Mechanism of Bimolecular Nucleophilic Substitution in β-Halo Ketones and Related Compounds

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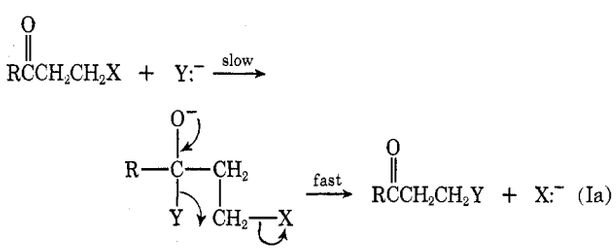
The rates of reaction of 4-chloro-3,3-difluorobutanone-2 (1) and of 1-chloro-2,2-difluoropropane (2) toward sodium iodide in anhydrous acetone have been measured and compared to literature values for 4-chlorobutanone-2 (3) and *n*-propyl chloride (4). The relative rates, calculated for 75°, for 1:2:3:4 are $0.10:6.3 \times 10^{-5}:6.4:1.00$. The much higher reactivity of 1 compared to 2 is due to a 10 kcal/mol more favorable $\Delta H^{\ddagger}$ counteracted by an unfavorable $\Delta S^{\ddagger}$. These results serve to eliminate a number of mechanistic hypotheses including one involving dehydrochlorination of the β-halo ketone followed by Michael addition of the elements of hydriodic acid. In agreement with this finding, α,α-dideuterio-β-chloropropiophenone undergoes bimolecular nucleophilic displacement without deuterium–hydrogen exchange, but ω-trimethylammoniumpropiophenone iodide exchanges one α hydrogen when treated with thiophenol-d_1 in methanol-d_1, indicating that it follows the elimination–addition pathway.

In the same papers on the reactivity of organic chlorides toward iodide ion in acetone in which he reported on the exceptional reactivity of phenacyl chloride, Conant also showed that β-chloropropiophenone exhibits enhanced reactivity.[2] More recent work has served to correct the rate constant assigned to the reference compound, *n*-butyl chloride,[3] but this does not alter the fact that β-halo ketones, although considerably less activated toward nucleophilic displacement than are the α-halo ketones, show significantly heightened reactivity comparable to that of allyl chloride. No satisfactory explanation for this marked reactivity has been advanced. It is clear that the activation provided by the carbonyl is not merely due to its inductive electron withdrawal. Hughes had suggested as an explanation for the exceptional reactivity of α-halo ketones the facilitation of approach of a negatively charged nucleophile toward a carbon made more positive by the strong inductive withdrawal of the adjacent carbonyl.[4] However, studies of 1,2-dihalides,[5] β-halo ethers,[6] and β-halo thioethers[8] all showed that inductive electron withdrawal leads to rate retardation. On theoretical grounds, one would not expect β-halo ketones to undergo SN1 reaction, since the halide is frequently on a primary carbon, the reactions are often run in relatively nonpolar media, and the presence of the carbonyl function β to the reaction site should increase the energy required for carbonium ion formation leading to depressed, rather than enhanced, reactivity compared to that of simple alkyl halides. In agreement with these expectations, displacements in β-halo ketones show second-order kinetics, first order in organic substrate and first order in nucleophile.[2,3] Also untenable on theoretical grounds is the proposal by Sneen and Larsen that there is a single mechanism of unimolecular and bimolecular nucleophilic substitution in which all displacements at a saturated carbon are described as occurring *via* a reversibly formed ion pair.[7] The central feature of this hypothetical, unifying mechanism requires the intermediacy of a configurationally stable ion pair, whose formation is rate determining at the first-order end of the mechanistic spectrum and whose destruction by nucleophilic attack is rate-determining at the second-order extreme. "Borderline" behavior is presumed to result when the rates of formation and destruction of the intermediate are competitive. Although ion pairs may play important roles in certain solvolyses, they would appear to be highly unlikely intermediates in the case of α- and β-halo ketones. As pointed out above, many of these systems involve primary halides and, since the reactions are clearly second order, the Sneen–Larsen mechanism requires that the generation of ion pairs involving primary carbonium ions further destabilized by the electron-withdrawing effect of an α- or β-carbonyl be rapid and that bimolecular attack on such destabilized ion pairs be rate determining.

There are a number of mechanistic hypotheses which are consistent with the known experimental facts and which could provide an explanation for the enhanced rate of nucleophilic displacement in β-halo ketones.



The fact that alkyl halides β substituted with electron-withdrawing halo, alkoxyl, or mercaptyl groups show depressed reactivity toward nucleophiles whereas β-halocarbonyl compounds are highly reactive suggests that it is the electrophilic character of the carbonyl group, rather than its inductive electron withdrawal, which increases reactivity. A mechanism analogous to Ia was suggested by Baker[8] to explain the enhanced reactivity of α-halo ketones. It is untenable in that case because it is inconsistent with the observation that bromide is displaced much more rapidly than chloride,[9] which suggests that carbon–halogen bond breaking is involved in the rate-determining process. However,

(1) Taken from the Ph.D. dissertation of T. J. W., Clark University, 1970.

(2) (a) J. B. Conant and W. R. Kirner, *J. Amer. Chem. Soc.*, **46**, 232 (1924); (b) J. B. Conant and R. E. Hussey, *ibid.*, **47**, 476 (1925); (c) J. B. Conant, W. R. Kirner, and R. E. Hussey, *ibid.*, **47**, 488 (1925).

(3) F. G. Bordwell and W. T. Brannen, Jr., *ibid.*, **86**, 4645 (1964).

