(177.0 mg, 2.28×10^{-4} mol) with 1 mL of HMPA added.

From runs of 4 and 24 h, recoveries of acetophenone ranged from 95.5% to 101.5% with at most a trace, <0.4%, of 1-phenylethanol from the 24-h runs containing HLADH, with or without DNB.

For the bromohydrin, 89 ± 10% of the starting material was present. Drying over K_2CO_3 instead of Na_2SO_4 for 40–44 h before GLPC analysis gave 34–44% styrene oxide. Longer exposure to K_2CO_3 increased the conversion. The corresponding chlorohydrin formed styrene oxide at a much slower rate. The mono- and trifluoro analogs did not. Even the bromohydrin gave, at most, traces of styrene oxide after prolonged storage over Na_2SO_4.

To test the extraction procedure used, a reaction mixture containing substrate and NADH in 20 mL of phosphate buffer and 1 mL of HMPA were extracted immediately after substrate addition by the method described above. Quantitative or near quantitative recoveries of substrate was achieved for 2-bromoacetophenone, 2-chloroacetophenone, 2,2-dichloroacetophenone, and 2-fluoroacetophenone.

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Registry No. HLADH, 9031-72-5; NADH, 58-68-4; α-fluoroacetophenone, 450-95-3; α-chloroacetophenone, 532-27-4; α-bromoacetophenone, 70-11-1; α,α-dichloroacetophenone, 2648-61-5; 2,2-dichloro-1-phenylethanol, 2612-36-4.

Substrate-Specific Reduction Mechanisms for NADH Models. Reduction of *N*-Methylacridinium Iodide and α,α,α-Trifluoroacetophenone[1]

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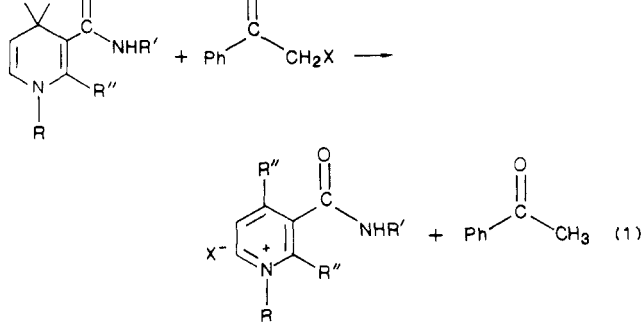
The reduction of α,α,α-trifluoroacetophenone by five N-substituted dihydronicotinamides (DHNAs) proceeds by a free radical chain process initiated by single electron transfer (SET). In dry acetonitrile the chain, whose propagation steps contain a SET–hydrogen atom transfer sequence, could be inhibited with *m*-dinitrobenzene or initiated by AIBN. Under the same reduction conditions methylacridinium iodide does not undergo homolytic chain reduction. The reduction of methylacridinium iodide by all five of the DHNAs followed clean second-order kinetics which were consistent with a bimolecular hydride transfer. Although a chain reaction involving solely cross termination can also follow second-order kinetics, no evidence could be obtained for either chain inhibition or initiation. The reduction mechanism followed by the NADH models appears to be substrate-specific and results reached from such model studies must be evaluated with some reservation.

Introduction

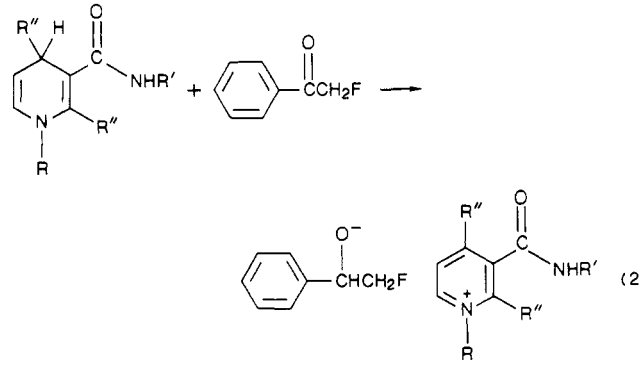
Recently[3] we have published the results of a study of the reduction of α-fluoro-, α-chloro-, and α-bromoacetophenone with four *N*-substituted-1,4-dihydronicotinamides (DHNAs), I–IV; eq 1. The reactivity of the DHNAs varied



