Photoreactivity of α-Fluorinated Phenyl Alkyl Ketones

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Abstract: The photoreactivities of the mono-, di-, and tri-α-fluorinated acetophenones have been compared to that of acetophenone itself. All four ketones have similar triplet excitation energies; the three fluorinated ketones have reduction potentials 0.5–0.7 eV lower than that of acetophenone. Triplet reactivity toward alkylbenzenes keeps increasing with fluorine substitution, since the rate-determining step becomes charge-transfer complexation as the ketone reduction potential decreases. The primary/tertiary C–H selectivity toward *p*-cymene increases with the number of fluorines. Triplet reactivity toward cyclopentane also is increased by fluorination but peaks at two fluorines, since the lowest triplet switches from n,π* to π,π* with two or three fluorines and π,π* triplets are unreactive in simple hydrogen atom abstraction. In contrast, α-fluorination of valerophenone does not significantly increase the rate of triplet γ-hydrogen abstraction. The inductive effect on reactivity apparently is offset by a conformational effect. The α-fluorinated phenones give predominantly cyclobutanols instead of Norrish type II elimination. α-Fluoroacetophenone forms predominantly acetophenone and HF when irradiated with 2-propanol, in what appears to be a short chain process involving electron transfer to ketone followed by fluoride ion loss. Finally, the radical coupling products in these reactions are formed in varying yields, depending on solvent and additives. It is suggested that radical solvation can affect radical coupling rates sufficiently to prevent statistical ratios of cross-coupling and homo-coupling.

The photoreactivities of α,α,α-trifluoroacetophenone (TFA) and acetophenone (AP) differ dramatically.[1-3] For example, we found that triplet TFA reacts with *p*-xylene 100 times faster than does triplet AP and concluded that TFA reacts with alkylbenzenes by a charge-transfer process rather than by simple hydrogen atom abstraction.[1,2,4] We originally thought that triplet AP reacted by the latter mechanism.[1] However, we have just found that both ketones react by charge transfer followed by hydrogen transfer but that the extent of electron transfer is far greater for TFA, such that the rate-determining step for the reaction becomes charge transfer.[4] The obvious reason is the huge decrease (0.7 eV) in reduction potential caused by the electronegative fluorine substitution.

More recently we observed that triplet TFA reacts with cyclopentane, presumably by simple hydrogen atom abstraction, only 3 times faster than does triplet AP.[3] We concluded that this small rate enhancement masks rather large effects of α-fluorination on the rate constant for hydrogen atom abstraction, since the lowest triplet of TFA is an unreactive π,π* state instead of a reactive n,π* state.

These differences between TFA and AP made it seem worthwhile to explore the effects of intermediate degrees of α-fluorination. Therefore we have studied the photoreduction of α-fluoroacetophenone (MFA) and α,α-difluoroacetophenone (DFA) and the type II photoelimination of α-fluorovalerophenone (MFVP) and α,α-difluorovalerophenone (DFVP). The results provide a clear-cut differentiation of n,π* and π,π* reactivity in exciplex formation. We also discovered huge effects on product yields in the type II reaction,[5] a facile reductive defluorination of MFA, and unprecedented solvent effects on product ratios in photoreduction.

Results

Photoreduction. Table I contains all of the pertinent spectroscopic and photokinetic data that we have obtained for MFA and DFA, as well as earlier data for AP and TFA for the sake of comparison.

The two new ketones showed phosphorescence spectra with well-resolved 0,0 bands. Cyclic voltammetry gave irreversible waves even at the highest scan rates, from which reduction potentials can nonetheless be estimated fairly accurately.[6] Rates of triplet decay in outgassed cyclopentane were measured by flash kinetics, as for a variety of other ketones.[3] Rate constants for reaction with toluene or xylene in acetonitrile or benzene were determined by measuring triplet lifetimes as a function of hydrocarbon concentration, with the lifetimes being measured either by flash kinetics or by Stern–Volmer plots for the quenching of bibenzyl product. Figure 1 shows data in benzene obtained by the latter method. The rate constant for triplet quenching by naphthalene is known to be 6×10^9 M^{-1} s^{-1}.[7] The ratios of primary/tertiary radicals formed from *p*-cymene were determined by analysis of the three bicymyl coupling products.[4,8]

In the irradiations of MFA with toluene and cymene, it was noticed that acetophenone is a reaction product. Irradiation of

Table I. Comparison of Acetophenones with Varying α-Fluorination

	ACP[a]	MFA	DFA	TFA[a]
λ_{max}, nm	238			250
E_T, kcal/mol[b]	73.5	69.1	70.9	71.0
τ_T^{77}, ms[b]	2	2	24	60
E_{red}, eV[c]	−2.14	−1.54	−1.46	−1.38
E_{red}*, kcal/mol[d]	24.2	33.7	37.3	38.1
$10^5 k_H$ (CP)[e,f]	6	36	52	14
$10^5 k_r$ ($PhCH_3$)[e,g]	(2)	20		94
$10^5 k_r$ ($PhCH_3$)[h,i]	1.2	15	30	65
$10^5 k_r$ ($PhCD_3$)[e,g]	(0.6)[j]	17		(94)[k]
$10^5 k_r$ (xylene)[g,i]	11	150	970	2200
P/T[m]	0.5	0.65	2.8	3.4

[a] Most data in ref 4. [b] In MCIP at 77 K. [c] In CH_3CN vs. SCE, Bu_4NClO_4 supporting electrolyte. [d] $E_T + E_{red}$. [e] By flash kinetics. [f] Cyclopentane solvent; cf. ref 3. [g] CH_3CN solvent. [h] Benzene solvent. [i] By steady-state quenching. [j] Based on measured effect for xylene. [k] Based on k_H/k_D in benzene. [m] Ratio of radicals formed from *p*-cymene.