(4) (a) E. D. Hughes, *Trans. Faraday Soc.*, **27** (2), 603 (1941); (b) E. D. Hughes, *Quart. Rev., Chem. Soc.*, **5**, 245 (1951).

(5) J. Hine and W. H. Brader, *J. Amer. Chem. Soc.*, **75**, 3964 (1953).

(6) F. B. Tutwiler and R. L. McKee, *ibid.*, **76**, 6342 (1954).

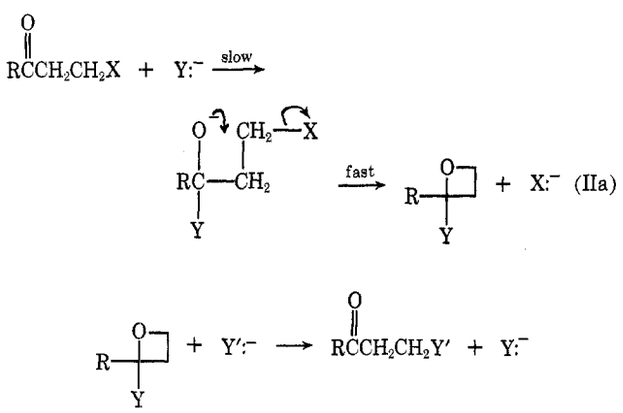
(7) (a) R. A. Sneen and J. W. Larsen, *ibid.*, **91**, 362 (1969); (b) R. A. Sneen and J. W. Larsen, *ibid.*, **91**, 6031 (1969).

(8) J. W. Baker, *Trans. Faraday Soc.*, **37**, 632 (1941).

(9) (a) H. T. Clarke, *J. Chem. Soc.*, **97**, 416 (1910); (b) R. G. Pearson, S. H. Langer, F. V. Williams, and W. J. McGuire, *J. Amer. Chem. Soc.*, **74**, 5130 (1952).

no such evidence exists with respect to β-halo ketones, and their enhanced reactivity could stem from the fact that in this mechanism the nucleophile adds to a polarized π-electron system rather than being required to break a σ bond in the rate-determining process.

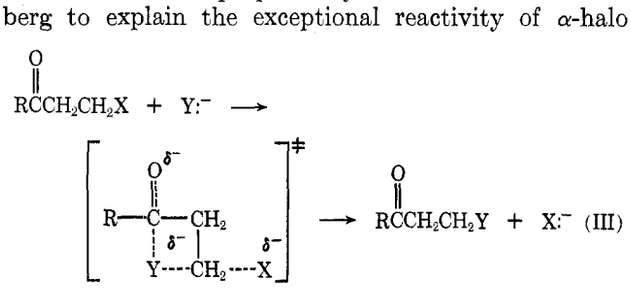
A variant of mechanism Ia in which the first step is rapid and reversible and the second rate determining (mechanism Ib) would also be in agreement with the observed second-order kinetics. It could explain the enhanced reactivity as resulting from more effective juxtaposition of the nucleophile back side to the β-carbon–halogen bond through its initial complexation to the carbonyl. If this is so, the rate enhancement should be manifested in the entropy of activation. Indeed, this would have to override a highly unfavorable enthalpy of activation term arising from several factors. The nucleophile should lose some of its activity because it is already complexed to the carbonyl, the carbon–halogen bond should for inductive effect reasons be less labile than in simple alkyl halides, and the necessity for closure to a sterically strained four-membered ring should all serve to increase the enthalpy of activation of the rate-determining step.



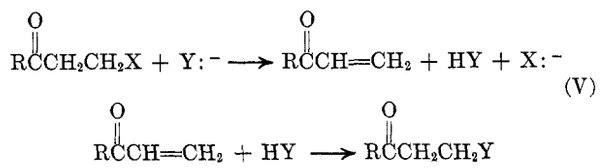
The proposal above (mechanism IIa) has the same rate-determining step as mechanism Ia but differs in that the nucleophilic species which is eventually incorporated in the product need not be the same as that which adds to carbonyl in the first step. Making use of this distinction, Pearson[9b] has shown it to be inoperative in the case of α-halo ketones, but it offers a feasible explanation for β-halo ketone reactivity, identical to that discussed for mechanism Ia.

Again in complete analogy to the relation between mechanisms Ia and Ib, there is that variant of mechanism IIa in which the second step is rate determining and which leads to the prediction that rate enhancement is due to a dominant favorable entropy of activation (mechanism IIb).

The proposal below (mechanism III) is in analogy to the mechanism proposed by Bartlett and Trachtenberg to explain the exceptional reactivity of α-halo ketones in nucleophilic displacement reactions.[10] In this mechanism, bond making is proposed to lead over bond breaking with the extra electron density of the nucleophile being accommodated on carbonyl carbon or alternatively with the carbonyl carbon acting as a Lewis acid to facilitate release of the β-halide.



Another possibility is that the enhanced reactivity stems from the dipole moment of the carbonyl helping the approach of the nucleophile (mechanism IV). This had been suggested by Pearson[9b] as an explanation for α-halo ketone reactivity, but it has been disputed by Bartlett and Trachtenberg[10] and by Sisti and Lowell.[11]



The above elimination–addition (mechanism V) has been proposed as the major pathway for reaction with nucleophiles of Mannich bases and Mannich–Robinson intermediates, *i.e.*, the cases where X is dialkylamine and trialkylammonium, respectively.[12] In general support of this suggestion is the observation that ω-dimethylaminoisobutyrophenone undergoes racemization during substitution reactions under conditions where the α carbon is not racemized through enolization.[13] Winstein's observation that tosylates undergo considerable elimination when treated with halide ion in acetone,[14] essentially Conant's conditions,[2] also lends support to this possibility. The fact that α,α-dialkylated Mannich bases do not undergo alkylation with active methylene compounds had been offered as evidence in favor of the elimination–addition mechanism. However, the fallacy in this argument has been pointed out.[15] Such compounds are for steric and/or electronic reasons incapable of reacting rapidly by any of the mechanisms under consideration.