(1)

I, R = C_6H_4; R′ = H; R″ = H
II, R = $C_6H_5CH_2$; R′ = H; R″ = H
III, R = *n*-C_3H_7; R′ = H; R″ = H
IV, R = *n*-C_3H_7; R′ = $PhCH(CH_3)$; R″ = H
V, R = *n*-C_3H_7; R′ = $PhCH(CH_3)$; R″ = CH_3

with substituents R, R′, and R″ and followed the order that depended upon the reagents ability to support a positive charge: IV > III > II > I. The mechanistic pathway followed for the reductions was shown to be a free radical chain reaction that involved an electron-transfer step both in its initiation and its propagation sequence. In the polar solvent, methanol, a small amount of hydride-transfer reduction takes place in competition with homolytic reduction. The heterolytic reduction showed some substrate specificity in that only α-fluoroacetophenone, the least reactive of the substrates, showed this competitive behavior (eq 2). The same reduction by two competing processes



(2)

is observed when the substrates, the chloride or fluoride, are reduced by triphenyltin hydride.[4,5] It was apparent that the donor–acceptor ability of the substrates was the factor that determined the dominance of one or the other mechanism.[3-5]

(1) Presented in part at the 192nd National Meeting of the American Chemical Society, Anaheim, CA, September 1986; PETR, Preprints, 1986, *31*, 897.
(2) Postdoctoral Fellow, University of Alberta, 1986–1987.
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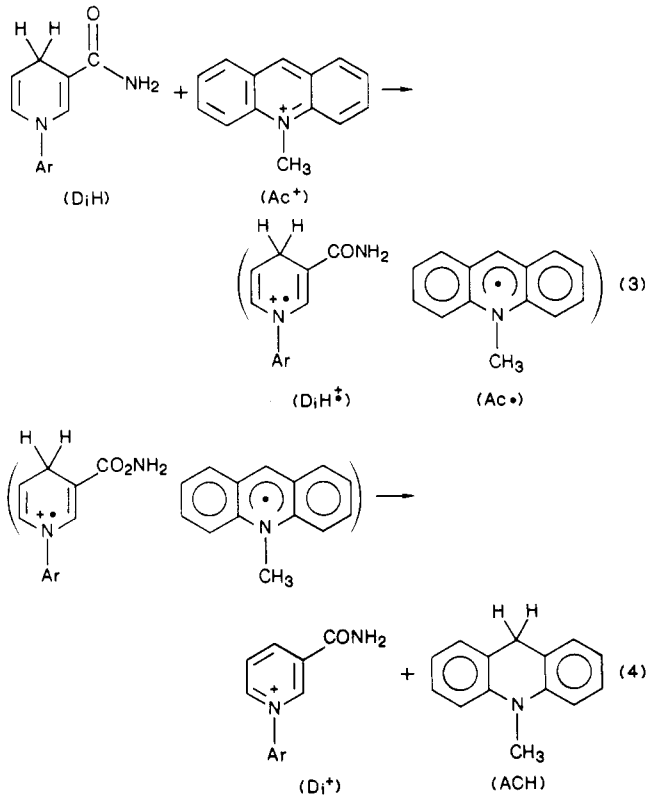
0022-3263/88/1953-1646$01.50/0

Biomimetic reductions by model NADH reductants have been carried out on a wide variety of structurally dissimilar substrates in an effort to model the mechanism(s) that takes place in the natural NADH enzyme controlled reductions.[6-8] Since it is possible that the mechanistic pathway followed by a reductant is determined by the substrate that is being reduced,[9] several of these model systems were studied.