Table II. Solvent Effects on Photoreduction Products

substrate	ketone	solvent	[BK]/[BB]	[BK]/[KK]
toluene	ACP	benzene	2.2	
toluene	ACP	CH_3CN	3.2	
p-cymene	TFA	benzene	2.4	2.2
p-cymene	TFA	CH_3CN	3.4	3.9
cumene	ACP	benzene	2.1	1.74
cumene	ACP	CH_3CN	2.4	2.2

† Fellow of the John Simon Guggenheim Foundation, 1984–1985.

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Table III. Effects of Trifluoroacetic Acid on Photoreduction Products[a]

ketone	[acid]	[PT]	[TT]	[PP]	[KP]	[KT]	P/T
AP[b]	0	0.92	1.40	0.20			0.35
AP[b]	0.05	3.30	2.19	1.59			0.84
TFA[b]	0	0.83	0.12	2.00	5.7	1.7	3.8
TFA[b]	0.05	2.00	0.51	2.20	9.1	5.0	1.9
TFA[c]	0	1.93	0.26	4.78	16.7	3.2	5.0
TFA[c]	0.07	1.74	0.17	3.89	18.1	3.6	4.8

[a] Products in units 10^{-3} M obtained from 0.5 M *p*-cymene. Each line represents a separate experiment, so vertical values cannot be compared directly. [b] In benzene. [c] In acetonitrile.

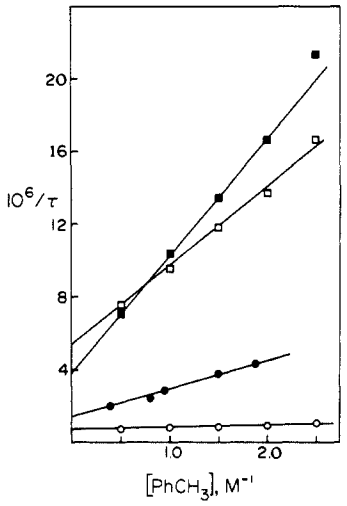
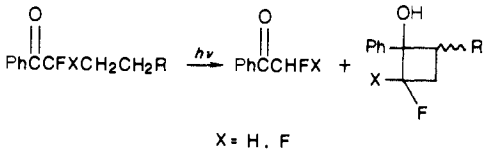


Figure 1. Triplet ketone lifetimes as a function of toluene concentration in benzene: (■) AP; (□) MFA; (●) DFA; (○) TFA.

0.1 M MFA in benzene containing 0.06–0.18 M 2-propanol led to acetophenone and acetone as the major products, with a quantum yield extrapolated to infinite 2-propanol concentration of 3.3 for formation of AP. The production of HF was indicated by a frosting of the Pyrex samples tubes.

Solvent Effects on Product Ratios. Table II lists yields of bibenzyl and benzylcarbinol products for several sets of conditions. It appears to be general that the amount of cross-coupled product is greater in acetonitrile than in benzene, accounting for 60% instead of only 50% of the radical coupling products. Likewise, the presence of added pyridine or trifluoroacetic acid changes the product ratios, also favoring cross-coupled product at the expense of bibenzyl. Figure 2 shows a plot for the quenching by pyridine of TFA photoreduction in benzene and in acetonitrile. In the hydrocarbon solvent, small amounts of pyridine actually enhance the yield of carbinol, so much is the product ratio altered. Finally, Table III lists the effects of added trifluoroacetic acid on product ratios obtained from *p*-cymene. The primary/tertiary selectivity is altered significantly. In all cases studied, the P/T ratio obtained from the two benzylcarbinols equals that obtained from the three bibenzyls.

Photoelimination. Irradiation to low conversion of degassed benzene solutions containing either MFVP or DFVP (0.04 M) gave the product ratios listed in Table IV. Stern–Volmer quenching studies, with 2,5-dimethyl-2,4-hexadiene as quencher, gave the slopes and triplet lifetimes listed. Samples of α,α-difluorobutyrophenone and α,α-difluoro-γ-methylvalerophenone were also prepared. Preparative-scale irradiation of all three difluoro ketones produced the difluorocyclobutanol products, with only traces of DFA being observed by GC analysis. γ-Fluorobutyrophenone and β-fluoro-β-methylbutyrophenone were irradiated in order to determine the effect on the product ratio of a fluorine elsewhere in the molecule.



