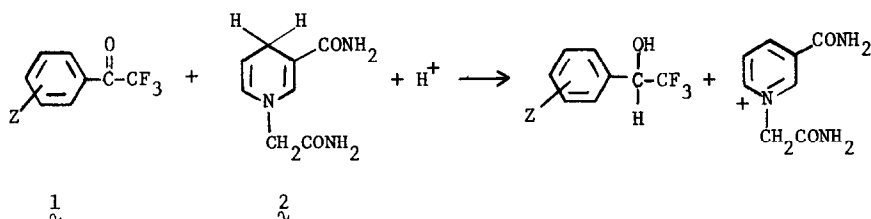


SUBSTITUENT EFFECTS IN THE REDUCTION OF TRIFLUOROACETOPHENONES BY A DIHYDRONICOTINAMIDE

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Summary: Trifluoroacetophenone reduction rates (by a dihydronicotinamide) and hydration equilibria are identically affected by ring substituents. High yields of alcohol are obtained when electron donating substituents are absent from the ring.

We are interested in the effect of substituents on organic oxidation reactions since the often vexing question of hydride transfer vs. hydrogen-atom transfer^{1,2} can sometimes be addressed through such studies. We accordingly have measured the rates of reduction of a series of *m*- and *p*-substituted trifluoroacetophenones³ by *N*-carbamoylmethyl-3-carbamoyl-1,4-dihydropyridine $\tilde{2}$, an NADH analogue with a relatively high degree of stability with respect to decomposition in aqueous buffer.⁴ (Most trifluoromethyl ketones are highly hydrated in aqueous media⁵ and their observed reduction rates must be corrected for the extent of hydration if meaningful results are to be obtained.)



The reaction was followed at 43.4°C in a 21.8% (v/v) sulfolane-water solution containing 0.40 M sodium perchlorate, 0.10 M triethanolamine, and 0.10 M triethanolamine hydrochloride buffer (glass electrode 'pH' 8.3) by following the disappearance of the 348 nm band of $\tilde{2}$. The latter's concentration was 10⁻⁴ M and the ketones were always present in excess (6-200 times). Accompanying each run was a determination of the rate of decomposition of $\tilde{2}$ under the same conditions, except for the absence of ketone. Each observed first-order rate constant was corrected for this decomposition by simply subtracting the first-order decomposition rate. A further correction was made for the degree of hydration of the ketone using equilibrium constants that are either known or that can be calculated.^{5b,c} The second-order rate constant *k*, which represents the rate of reaction of $\tilde{1}$ and $\tilde{2}$, was then obtained. (The relaxation rate for the dehydration equilibria was much faster than the reduction in all the cases studied.)

Detailed product analyses were performed on the reaction products of six of the ketones by extracting the reaction mixture after six days with an equal volume of ether-pentane ($v/v = 1$, four times). The combined organic extract was washed, dried, concentrated, and then subjected to analysis by gas-liquid chromatography, mass spectrometry, and high performance liquid chromatography.

Two general conclusions emerge from the rate and product studies. First, we find high yields of alcohol in the cases where the ring lacks an electron-donating substituent - 75% alcohol for $m\text{-NO}_2$, 87% for $m\text{-CF}_3$, and 73% for the unsubstituted compound. The yield drops to 21% for $p\text{-MeO}$ and is minuscule (0.1%) for both $p\text{-NH}_2$ and $p\text{-Me}_2\text{N}$. Difficulties were encountered in getting reproducible rates of reduction for the latter compounds and in identifying the reaction products, most of which appeared to be the products of decomposition of 2 .

Secondly, the ketones containing substituents ranging from the most strongly electron withdrawing down to the alkyl groups not only give generally good yields of alcohol but, moreover, have reduction rates with 2 that correlate closely with the equilibrium constants

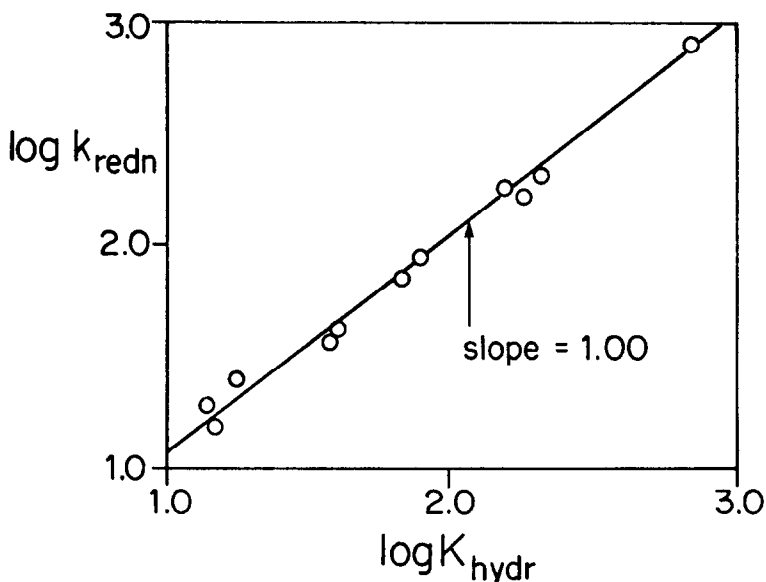
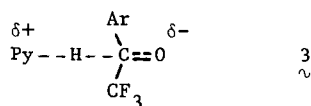