With the exception of mechanism V, which would not even be possible in the case of chloromethyl ketones, the other working hypotheses are based on analogies to mechanisms proposed to explain α-halo ketone reactivity. However, Bordwell and Brannen have suggested that the "mild activating effect of the β-C_6H_5CO group... would appear to be different in type from that of the α-C_6H_5CO group..."[3] This would imply that α- and β-halo ketones do not react by analogous mechanisms. Their suggestion is based on admittedly small effects, but they do assert that electron-withdrawing groups cause rate retardation in ω-chloropropiophenone but rate acceleration in ω-chloroacetophenone. The effect in the latter is probably correct, since Baker's data[8] on the reaction of ω-bromoacetophenone with pyridine in dry acetone leads to a Hammett ρ of +0.56 ± 0.09, although Bordwell and Brannen's data sur-

(10) P. D. Bartlett and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **80**, 5808 (1958).

(11) A. J. Sisti and S. Lowell, *Can. J. Chem.*, **42**, 1896 (1964).

(12) (a) E. D. du Feu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937); (b) F. F. Blicke in "Organic Reactions," Vol. I, Wiley, New York, N. Y., 1942, pp 320, 321; (c) H. Hellmann and G. Opitz, "Alpha-Aminoalkylierung," Verlag Chemie, Weinheim/Bergstr., Germany, 1963, p 12.

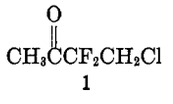
(13) A. F. Casey and J. L. Myers, *J. Chem. Soc.*, 4639 (1964).

(14) (a) A. J. Parker, M. Ruane, G. Beale, and S. Winstein, *Tetrahedron Lett.*, 2113 (1969), and references cited therein; (b) S. Winstein, D. Darwish, and N. J. Holness, *J. Amer. Chem. Soc.*, **78**, 2915 (1956).

(15) H. R. Snyder and J. H. Brewster, *J. Amer. Chem. Soc.*, **71**, 1061 (1949).

prisingly show that the *p*-methoxy group also slightly enhances the rate of reaction of ω-chloroacetophenone with potassium iodide in acetone. Their results on the ω-chloropropiophenone system are dubious. Despite the fact that they studied only para substituents and should, therefore, have avoided random entropy of activation effects, their data indicate otherwise. Rather than showing a negative ρ, a least-squares plot of their data against Hammett σ constants yields a ρ value of +0.39 ± 0.52, an obviously meaningless result.

In order to elucidate the mechanism of nucleophilic substitution in β-halo ketones, the rates of reaction with iodide ion in acetone of 4-chloro-3,3-difluorobutanone-2 (**1**) and of 1-chloro-2,2-difluoropropane (**2**) were measured and compared to previously determined values for their respective unfluorinated analogs, 4-chlorobutanone-2 (**3**)[3] and *n*-propyl chloride (**4**).[2]



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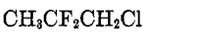

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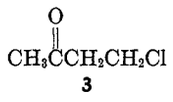

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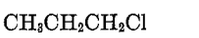

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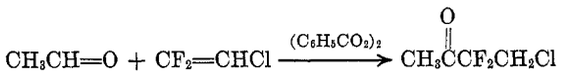
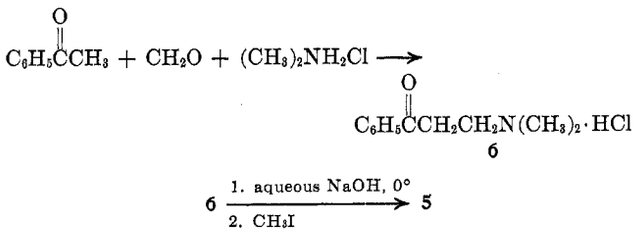
Compound **1** was synthesized by the free radical induced addition of acetaldehyde to 2-chloro-1,1-difluoroethylene.



Compound **2** was commercially available, and its chemical and physical properties agree with literature values.

Also studied was the reaction of β-trimethylammoniumpropiophenone iodide (**5**) with thiophenol-d_1 in methanol-d_1. Thiophenol reacts with **5** at a conveniently measurable rate whereas iodide ion does not. Furthermore, thiophenol combines the property of being a very good nucleophile without being very basic.[16] It thus makes less likely the elimination of trimethylamine from **5** to generate acrylophenone. Compound **5** was synthesized in straightforward manner by methylation of ω-dimethylaminopropiophenone (**6**), itself formed by a Mannich reaction.



Results and Conclusions

The reaction of 4-chloro-3,3-difluorobutanone-2 (**1**) with sodium iodide in anhydrous acetone proceeded cleanly to yield 4-iodo-3,3-difluorobutanone-2 (**7**). The structure of **1** followed from its method of synthesis, elemental analysis, high carbonyl stretching frequency (1750 cm^{-1}) commonly observed for α-fluorinated ketones,[17] and proton nmr spectrum. Although the synthesis involving free-radical addition of acetaldehyde to 1,1-difluoro-2-chloroethylene can go in the opposite sense to yield 3-chloro-4,4-difluorobutanone-2, such product would have given a more complex nmr than the one observed. The nmr of **1** showed a triplet at δ 3.85 due to the β CH_2 coupled to the α,α-difluoro group. The signal from the methyl group at δ 2.40 was also split into a triplet (J = 2 Hz) due to long range spin–spin interaction with the α,α-difluoro group.[18] The structure of **7** followed from its elemental analysis and the fact that its carbonyl stretching frequency and proton nmr splitting patterns were similar to those of **1**.