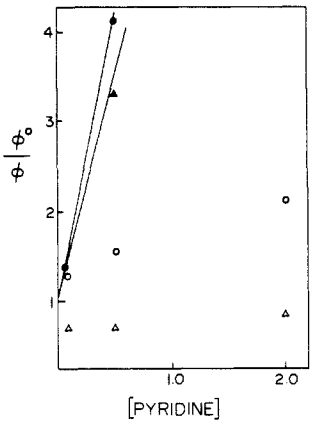


Figure 2. Effect of added pyridine on product ratios obtained from irradiation of TFA and toluene: (● and ▲) BB and BK in CH_3CN; (○ and △) BB and BK in benzene.

Table IV. Effect of Fluorination on Type II Photoelimination[a]

ketone	Φ_{elim}[b]	Φ_{cyc}[c]	$k_q\tau$[d]	$1/\tau$[e]
VP[f]	0.31	0.07	40	1.5
MFVP	0.34	0.35	18	3.3
DFVP	≤0.01	0.60	36	1.7
GFBP[g]	0.41	0.08	780	0.08
BFBP[h]	(1.3)	(1.0)		

[a] 0.04 M ketone in degassed benzene irradiated at 313 nm. [b] Formation of (fluorinated) acetophenone. [c] Cyclobutanol. [d] M^{-1}, average of duplicate runs. [e] 10^8 s^{-1}, $k_q = 6 \times 10^9$ M^{-1} s^{-1}. [f] Valerophenone, ref 12. [g] γ-Fluorobutyrophenone. [h] β-Methyl-β-fluorobutyrophenone, relative yields.

Discussion

Spectroscopy. The first α-fluorine produces a huge 0.5-eV decrease in ketone reduction potential, with the second two fluorines adding only a ~0.1-eV drop each. We presume that this nonadditivity implies a stereoelectronic effect, with the alignment of the C–F bond in relation to the C=O π system being crucial. The values measured are not exact because of the irreversible reductions. However, Kochi has shown that such measurements can still be reliable.[6]

The ketones' phosphorescence behavior is quite intriguing. All three fluorinated APs have very similar triplet energies. The relatively long emission lifetimes of DFA and TFA at 77 K indicate that these two ketones have π,π^* lowest triplets. It is clear that the first α-fluorine lowers the n,π^* triplet energy substantially, as expected, but that extra fluorines produce no further lowering. The good correlation between n,π^* energies and ground-state reduction potentials observed for ring-substituted phenyl ketones[9] is not so pronounced for α-fluorination. That α-fluorination would lower triplet π,π^* energies is apparent from the behavior of the L_a band in the ketones' UV spectra. The decrease upon going from AP to TFA is 6 kcal/mol; since the lowest triplet has a major contribution from the L_a configuration,[10] a comparable decrease in triplet energy is expected. The two intermediate ketones must

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have two nearly isoenergetic triplet levels. What is not obvious is why DFA has a higher 0,0 energy than does MFA; this subject will be addressed separately.

The most striking conclusion from the spectroscopic data is that MFA and DFA have lowest triplets of opposite configurations but with comparable reduction potentials. Therefore a comparison of their reactivity offers one of the simplest, cleanest differentiations possible between n,π* and π,π* states.

Comparison of n,π* and π,π* Triplet Reactivity. Figure 3 plots the reactivity of AP and its three α-fluorinated derivatives toward cyclopentane, toluene, and xylene as a function of triplet ketone reduction potential. It is immediately obvious that the rate constant for reaction with both alkylbenzenes keeps rising with successive fluorine substitution, whereas that for hydrogen abstraction from cyclopentane peaks at two fluorines. Since DFA and TFA have π,π* lowest triplets, the decrease in the rate constant for hydrogen abstraction in TFA relative to DFA and MFA reflects the low population of the reactive n,π* triplet.[3,11,12] Each additional fluorine on AP increases the value of k_H^n, but the second and third ones also lower χ_n. The result is comparable k_H^{obsd} values for MFA and DFA but a lower value for TFA.

$$k_H^{obsd} = \chi_n k_H^n \quad (1)$$

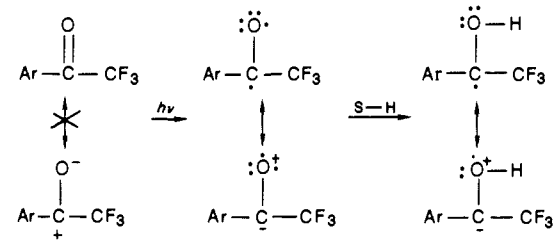
$$\chi_n = 1 - \chi_\pi \quad (2)$$

In contrast, the constant increase in triplet reactivity toward alkylbenzenes indicates that the mechanism of photoreduction cannot be simple hydrogen atom abstraction. As indicated in our earlier work and in the accompanying paper, the mechanism appears to be charge-transfer complexation followed by hydrogen transfer. In the case of AP, the extent of CT is so small that the second step remains rate-determining, as judged by the significant isotope effect observed.[4] A single α-fluorine enhances k_{CT} 10-fold, primarily because of the major decrease in ketone reduction potential. The small isotope effect observed with toluene-d_8 indicates that the second step no longer is rate-determining. We did not even bother measuring an isotope effect for DFA, since a k_H/k_D value of 1 could be interpolated from the behavior of MFA and TFA. As the figure shows, CT reactivity is a smoothly increasing function of reaction thermodynamics independent of the nature of the lowest triplet. These results provide clear evidence for the important conclusion that there is no fixed intrinsic difference in reactivity between n,π* and π,π* triplets in CT complexation. This conclusion was also reached by a careful comparison of the effects of ring substituents.[4]

