined by similar Grignard reaction and dehydration. Details will be published elsewhere in the near future.
11) Trifluoroacetalddehyde polymerizes in the reaction condition. The yield, based on the used cyclohexene was quantitative.
13) The dehydration reactions were carried out as in ref. 11 and the structures of dienes were determined similarly. The relative ratios are estimated from the 19F-NMR (90MHz), 1H-NMR (400MHz), and peak area on GLC.

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