The conversion of 1-chloro-2,2-difluoropropane to 1-iodo-2,2-difluoropropane also proceeded smoothly. The assigned structures followed from their elemental analyses and ir and proton nmr spectra.

A summary of the kinetic results obtained for the reaction of 4-chloro-3,3-difluorobutanone-2 (**1**) and 1-chloro-2,2-difluoropropane (**2**) with sodium iodide in anhydrous acetone is contained in Table I.

The activation parameters are in Table II and rates relative to the unfluorinated analogs, 4-chlorobutanone-2 (**3**) and *n*-propyl chloride (**4**), are in Table III.

TABLE I

Compd	Temp, °C	Number of runs	$k \times 10^5$, l. mol^{-1} sec^{-1}
1	148.90	19	190.0 ± 4.5
1	158.90	23	313.3 ± 5.0
2	148.90	29	1.555 ± 0.033
2	158.90	24	3.400 ± 0.078

TABLE II

Compd	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, cal/deg mol
1	17.3 ± 0.3	−30.7 ± 1.0
2	27.5 ± 0.6	−16.0 ± 2.0

TABLE III

Compd	Relative rates of reaction with NaI in acetone at 75°
1	1.024×10^{-1}
2	6.29×10^{-5}
3	6.36[a]
4	1.00[b]

[a] Calculated from data in ref 3. [b] Calculated from data in ref 2.

The fact that **3** is some 60-fold more reactive than **1** serves to rule out mechanisms Ia and IIa, both of which require rate-determining addition of the nucleophile to the carbonyl carbon and both of which, therefore, predict higher reactivity for **1** whose carbonyl is made more electrophilic by the two α-fluorines. Also ruled out are mechanisms Ib and IIb, since, as pointed out before, they predict that the rate-enhancing effect of the carbonyl should be due to a highly favorable $\Delta S^{\pm}$ dominating over an unfavorable $\Delta H^{\pm}$. The data in Table II show that just the opposite is true.

The experimental results can be accommodated by mechanism III, which requires in its four-membered

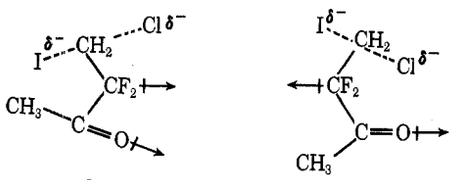
(16) U. Belluco, L. Cattalini, F. Basolo, R. G. Pearson, and A. Turco, *J. Amer. Chem. Soc.*, **87**, 241 (1965).

(17) J. K. Brown and K. J. Morgan in "Advances in Fluorine Chemistry," Vol. 4, Butterworths, Washington, D. C., 1965, p 284, and references cited therein.

(18) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1955, p 86.

ring transition state that nucleophilic addition to the carbonyl and bond breaking of the β-carbon–halogen bond both occur within the rate-determining process. Previous work has shown that β-fluorinated alkyl halides and tosylates react with iodide ion in acetone at a rate some four powers of ten slower than for the corresponding unfluorinated analog.[19] The results here reported for **2** and **4** support this. By contrast, fluorination of the analogous position in a β-halo ketone only leads to a 60-fold rate retardation or, to put it another way, the presence of the carbonyl leads to a compensating accelerating factor of between 10^2 and 10^3. This is readily explicable if carbonyl addition by the nucleophile is required. Evidence of the enhanced electrophilic character of a carbonyl group when α fluorinated comes from studies of hydration of aldehydes and ketones,[20] carboxylic acid acidity,[21] and the extent of addition of alkoxide to esters.[22] The fact that **1** has a $\Delta H^{\pm}$ about 10 kcal more favorable than **2** but that much of this advantage is lost through an unfavorable $\Delta S^{\pm}$ difference of about 15 eu is in striking similarity to the results found in support of mechanism III in the case of the α-halo ketones.[10]

Mechanism IV attributes carbonyl activation to a favorable dipole interaction with the attacking nucleophile. According to this mechanism, the transition state for reaction of **1** should be represented by **8** or **9** or by some intermediate conformation. The presence of the fluorines in **8** is clearly unfavorable compared to



8 **9**

the analogous transition state from **3**, since one is forced to align the CF_2 and the C=O dipoles. This destabilizing influence should more than outweigh the extra benefit afforded the approach of the nucleophile. In **9**, the bad alignment of dipoles is avoided but then the approach of the nucleophile is hindered by the CF_2 dipole. One, therefore, predicts and finds that **1** is slower than **3**. A difficulty with this hypothesis shows up when one examines the conformation of the transition states for **2** and **4**. The dipole of the CF_2 group in **2** should be at least comparable to that of the carbonyl and **2** can assume a conformation favorable for the approach of the nucleophile without alignment of its dipole with that of an adjacent carbonyl. Notwithstanding this favorable situation, **2** is over 10^4 slower than **4** whereas the factor is only 60 for **1** *vs.* **3**. A further difficulty with mechanism IV is that it fails to provide an explanation for the observed difference in $\Delta S^{\pm}$ between **1** and **2**.

Finally, the fact that **1** is 1600 times faster than **2** whereas **3** is only six times faster than **4** clearly disposes of mechanism V. This follows from the fact that the carbonyl activating influence is much larger in the fluorinated substrate and yet it is unable to undergo the elimination step required by mechanism V.