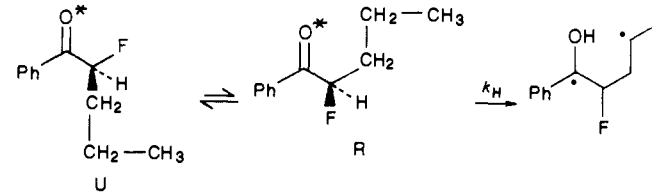
MFA and DFA do show a dramatic difference in proton selectivy when reacted with *p*-cymene. MFA preferentially abstracts a tertiary hydrogen, whereas DFA prefers the primary hydrogen. This behavior indicates that the two different triplet configurations must form complexes with alkylbenzenes of significantly different nature. The π,π*-derived complex apparently involves face-to-face overlap of the benzene rings of donor and acceptor, such that stereoelectronic effects can influence proton transfer.[4] The n,π*-derived complex apparently involves looser overlap of the alkylbenzene with the carbonyl n-orbital, such that stereoelectronic effects are not possible and product thermodynamics control selectivity.

Hydrogen Atom Abstraction. The effect of α-fluorination on rates of hydrogen atom abstraction is much larger for the bimolecular reaction of triplet acetophenone with cyclopentane than for the intramolecular reaction of valerophenone (VP). Triplet MFVP is only twice as reactive as triplet VP, whereas triplet MFA is 7.5 times more reactive than triplet AP. Likewise, DFVP has the same triplet reactivity as VP, whereas DFA is 10 times more reactive than AP. Thus one must explain both why there is a large effect in bimolecular reaction and why it disappears in intramolecular reaction.

Bimolecular reactions are free of internal conformational restraints[13] and therefore best demonstrate the intrinsic electronic effects of substitution. We have already noted that fluorine substitution on the ring produces larger increases in k_H^n than would be predicted from the effects of other ring substituents.[3] The 7.5-fold effect of a single α-fluorine is 4 times larger than the largest effect of a single ring substituent. Thus fluorines produce unusually large enhancements of reactivity. We presume that the effect of α-fluorination reflects both a destabilization of the carbonyl double bond and a specific hyperconjugative stabilization of the hemipinacol radical, which is reflected in the transition state for hydrogen transfer.



Why then does this rate enhancement disappear in the intramolecular hydrogen abstractions? The only possible explanation is that the α-fluorines stabilize conformations in which a γ-hydrogen is not accessible to the carbonyl oxygen. We previously have interpreted conformational effects on such Norrish type II reactions in terms of the largest α-substituent eclipsing the carbonyl,[14] such that only normal rotational barriers need be overcome for internal reaction. It has been observed that both α-halo and α,α-dihalo carbonyl compounds show distinct preferences for conformations in which a carbon-halogen bond eclipses the carbonyl group, especially in aromatic and polar solvents.[15] We suggest that this conformational effect lowers the rate constant for intramolecular hydrogen abstraction in the α-fluoro ketones. With a halogen atom preferentially eclipsing the carbonyl, the propyl group would be held at an angle such that a γ-hydrogen could not approach within bonding distance of the oxygen. Thus the fluorine introduces rotational barriers that decrease the probability that the molecule will attain the cyclic arrangement required for internal hydrogen transfer. In terms of the simplest kinetic model, the fraction χ_r of reactive conformations is lowered by fluorination more than k_H° is raised. It is interesting that the relative deactivation of the intramolecular reaction caused by two α-fluorines is double that produced by one. This observation is in accord with the phenomenon being due to competing conformational preferences, with two fluorines having twice the effect of one.



$$k_H^{obsd} = \chi_r k_H^\circ$$

$$\chi_r + \chi_u = 1$$

Type II Product Ratios. The huge enhancement of cyclization efficiency produced by α-fluorination represents an overall increase in product quantum efficiency and therefore a significant decrease in the reversion of biradical to starting ketone. Since our original communication of this finding,[5] Swenton has found other cases in which fluorination significantly alters biradical product ratios.[16]

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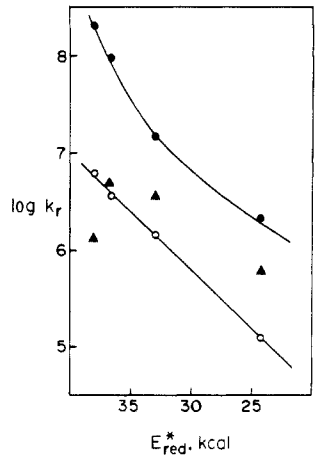
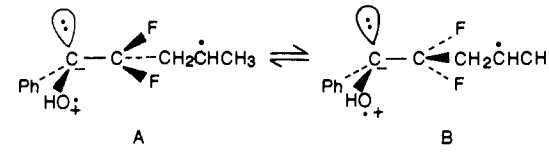


Figure 3. Triplet reactivities of AP, MFA, DFA, and TFA toward (▲) cyclopentane, (○) toluene, and (●) *p*-xylene as a function of ketone triplet reduction potential.