The mechanism for the reduction of *N*-methylacridinium salts by several 1,4-dihydronicotinamides has been reported.[6b,7b,8c,10-12] The most recent studies, designed to establish the mechanistic path involved in the reductions, have led to divergent conclusions.[7b,8c,10-12] These studies have been carried out in both protic and aprotic solvents. The studies carried out in aprotic solvent appear to be more straightforward than those carried out in protic solution.[11,12]

Reactions carried out in dry acetonitrile have been reported to follow clean pseudo-first-order kinetics[8c,11,12] to at least 90% reaction. These reductions have been proposed to proceed by either a heterolytic hydride transfer,[8c] a homolytic nonchain process[7b] (e^-, H^+, e^-), or more recently by an (e^-, $H^\bullet$) process,[12] eq 3 and 4. The strongest evidence presented to support the homolytic (e^-, H^+, e^-) mechanism was the report[7b] that the kinetic and product deuterium isotope effects observed in the reduction carried out with the 4-deuterio analogues of D_iH were not the same. This observation could not be correct for the cage process (eq 3 and 4). Subsequent to the (e^-, H^+, e^-) proposal Powell and Bruice demonstrated that the discrepancy between the product and kinetic deuterium isotope effects could be explained by isotope scrambling between the products and the reactants.[8c] These authors concluded that the reduction proceeds via a hydride-transfer process. The heterolytic mechanism has been further substantiated, however, in an even more recent report.[11]

Chipman suggested that during DHNA reductions a difference between the product and kinetic deuterium isotope effects could be used as a diagnostic tool to differentiate between a one-step and a two- (or more) step mechanism.[6g] The authors used a multistep homolytic mechanism to explain the results obtained from a study of the mechanism for the reduction of α,α,α-trifluoroacetophenone by *N*-propyl-1,4-dihydronicotinamide in aqueous acetonitrile. Subsequently these authors demonstrated that their original observations were due to the reversible formation of a nicotinamide hydrate and the addition of this hydrate to the ketone.[6h] Other evidence for a multistep homolytic mechanism in such reduction processes remained unexplained.[13]



Since we have reported that α-halo ketones are reduced with loss of halide by *N*-substituted-1,4-dihydronicotinamides via a free radical chain process,[3] and that the free radical chain reduction of α,α,α-trifluoroacetophenone (TFA), using triphenyltin hydride, proceeds via a ketyl intermediate, which does not expel halide,[4] it was of interest to investigate the reduction in the same solvent (acetonitrile) of both α,α,α-trifluoroacetophenone and the *N*-methylacridinium cation with the same series of substituted dihydronicotinamides used for the reductions of the α-halo ketones.

Discussion and Results

Reduction of α,α,α-Trifluoroacetophenone (TFA). The reduction of TFA was carried out in acetonitrile (61°) with the dihydronicotinamides (DHNAs) I–IV used to reduce the other α-halo ketones previously reported.[3] The sole product of reductions, using I–IV and an additional DHNA, V, was 1-phenyl-2,2,2-trifluoroethanol. The reductions were carried out to partial completion, and under the conditions used, all five of the reductants underwent reaction; see Table I. As expected the order of reactivity, V > IV > III > II > I, for these reductions was consistent with that found previously for the ketone reductions, but unlike the other halo ketones no loss of halide is observed. Cyclic voltammetry of the α-halo ketones in acetonitrile has been found to be irreversible even at scan rates (ν) >

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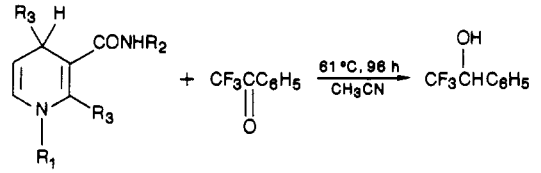
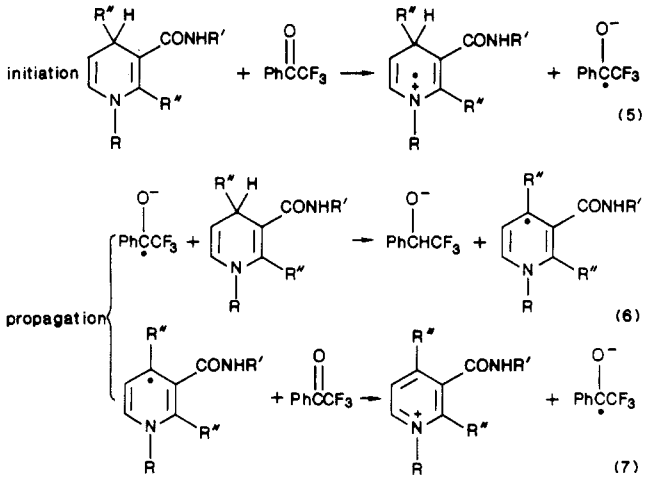
Table I. Reduction of α,α,α-Trifluoroacetophenone with 1,4-Dihydronicotinamides