Further evidence against mechanism V was obtained when α,α-dideuterio-β-chloropropiophenone (**10**) was treated with iodide ion in *tert*-butyl alcohol–acetone to yield α,α-dideuterio-β-iodopropiophenone (**11**). No hydrogen–deuterium exchange at the α position was observed. Compound **10** was synthesized by acid-catalyzed deuterium–hydrogen exchange on β-chloropropiophenone, itself made by Friedel–Crafts acylation of benzene with β-chloropropionyl chloride. The nmr spectrum of **10** established that the position α to the carbonyl was fully deuterated. There was a broadened singlet at δ 3.90 due to the chloromethylene group.[23] Because the coupling constant between deuterium atoms and protons on adjacent carbons is very small (0–2 Hz),[24] the observed singlet was to be expected only if deuterium exchange α to the carbonyl was complete. Had it only been partial, a more complex proton nmr spectrum such as that for β-chloropropiophenone with a triplet at δ 3.90 (CH_2Cl) and a triplet at δ 3.50 (CH_2CO) would have been observed. The absence of deuterium–hydrogen exchange during reaction of **10** with iodide ion in a protonic solvent followed from the fact that **11** also gave a singlet at δ 3.45 due to the CH_2I rather than the more complex pattern expected from coupling with any available protons on an adjacent carbon. Thus β-chloropropiophenone, although fully capable of dehydrohalogenating, does not do so under these conditions for nucleophilic displacement. However, ω-trimethylammoniumpropiophenone iodide (**5**) does eliminate when treated with thiophenol-d_1 in methanol-d_1. Both **5** and ω-dimethylaminopropiophenone hydrochloride (**6**) failed to react with iodide ion to give ω-iodopropiophenone even when refluxed in acetonitrile or methanol for extended periods. Nor did **6** react in refluxing acetone, a solvent in which **5** was not soluble enough to test reactivity. The only products formed other than by replacing the ionic chlorides in **5** and **6** by iodide were acrylophenone and ω-methoxypropiophenone, and these only formed in very low yield (≤8%). On the other hand, **5** reacted quantitatively with thiophenol in methanol to give β-phenylthiopropiophenone (**12**). When this reaction was investigated with thiophenol-d_1 in methanol-d_1, the product **12** was found by mass spectroscopic analysis to be 94% monodeuterated at the α carbon. Thus in the case of this Mannich–Robinson intermediate, the elimination–addition pathway is favored. It is not clear whether this shift in mechanism is brought about because of enhanced acidity of the α hydrogens in the Mannich–Robinson intermediate or because the steric requirements of the trialkylamine group destabilize the transition state for displacement more seriously than for elimination.

Experimental Section

Infrared spectra were taken on samples in potassium bromide, Nujol, or carbon tetrachloride, or neat as film on sodium chloride plates with a Perkin-Elmer Model 137 double-beam spectrophotometer.

(19) E. T. McBee, R. D. Battershell, and H. P. Braendlin, *J. Amer. Chem. Soc.*, **84**, 3157 (1962), and references cited therein.

(20) H. P. Braendlin and E. T. McBee in "Advances in Fluorine Chemistry," Vol. 4, Butterworths, Washington, D. C., 1965, pp 1–18, and references cited therein.

(21) J. E. Dippy, *Chem. Rev.*, **25**, 151 (1939).

(22) M. L. Bender, *J. Amer. Chem. Soc.*, **75**, 5986 (1953).

(23) R. N. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 16, and references cited therein.

(24) Reference 23, p 61.

Nuclear magnetic resonance spectra were measured on a Jeolco JNM-C-60H spectrometer on samples dissolved in deuteriochloroform containing tetramethylsilane (TMS) as internal standard and are reported in δ units in parts per million from TMS.

Refractive indices were measured with a Bausch and Lomb Abbe 3-L refractometer. Melting points were determined in soft glass capillaries on a Thomas-Hoover apparatus and are corrected. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich., or Spang Microanalytical Laboratory, Ann Arbor, Mich.

Thin layer chromatography was done with silica gel H (Brinkmann) or "Silac AR" 7G (Mallinckrodt) as the solid support and iodine vapor development. Glpc analyses and separations were performed on a Wilkens Aerograph Model A-700 Autoprep equipped with a thermal conductivity detector unit with helium gas as carrier. The column was $^3/_8$ in. $\times$ 10 ft stainless steel containing 20% silicone (Fluoro) QF-1 (Varian Aerograph) coated on 60/80 mesh, acid washed and DMCS (dimethyldichlorosilane) treated Chromosorb W (diatomaceous earth, manufactured by Johns-Manville).

4-Chloro-3,3-difluorobutanone-2 (1).—The free radical addition of acetaldehyde to 2-chloro-1,1-difluoroethylene was carried out according to a modification of the procedure of Muramatsu and Inukai.[25] To a Carius tube cooled in an ethylene glycol monoethyl ether–Dry Ice bath were added 18.5 g (0.189 mol) of Pierce 2-chloro-1,1-difluoroethylene, 14.0 g (0.318 mol) of freshly distilled acetaldehyde, and 3.0 g (0.012 mol) of recrystallized dibenzoyl peroxide. The tube was sealed and the mixture was agitated at 105–110° for 21 hr. The tube was then cooled to Dry Ice temperature and opened, and unreacted starting material was distilled off under reduced pressure. The residue was taken up in 100 ml of ether and washed with 5% sodium bicarbonate. The ethereal solution was then rotary evaporated and the residue was distilled at atmospheric pressure to yield 4.83 g (18%) of 1, bp 101–102°. Final purification was effected by glpc (75°, retention time 3.3 min): ir, strong carbonyl stretch at 1748 cm^{-1}; nmr δ 3.85 (t, 2, J = 13 Hz, CF_2CH_2Cl) and 2.40 (t, 3, J = 2 Hz, CH_3COCF_2). The 2,4-dinitrophenylhydrazone (95% ethanol) melts at 130–131°.