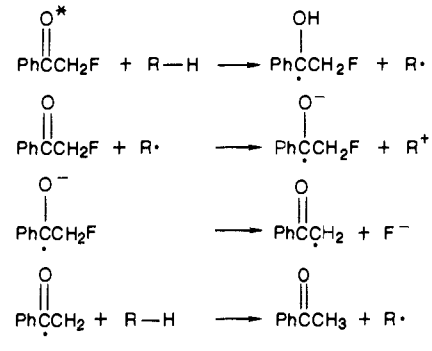
Several explanations for this apparently general effect can be advanced. We originally suggested that product selectivity reflects conformational preferences in the biradical intermediate.[5] The similar effect on type II product ratios produced by α-methylation has been ascribed to steric effects on biradical rotation.[17] However, fluorines do not seem large enough to produce a comparable steric effect. Since the benzylic end of the 1,4-biradical is a hemipinacol radical site, we suggested that the fluorine atom enhances by hyperconjugation[18] the charge-separated resonance form known to be important in α-oxy radicals.[19] This effect would stabilize conformations such as A and B in which the two half-occupied p-orbitals cannot both be parallel to the 2,3 C–C bond, such as is required for cleavage of 1,4-biradicals.[20,21] We have now observed enhanced cyclization for the β-fluorobutyrophenone, and Swenton has made the same observation for several β-fluorobutyrophenone derivatives.[22] Although there are measurable conformational preferences in simple β-fluoroalkyl radicals,[23] we are not convinced that they are strong enough to force large product selectivity on these biradicals. The 3-fold and 5-fold changes in product ratios produced, respectively, by a single β- or α-fluorine substituent represent 700–1000 cal/mol changes in relative barrier energies.

An explanation invoking C–F bond energies has been a favorite of referees. Since it is well-known that fluorine atoms show a preference for bonding to sp^3 rather than to sp^2 carbons,[24] the biradical might cleave more slowly than usual because of the required change from sp^3 to sp^2 at the C–F carbon. This suggestion seems unsatisfactory for several reasons. It has been apparent for some time that relative product energies have only minimal effects on biradical reactivity, since product formation is so exothermic that barriers are expected to be small. In other cases of preferential cyclization, such as with benzoylcyclobutane,[25] stereoelectronic effects clearly are much more important than are relative product energies. The large percentage of cleavage observed for γ-fluorobutyrophenone provides some evidence that the preference for cyclization caused by α-fluorines cannot be explained by relative C–F bond energies in the products. Cyclization of the 1,4-biradical converts the fluorine from an sp^2 carbon to an sp^3 carbon; yet no more cyclization occurs than in simple butyrophenone.



Since our original report, there has been more attention given to the competition between product formation and spin-state interconversion in biradical reactions. Perhaps the most popular current model of the type II photoreaction concludes that product ratios are determined by biradical geometries at the moment of intersystem crossing from triplet to singlet biradical.[26] In this model, the effects of α-substituents could reflect specific electronic effects on rates of intersystem crossing as well as the stereoelectronic effect on conformational equilibria and dynamics that we originally suggested, but not hybridization effects on product energies. In terms of the first intriguing possibility, the well-known large hyperfine interaction of β-fluorine atoms on free radicals[27] might enhance intersystem crossing rates in these 1,4-biradicals. Interestingly, the conformations that would maximize hyperfine coupling are the same as those that would maximize fluorine hyperconjugation. However, we have found separately that α-fluorination does not shorten biradical lifetimes,[28] apparently ruling out any major contribution of hyperfine-induced intersystem crossing to our product ratios. Moreover, recent studies on acyl-alkyl biradicals suggest that spin-orbit mixing is much more important than hyperfine interactions at inducing intersystem crossing in small biradicals.[29] Therefore we continue to look at more conventional effects to explain the enhanced cyclization. Still unresolved by any explanation is why the biradical disproportionation/cleavage ratio is decreased an order of magnitude by α-fluorination, when both cyclization and reverse hydrogen transfer necessarily occur from similar geometries.

Defluorination of MFA. The efficient defluorination of MFA during photoreduction was unanticipated, but other examples have been reported[30,31] since our original observation.[32] Although we have just begun a further investigation of the phenomenon, the following mechanism seems likely based on the ability of various electron donors including radicals[31] to reduce ground-state MFA.



We cannot yet eliminate the possibility that the hemipinacol radical itself undergoes intramolecular loss of HF to yield the phenacyl radical, either by a concerted five-center reaction or by

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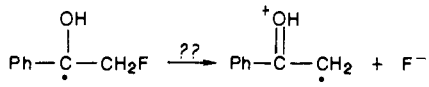
some process similar to the known heterolysis of β-substituted radicals.[33] In this regard it is quite interesting that neither DFA nor TFA shows any sign of losing an α-fluorine, although they are equally easy to reduce. The destabilization involved in changing from a $C(sp^3)$–F to a $C(sp^2)$–F bond, which was mentioned above, may be responsible for the difference.