Figure. Relation between reduction rate and hydration equilibrium for substituted ketones in water at 43.4°C . The substituents are, in order of increasing rate, with K_{hydr} in parentheses: $p\text{-Et}$ (14.9), $p\text{-Me}$ (14.1), $p\text{-t-Bu}$ (17.4), H (38.0), $p\text{-F}$ (39.8), $p\text{-Cl}$ (67.2), $p\text{-Br}$ (76.8), $m\text{-Cl}$ (178), $m\text{-F}$ (155), $m\text{-CF}_3$ (208), $m\text{-NO}_2$ (691). $K_{\text{hydr}} = [\text{ketone hydrate}]/[\text{ketone}]$; k in units of $\text{M}^{-1}\text{hr}^{-1}$.

for hydration of the same compounds. In the Figure log k values for the reduction of $\overset{1}{\underset{\sim}{C}}$ by $\overset{2}{\underset{\sim}{C}}$ are plotted against the logarithm of the equilibrium constant for hydration of the same ketones.^{5b,7} The straight line shown there has been drawn with unit slope. Since the ketone is common to both reactions the linear relation shows that substituent effects on the ketone hydrate molecule and the transition state of the reduction are identical: i.e. $\Delta\Delta G_{\text{hyd}}^{\ddagger} = \Delta\Delta G_{\text{redn}}^{\ddagger}$.

It is clear that the driving force for both carbonyl hydration and carbonyl reduction in $\overset{1}{\underset{\sim}{C}}$ is the powerful electron withdrawing effect of the trifluoromethyl group. Much of the effect of ring substituents on the hydration equilibrium can be traced to their effect on the stability of the unhydrated ketone⁸ and one can conclude that the reduction is similarly influenced. The reduction almost certainly proceeds by way of transfer of negative charge from $\overset{2}{\underset{\sim}{C}}$ to $\overset{1}{\underset{\sim}{C}}$ to give either transition state $\overset{3}{\underset{\sim}{C}}$ (simple hydride transfer from C-4 of $\overset{2}{\underset{\sim}{C}}$) or a transition state with a broadly similar charge distribution.^{2,3,9} It appears from the present results that dispersal or build-up of negative charge in the carbonyl group in the transition state by electron withdrawing or donating groups is less important than their effect on the energies of the neutral carbonyl compounds.



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References and Notes

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- 3) Trifluoroacetophenone ($\overset{1}{\underset{\sim}{C}}$, Z=H) has played an important role in investigations of the mechanism of reduction of carbonyl compounds by NADH and model compounds thereof. In particular, a study of the isotope effects found in the reduction of $\overset{1}{\underset{\sim}{C}}$ (Z=H) by N-alkyldihydronicotinamides indicated that an intermediate intervened between reactants and transition state. (J.J. Steffens and D.M. Chipman, J. Am. Chem. Soc., 93, 6694 (1971). See also A. Ohno, H. Yamamoto, T. Okamoto, S. Oka, and Y. Ohnishi, Chem. Letters (Japan) 1978, 65.)
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- 6) The rate constants for the ketones containing groups more strongly electron-donating than alkyl were considerably greater than expected on the basis of σ or σ^+ values, although difficulties in obtaining reproducible results and in identifying the reaction products in these cases make the reasons for the rate increases obscure.
- 7) K_{hyd} at 43.4° calculated from data at 31.4° using the relation $K(43.4^\circ) = K(31.4^\circ) / 1.55$, which is based on the ΔH value of $-6.7 \text{ kcal. mole}^{-1}$ for the p-methoxy compound.^{5a}
- 8) Evidence for such a conclusion is the σ^+ dependency of the hydration reaction ($\rho^+ = 1.61$), which requires conjugation to be important and which is possible only for the carbonyl form of the ketone. The normalcy of the Hammett reaction constant for ionization of the ketone hydrates in water ($\rho = +1.11$)^{5c} is a further indication that the stability of the ketone hydrate molecules is not particularly sensitive to ring substituents.
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