Anal. Calcd for $C_{10}H_9ClF_2N_4O_4$ (322.69): C, 37.22; H, 2.82. Found: C, 37.40; H, 2.93.

1-Chloro-2,2-difluoropropane (2).—A sample of K and K Laboratories 1-chloro-2,2-difluoropropane was used without further purification: atmospheric bp 55.1° (lit.[26] bp 55.0–55.2°); $n^{20}D$ 1.3520 (lit.[26] $n^{20}D$ 1.3520); nmr δ 3.60 (t, 2, J = 12 Hz, CF_2CH_2Cl) and 1.70 (t, 3, J = 20 Hz, CH_3CF_2). It gave only a single peak on glpc at three different column temperatures (35, 50, 100°) and showed the expected ir spectrum.

Reaction of 4-Chloro-3,3-difluorobutanone-2 (1) **with Sodium Iodide in Anhydrous Acetone.**—A sample of 0.3453 g (2.423 mmol) of 1 was treated with 1.8854 g (12.569 mmol) of Fisher reagent grade sodium iodide in 5 ml of anhydrous acetone for 3 days at 100° in a sealed combustion tube. The tube was then cooled in Dry Ice and opened. The contents were concentrated under reduced pressure and the organic material in the residue was extracted with anhydrous ether and chloroform. The combined extracts were rotary evaporated and glpc analyzed (75°) to show two peaks. The first (retention time 3.3 min) was unreacted 1 as shown by peak enhancement and the second (retention time 8.4 min) was 4-iodo-3,3-difluorobutanone-2 (7): ir, strong carbonyl stretch at 1748 cm^{-1}; nmr δ 3.50 (t, 2, J = 15 Hz, CF_2CH_2I) and 2.30 (t, 3, J = 2 Hz, CH_3COCF_2). Its 2,4-dinitrophenylhydrazone (95% ethanol) melts at 128–130°.

Anal. Calcd for $C_{10}H_9IF_2N_4O_4$ (414.02): C, 28.99; H, 2.17. Found: C, 28.63; H, 2.26.

Reaction of 1-Chloro-2,2 difluoropropane (2) **with Sodium Iodide in Anhydrous Acetone.**—A sample of 0.57 g (5.0 mmol) of 2 was treated with 0.3773 g (2.515 mmol) of Fisher reagent grade sodium iodide in 50 ml of anhydrous acetone for 8 days at 160° in a sealed combustion tube. The work-up procedure was essentially identical with that used for reaction of 1 (*vide supra*). Glpc analysis (70°) showed two peaks. The first (retention time 1.4 min) was unreacted 2 as shown by peak enhancement and the second (retention time 2.4 min) was 1-iodo-2,2-difluoropropane. It showed the expected ir and its nmr exhibited absorptions at δ 3.50 (t, 2, J = 14 Hz, CF_2CH_2I) and 1.80 (t, 3, J = 16 Hz, CH_3CF_2).

Anal. Calcd for $C_3H_5F_2I$ (205.96): C, 17.47; H, 2.43. Found: C, 17.30; H, 2.39.

β-Trimethylammoniumpropiophenone Iodide (5).—β-Dimethylaminopropiophenone hydrochloride was prepared in 68% yield by the method of Maxwell.[27] A sample of 64.2 g (0.300 mol) of this compound, mp 153–154° (lit.[27] mp 152–153°), was treated with an ice-cold solution of 15 g (0.375 mol) of sodium hydroxide in 500 ml of water. The solution was ether extracted and the extract was repeatedly washed with water, dried ($MgSO_4$), filtered, and rotary evaporated to yield 49.6 g (93.3%) of β-dimethylaminopropiophenone as a clear, colorless oil, bp 106–108° (10 mm) [lit.[28] bp 106–109° (10 mm)]. Upon standing at 10° for 3 days, this oil crystallized to yield 39.7 g (80%) of β-dimethylaminopropiophenone, mp 29–31° (lit.[29] mp 30–32°), which showed the expected ir and nmr spectra. To a solution of 10.25 g (0.058 mol) of β-dimethylaminopropiophenone in 100 ml of ice-cold 3:1 (v:v) ether–benzene was added 8.45 g (0.060 mol) of methyl iodide. On standing overnight at 10°, product crystallized. It was filtered and recrystallized from methanol to yield 13.9 g (87%) of 5, mp 262.5–264° (sealed capillary) (lit.[30] mp 261–264° dec).

Reaction of β-Trimethylammoniumpropiophenone Iodide (5) **with Sodium Iodide.**—A solution of 0.4812 g (1.507 mmol) of 5 and 2.1285 g (14.20 mmol) of sodium iodide in 80 ml of methanol was refluxed for 11 days. The solvent was distilled off under reduced pressure and the solid residue was triturated with ether. The only ether-soluble product, obtained by concentration of the ether solution, was β-methoxypropiophenone (0.0164 g, 6.7%). It had the expected ir spectrum and its 2,4-dinitrophenylhydrazone had mp 175–176° (lit.[31] mp 175.5–176.5°).