Solvent Effects on Photoreduction Product Ratios. For years 1:2:1 ratios of radical coupling products have been expected in photoreductions[34] on the basis that random coupling of two different radicals (B and K) formed in equal yields would necessarily provide such a statistical ratio. Simple consideration of the kinetics equations indicates that product ratios depend on the values of the three bimolecular coupling rate constants. If these were all to have the same value, which happens when coupling is diffusion-controlled, then a 1:2:1 product ratio is expected. If, however, the homo-coupling rate constant for one of the radicals were significantly lower than both the homo-coupling rate constant for the other radical and the cross-coupling rate constant, then excess cross-coupling would occur. The reason is that the steady-state concentrations of B and K would become unequal, favoring the more slowly coupling one.

$$2B^{\bullet} \xrightarrow{k_{BB}} B\text{–}B$$

$$2K^{\bullet} \xrightarrow{k_{KK}} K\text{–}K$$

$$K^{\bullet} + B^{\bullet} \xrightarrow{k_{BK}} B\text{–}K$$

$$d[BB]/dt = k_{BB}[B^{\bullet}]^2$$

$$d[KK]/dt = k_{KK}[K^{\bullet}]^2$$

$$d[BK]/dt = 2k_{BK}[K^{\bullet}][B^{\bullet}]$$

$$([K^{\bullet}]/[B^{\bullet}])_{ss} = (k_{BB}/k_{KK})^{1/2}$$

It appears that a 1:2:1 ratio is obtained for several photoreductions in hydrocarbon solvent. However, in acetonitrile solvent, or in the presence of added pyridine or acid, the percentage of BK among the products is considerably higher than 50%. It is now well-known that steric factors can slow down radical coupling to orders of magnitude slower than those of diffusion.[35] We believe that solvation of the hemipinacol radicals (K) by hydrogen bonding undoubtedly makes the radicals bulky enough to lower the k_{KK} relative to k_{BB}. It would take only a 4-fold decrease to produce a 2-fold increase in cross-coupling. It is likely that solvation would also impede cross-coupling but not as much as homo-coupling of two hemipinacol radicals. Fischer has recently recognized the general importance of this phenomenon of uneven coupling rate constants.[36] Lewis has already observed another likely manifestation of sterically hindered coupling in the shift from pinacol to alcohol observed in the photoreduction of acetophenones with increasing alkyl substitution at the α-carbon.[37]

Experimental Section

Chemicals. All solvents and reagents were obtained and purified as described in the accompanying pater, as were acetophenone and α,α,α-trifluoroacetophenone.[4]

α-Fluoroacetophenone was prepared by treating 25 g of phenacyl bromide with 25 g of potassium fluoride, which had previously been flame-dried, ground to a fine powder, and left overnight in an oven at 140 °C. The reagents were added to 170 mL of dry glycerin heated to 60 °C. A vacuum was then applied, and the mixture was heated with vigorous stirring so that its temperature rose to 130 °C over 30 min. During this period the crude product was distilled out through a short-path distillation head. It was dissolved in ether, washed with water, dried (Na_2SO_4), and evaporated. Spinning-band distillation produced pure ketone in 52% yield: bp 103 °C (5 torr); IR (neat) 3070, 2940, 1715, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.5 (d, 2 H, J = 48 Hz), 7.5 (m, 3 H), 7.8 (m, 2 H); ^{19}F NMR δ 231 (t, J = 48 Hz); MS, m/z 138, 137, 105, 77.

α,α-Difluoroacetophenone was prepared from 24 g of Aldrich α,α-dichloroacetophenone and 48 g of similarly dried KF in 200 mL of glycerin, by the above procedure, with the temperature being raised to 150 °C to distill off crude product. Spinning-band distillation provided a 28% yield: bp 60 °C (4 torr); IR (neat) 3060, 1705, 1601, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.2 (t, 1 H, J = 54 Hz), 7.5 (m, 3 H), 7.9 (m, 2 H); ^{19}F NMR δ 122.3 (d, J = 54 Hz); MS, m/z 156, 155, 105, 77.

α-Fluorovalerophenone was prepared by treating α-bromovalerophenone with KF as described above. The bromo ketone was prepared either by direct bromination of valerophenone or by Friedel–Crafts reaction of α-bromovaleryl chloride with $AlCl_3$ in benzene at 0–25 °C: bp 81 °C (0.8 torr); IR (neat) 3065, 2960, 2880, 1700, 1455, 1280, 1140, 1075, 1010, 950, 875, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (t, 3 H, J = 7 Hz), 1.6–2.0 (complex m, 4 H), 5.62 (d of t, 1 H, J_{HH} = 7, J_{HF} = 50 Hz), 7.3–7.7 (m, 3 H), 7.8–8.1 (m, 2 H); MS, m/e 180, 160, 138, 105, 77.