A solution of 0.2983 g (0.934 mmol) of 5 and 1.5989 g (10.66 mmol) of sodium iodide in 80 ml of acetonitrile was refluxed for 26 days. The solvent was distilled off under reduced pressure and the solid residue was triturated with ether. The ethereal solution was concentrated to yield 0.0094 g (7.63%) of acrylophenone. The ir spectrum of the product was identical with that of authentic sample prepared by dehydrochlorinating β-chloropropiophenone with potassium acetate.

Reaction of β-Dimethylaminopropiophenone Hydrochloride with Sodium or Potassium Iodide.—A solution of 1.63 g (7.63 mmol) of β-dimethylaminopropiophenone hydrochloride and 4.48 g (27.0 mmol) of potassium iodide in 100 ml of methanol was refluxed for 6 days. The solvent was distilled off under reduced pressure and the solid residue was triturated with ether. The only ether-soluble product, obtained by concentration of the ether solution, was β-methoxypropiophenone (0.069 g, 5.5%), identical in all respects with the product obtained from similar treatment of 5.

To a solution of 5.44 g (0.0255 mol) of β-dimethylaminopropiophenone hydrochloride in 160 ml of hot acetonitrile was added 9.60 g (0.064 mol) of sodium iodide in 160 ml of hot acetonitrile. After being refluxed for 15 days, the mixture was filtered to remove 1.437 g (96.4%) of sodium chloride which had precipitated almost immediately. Concentration of the filtrate yielded a water-soluble, white powder which was triturated with ether. The ethereal extracts were rotary evaporated to yield 0.1004 g (3.0%) of acrylophenone, identical in all respects with the material formed by similar treatment of 5.

The white, water-soluble, ether-insoluble product formed both in methanol and in acetonitrile (and also produced under similar treatment in acetone) proved to be β-dimethylaminopropiophenone hydriodide, mp 203–205°. It had the expected ir spectrum.

Anal. Calcd for $C_{11}H_{16}ONI$ (305.25): C, 43.28; H, 5.28. Found: C, 42.98; H, 5.23.

Reaction of β-Trimethylammoniumpropiophenone Iodide (5) **with Thiophenol in Methanol.**—An anhydrous solution of 0.123 g (0.386 mmol) of 5 in 30 ml of methanol was prepared by gentle warming and magnetic stirring under a nitrogen atmosphere. After solution had been effected, a solution of 0.0844 g (0.766

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mmol) of Eastman thiophenol in 5 ml of methanol was added and the resulting solution was refluxed for 1.5 hr. The methanol was distilled off under reduced pressure and the solid residue was triturated with ether. The ethereal solution was then concentrated to a white residue which on recrystallization from methanol yielded 0.0802 g (85.8%) of β-phenylthiopropiophenone (**12**), mp 74–75° (lit.[32] mp 75°). Compound **12** showed the expected ir and its 2,4-dinitrophenylhydrazone, prepared by standard techniques and recrystallized from 95% ethanol, had mp 147–148° (lit.[32] mp 147.5°).

Exactly the same results were obtained when the reaction was run in the dark or in the presence of hydroquinone.

Reaction of β-Trimethylammoniumpropiophenone Iodide (5) with Thiophenol-d_1 in Methanol-d_1.—By exactly the same procedure used for nondeuterated substrates (*vide supra*), 0.0612 g (0.191 mmol) of **5** was treated with 0.0425 g (0.382 mmol) of Stohler thiophenol-d_1 (98% D) in 17.5 ml of Stohler methanol-d_1. The product (0.0396 g, 85.2%) was α-deuterio-β-phenylthiopropiophenone, mp 74–75°. It was shown to be 94% monodeuterated by mass spectroscopic analysis.[33]

α,α-Dideuterio-β-chloropropiophenone (10).—β-Chloropropiophenone (**6**) was synthesized in 61% yield by the method of Conant.[2a] It melted at 49–50° (lit.[2a] mp 49–50°), had the expected ir spectrum, and its nmr showed peaks at δ 7.20–8.18 (AA'BB'C, 5, C_6H_5), 3.9 (t, 2, CH_2Cl), and 3.5 (t, 2, CH_2CO). In a variation of the method of Karabatsos[34] in which acid, rather than base, catalysis was employed, **6** was α,α-dideuterated. To a solution of 0.60 g (3.56 mmol) of **6** in 10 ml of anhydrous ether contained in a pressure bottle was added 10 ml of Bio-Rad 38% deuterium chloride in deuterium oxide. The bottle was sealed and shaken in a Parr apparatus for 22 hr. The organic layer was separated, dried ($MgSO_4$), and concentrated. The entire procedure was then repeated a second time and the resulting solid residue was twice recrystallized from anhydrous ether to yield 0.54 g (89%) of **10**, mp 49–50°, nmr δ 7.2–8.1 (AA'BB'C, 5, C_6H_5) and 3.9 (s, 2, CH_2Cl).

Reaction of β-Chloropropiophenone (6) with Sodium Iodide in Anhydrous Acetone.—To a solution of 1.078 g (7.187 mmol) of sodium iodide in 15 ml of anhydrous acetone was added a solution of 0.145 g (0.862 mmol) of **6** in 10 ml of anhydrous acetone. The solution was refluxed for 4 hr and concentrated under reduced pressure to a solid residue which was triturated with ether. The ethereal solution was then concentrated and the residue was recrystallized from petroleum ether (bp 30–60°) to yield 0.1953 g (0.753 mmol, 87%) of β-iodopropiophenone, mp 61.5–63° (lit.[35] mp 61–62°), ir as expected, nmr δ 7.2–8.1 (AA'BB'C, 5, C_6H_5) and 3.5 (A_2B_2, 4, CH_2CH_2).

Reaction of α,α-Dideuterio-β-chloropropiophenone (10) with Sodium Iodide in Anhydrous Acetone Containing *tert*-Butyl Alcohol.—A solution of 0.107 g (0.63 mmol) of **10** and 0.908 g (6.05 mmol) of sodium iodide in 16.5 ml of anhydrous acetone and 3.5 ml of *tert*-butyl alcohol was refluxed for 60 hr and then worked up as indicated above for the undeuterated substrate **6** to yield 0.124 g of a white, crystalline product, mp 43–50°. The nmr spectrum showed peaks at δ 7.2–8.1 (AA'BB'C, 10, C_6H_5), 3.9 (broadened s, 2, CH_2Cl), and 3.45 (broadened s, 2, CH_2I). This spectrum corresponds to an equimolar mixture of **10** and α,α-dideuterio-β-iodopropiophenone (**11**). A similar mixture of the undeuterated analogs **6** and β-iodopropiophenone showed nmr peaks at δ 7.2–8.2 (AA'BB'C, 10, C_6H_5) and 3.4–4.1 (two overlapping A_2B_2, 8, CH_2CH_2Cl and CH_2CH_2I).

Kinetic Measurements. Reagents.—Reagent-grade Fisher chloroform, Du Pont reagent grade hydrochloric acid, and Fisher Certified Reagent grade potassium iodide, sodium iodide, and potassium iodate were employed. The latter three salts were dried for 24 hr at 110° and cooled in a desiccator. Fisher Certified Reagent grade acetone was purified by refluxing each liter with 25 g of potassium permanganate until the color disappeared, filtering the precipitated manganese dioxide, drying the filtrate over phosphorus pentoxide, and then distilling from the latter.

Thermal Control.—By a combination of a continuous heat supply (a 250-W blade heater) and an intermittent heat supply (a coil of nichrome wire) controlled by a mercury thermoregulator, temperature was maintained to ±0.03°. Temperature was determined on a Beckmann thermometer calibrated against a National Bureau of Standards thermometer.

Procedure.—The pure organic substrates (**1** or **2**) were placed in tared, thin-walled soft glass ampoules prepared from soft glass disposable pipets and then weighed and sealed. The ampoule, 5 ml of a standard solution of sodium iodide in dry acetone, and a piece of 2 × 0.7 cm glass rod were placed in a clean combustion tube, 1.2 × 30 cm. The tube was protected from the atmosphere by a calcium chloride drying tube, cooled in a freezing mixture of Dry Ice in ethylene glycol monoethyl ether, and quickly sealed in such a manner that the free space above the liquid was approximately equal to the volume of the liquid. The tubes, which were placed in a vertical position in the constant-temperature bath and thermally equilibrated for at least 30 min, were quickly withdrawn, shaken vigorously ($t = 0$) to break the ampoule and initiate reaction, and then returned to the bath. This operation required less than 15 sec. After measured time intervals, tubes were withdrawn and quenched in an ethylene glycol monoethyl ether–Dry Ice bath. After 5 min, the tubes were opened and wiped clean, and the contents and distilled water washings were poured into a 250-ml glass-stoppered bottle containing 5 ml of chloroform, 20 ml of concentrated hydrochloric acid, and 20 g of ice. The amount of unreacted iodide ion was then determined by the standard Andrews titration procedure[36] with a standard solution of potassium iodate according to the equation

$$2KI + KIO_3 + 6HCl \longrightarrow 3KCl + 3ICl + 3H_2O$$

The iodate solution was added rapidly with swirling. This caused an iodine color to develop, which color began to lighten at the equivalence point. At this point, 30 g more of ice was added and the titration was continued with ever-decreasing increments of iodate, with vigorous shaking between each addition, until the end point was approached. The end point was taken as the point at which the chloroform layer became colorless.

This titration is sensitive to acid concentration, and optimum conditions were previously determined by titration of solutions with known concentrations of iodide. Thus, in the later points of the kinetic runs, it was found necessary to employ lesser amounts of hydrochloric acid. It was also found desirable to work rapidly and to keep the solutions cold during the titration by addition of ice. If one uses too low an acid concentration or permits the solutions to warm up, the iodine chloride is hydrolyzed. Too high an acid concentration results in indistinct end points, which come far before the equivalence point. By observing the above precautions, the values obtained titrametrically for standard solutions were found to agree with gravimetrically determined values.

At each temperature, 19 or more points were taken to determine each rate constant. Different ratios of organic substrate to sodium iodide were used. The second-order rate constants were calculated by the method of least squares from the usual second-order rate equation

$$k = \frac{2.303}{t(a - b)} \log \frac{b(a - x)}{a(b - x)}$$

where a = [RCl], b = [NaI], and x = amount of I^- reacting in time t. The standard deviations were determined by the method of least squares. The reactions generally were followed beyond 70% completion. The sodium iodide concentration was in the 2×10^{-2} molar range and the organic substrate in the range of 2×10^{-2} to 12×10^{-2} M. Blanks were run in all cases to check the initial iodide titer, and these were found to agree with the amounts determined by weight to within three parts per thousand.

Registry No.—**1**, 34236-28-7; **1** 2,4-DNP, 34236-29-8; **2**, 420-99-5; **5**, 5724-15-2; **7**, 34236-32-3; **7** 2,4-DNP, 34236-33-4; **10**, 34236-34-5; 1-iodo-2,2-difluoropropane, 34280-36-9; β-dimethylaminopropiophenone HI, 34236-46-9.

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