α,α-Difluorovalerophenone was prepared by bromination of the monofluoro ketone and treatment with KF, as described for the acetophenone: bp 91 °C (1.7 torr); IR (neat) 2960, 1700, 1440, 1250, 1140, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (t, 3 H, J = 7 Hz), 1.95 (m, 2 H), 2.10 (t of t, 2 H, J_{HH} = 7, J_{HF} = 25 Hz), 7.3–7.7 (m, 3 H), 8.1–8.2 (m, 2 H); MS, m/e 199, 198, 156, 105, 77.

β-Fluoro-β-methylbutyrophenone. 3-Methyl-2-butenoic acid (144 g) was treated with 250 mL of thionyl chloride. After volatiles had been removed, the crude acid chloride was dissolved in 600 mL of benzene, cooled to 0 °C, and subjected to a water-aspirator vacuum. Then 272 g of $AlCl_3$ was added slowly with stirring. After 5 h, the reaction was worked up and distilled to yield 3-methyl-1-phenyl-2-buten-1-one: ^1H NMR ($CDCl_3$) δ 1.6 (s, 3 H), 1.7 (s, 3 H), 6.5 (s, 1 H), 7.2 (m, 3 H), 7.8 (d, 2 H).

This ketone (25 g) was dissolved in 100 mL of 1:1 ether/methylene chloride and added slowly to 120 g of HF at −78 °C. *N*-Bromosuccinimide (36.4 g) was added in small portions; after 2 h the temperature was raised to 0 °C and the mixture was stirred for 18 h. The mixture was then added to excess aqueous sodium bicarbonate; workup gave crude 2-bromo-3-fluoro-3-methyl-1-phenylbutan-1-one. The bromo ketone (2.9 g) was mixed with 4 g of tributylstannane in 1 mL of ether. After 4 h the mixture was distilled, yielding impure fluoro ketone, bp 93 °C (1.1 torr). Material contaminated by a few percent of 3-methyl-1-phenyl-3-buten-1-one was obtained by preparative GC, but glass wool column packing had to be removed; otherwise most of the fluoro ketone eliminated HF.

γ-Fluorobutyrophenone. The pyranyl ether of benzaldehyde cyanohydrin was prepared by literature procedures.[38] 3-Fluoropropyl tosylate was prepared separately from 3-fluoro-1-propanol. To 200 mL of dry Me_2SO under argon were added with stirring 4.7 g of NaH and then 20 g of the pyranyl ether. After 2 h, 21.3 g of the fluoro tosylate was added slowly. After another 2 h the reaction mixture was added to 400 mL of 1 N HCl and stirred for 1 h. The organic residue after workup was stirred with 0.3 N sodium bicarbonate for 2 h, then extracted into ether, and dried. Distillation gave 10 g of crude γ-fluorobutyrophenone, which was dissolved in 99:1 hexane/benzene. Upon being cooled over dry ice, the cloudy solution produced a brown oil. The clear supernatant was poured off and produced 7.8 g of white crystals at 0 °C, which melted at room temperature and were 96% pure by GC analysis: ^1H NMR ($CDCl_3$) δ 2.15 (d of quintuplets, 2 H, J_{HH} = 7, J_{HF} = 25 Hz), 3.05 (t, 2 H, J = 7 Hz), 4.54 (d of t, 2 H, J_{HH} = 7, J_{HF} = 47 Hz), 7.1–7.5 (m, 3 H), 7.8–8.0 (m, 2 H).

Procedures were followed as described in the accompanying paper.

Acknowledgment. This work was supported by the National Science Foundation. We thank Dr. J. C. Scaiano and the National Research Council of Canada for their hospitality and cooperation in the measurement of some flash kinetics.

Registry No. ACP, 98-86-2; MFA, 450-95-3; DFA, 395-01-7; TFA, 434-45-7; VP, 1009-14-9; MFVP, 29114-66-7; DFVP, 58534-47-7; GFBP, 2248-17-1; BFBP, 104740-58-1; H, 1333-74-0; D, 7782-39-0;

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$PhCH_3$, 108-88-3; $PhCH(Cl)CH(Br)CH_2CH_2CH_3$, 104740-59-2; $(CH_3)_2C{=}CCO_2H$, 541-47-9; $(CH_3)_2C{=}CHCOCl$, 3350-78-5; $PhCOCH{=}C(CH_3)_2$, 5650-07-7; $PhCOCH(Br)(CCF)(CH_3)_2$, 104740-60-5; $FCH_2CH_2CH_2OTs$, 312-68-5; $FCH_2CH_2CH_2OH$, 462-43-1; cyclopentane, 287-92-3; *p*-cymene, 99-87-6; *p*-xylene, 106-42-3; cumene, 98-82-8; phenacyl bromide, 70-11-1; α,α-dichloroacetophenone, 2648-61-5; α-bromovalerophenone, 49851-31-2; benzaldehyde cyanohydrin (pyranyl ether), 41865-47-8.

Nucleophilic Addition to Olefins. 19.[1] Abnormally High Intrinsic Barrier in the Reaction of Piperidine and Morpholine with Benzylideneacetylacetone[†]

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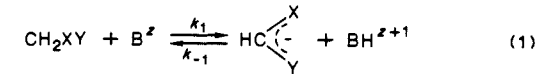
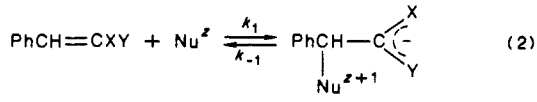
Contribution from the Thimann Laboratories of the University of California, Santa Cruz, California 95064. *Received June 12, 1986*

Abstract: The title reaction leads to the formation of the zwitterionic Michael adduct $T^{\pm}$ ($PhCH(R_2NH^+)C(COCH_3)_2^-$) which is in rapid acid–base equilibrium with its anionic form T^- ($PhCH(R_2N)C(COCH_3)_2^-$). Rate (k_1, k_{-1}) and equilibrium constants (K_1) for nucleophilic addition and the pK_a of the $T^{\pm}$-adducts were determined in 50% Me_2SO–50% water at 20 °C. From an interpolation of the rate constants to $K_1 = 1$ an intrinsic rate constant, log $k_0 = 0.3$, was determined. This value deviates negatively by approximately 2.5 log units from a correlation of log k_0 for amine addition to five olefins of the type $PhCH{=}CXY$, with log k_0 for the deprotonation of the corresponding carbon acids CH_2XY. Two major factors are believed to contribute to this depressed intrinsic rate constant or enhanced intrinsic barrier: (1) steric inhibition of resonance in $T^{\pm}$ with the steric effect developing ahead of C–N bond formation (this conclusion is supported by an X-ray crystallographic study of *p*-methoxybenzylideneacetylacetone which shows that steric hindrance to optimal π-overlap in the adduct $T^{\pm}$ is already present in the substrate); (2) intramolecular hydrogen bonding in $T^{\pm}$, which is inferred from abnormally high pK_a values and whose development lags behind C–N bond formation. These effects are shown to be manifestations of the Principle of Nonperfect Synchronization.

In a series of recent papers[2-8] we have reported intrinsic barriers ($\Delta G_0^{\ddagger}$) or intrinsic rate constants (k_0) for carbanion forming reactions such as proton transfers (eq 1) and nucleophilic additions to activated olefins (eq 2). Table I summarizes log k_0 values for



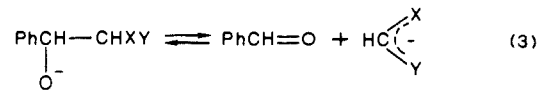
(1)



(2)

five different XY with $B^z = Nu^z$ = piperidine and morpholine in 50% Me_2SO–50% water (v/v) at 20 °C. For the proton transfers we have defined k_0 as $k_1/q = k_{-1}/p$ at $\Delta pK + \log(p/q) = 0$, while for the nucleophilic addition reactions we use the definition $k_0 = k_1 = k_{-1}$ when $K_1 = k_1/k_{-1} = 1$.[9]

It is apparent that in both reaction series log k_0 decreases in the order $(CN)_2 > (CN)C_6H_4\text{-}4\text{-}NO_2 > (CN)C_6H_3\text{-}2,4\text{-}(NO_2)_2 > (H)NO_2 > (C_6H_5)NO_2$ which is essentially the inverse order of resonance stabilization of the respective carbanions. In other words, the formation of the most strongly resonance stabilized carbanions occurs with the slowest intrinsic rates. Similar trends have been observed with other nucleophiles (e.g., $Nu^z = OH^-$ in eq 2)[10,11] and in other carbanion forming reactions such as eq 3[10,11] and eq 4.[12]



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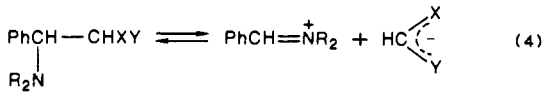

(4)

[†] This paper is dedicated to Professor Joseph F. Bunnett for his 65th birthday.

It thus appears that increased resonance stabilization of the carbanion lowers k_0 irrespective of the type of reaction that leads to the formation of the carbanion. It has been suggested that at least part of the lowering of k_0 is a consequence of a lag in the development of resonance and concomitant solvation at the transition state.[13,14] The fact that k_0 shows a stronger dependence on XY in the proton transfers than in the addition reactions (Table I) is probably due to two factors: hydrogen bonding stabilization of the transition state of proton transfers which enhances the sensitivity of k_0 to XY in the proton transfers, and the sp^2-hybridization of the carbon attached to XY in the olefins which

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(9) (a) For reactions which are unimolecular in one direction but bimolecular in the other (eq 2–4) this simple definition creates a slight problem in that k_1 and k_{-1} have different units. Hine[9b] has suggested a way to deal with this problem by breaking down the reaction into two steps: encounter complex formation and actual chemical transformation. For the kind of qualitative or semiqualitative considerations we are interested in, the Hine formalism is not necessary; this formalism may also introduce some error because the value of the encounter complex equilibrium constant has to be assumed. (b) Hine, J. *J. Am. Chem. Soc.* **1971**, *93*, 3701.
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