reactn	DHNA[a]	conditions	product alcohol (%)
1	I		9.8 ± 0.7
2		DNB (4%)	1.0 ± 0.1
3		AIBN (3%)	42.4 ± 1.5
4	II		13.6 ± 0.6
5		DNB (4%)	1.4 ± 0.1
6		AIBN (3%)	50.1 ± 0.2
	III		21.7 ± 1.1
8		DNB (4%)	1.3 ± 0.5
9		AIBN (3%)	57.1 ± 2.2
10	IV		28.3 ± 2.6
11		DNB (4%)	10.8 ± 0.2
12		AIBN (3%)	69.1 ± 0.9
13	V		42.7 ± 1.5
14		DNB (4%)	12.8 ± 0.3
15		AIBN (3%)	82.3 ± 2.1

[a] Structures defined in eq 1.

Scheme I



1000 V/s, while the trifluoro ketone showed a reversible wave at $E_{1/2}$ = −1.69 vs Ag/AgClO$_4$ (ν > 1 V/s). The reversible wave is assigned to the reduction and reoxidation of the ketyl radical anion of TFA. The $E_{1/2}$ for the TFA was between that found for the irreversible half-wave reported for the monofluoro- and monochloroacetophenones,[3] and it can be argued qualitatively that the reduction of TFA is able to proceed by the electron-transfer process shown to be operative in the reduction of the other halo ketones. The rate of reduction by all five of the DHNAs could be inhibited by the addition of small amounts of *m*-dinitrobenzene (DNB) and initiated by the addition of α,α′-azobis(isobutyronitrile) (AIBN); see Table I. The initiation and inhibition studies clearly establish that the reductions of TFA in acetonitrile proceed by a free radical chain process, eq 6 and 7. As had been proposed before, the initiation step is an electron transfer from the DHNA (D_iH) to the halo ketone, eq 5 (Scheme I). The order of reactivity found for the DHNAs suggests that electron transfer in the propagation reaction between the trifluoro ketone and the dihydropyridyl radical (eq 7) is favored by electron-donating substituents. The increased ability of the dihydropyridyl to support a positive charge

Scheme II

$$D_iH + Ac^+ \xrightarrow{k_i} D_iH^{\bullet+} + Ac^\bullet \quad (8)$$

$$D_iH + Ac^\bullet \xrightarrow{k_1} D_i^\bullet + AcH \quad (9)$$

$$D_i^\bullet + Ac^+ \xrightarrow{k_2} D_i^+ + Ac^\bullet \quad (10)$$

$$2D_i^\bullet \xrightarrow{2k_3} P_1 \quad (11)$$

$$Ac^\bullet + D_i^\bullet \xrightarrow{k_4} P_2 \quad (12)$$

$$2Ac^\bullet \xrightarrow{2k_5} P_3 \quad (13)$$

is consistent with the proposed electron transfer.

The mechanism predicts that if (as is most likely) the rate-determining step in the propagation sequence is the hydrogen-atom transfer, eq 6, the kinetic isotope effect, k_H/k_D, for reduction by dihydronicotinamide-*4-d* would be the same as the product deuterium isotope effect, y_H/y_D. In the one case where the reduction of TFA was carried out with III in anhydrous acetonitrile, the kinetic and product isotope effects were the same.[7b,f]

Reduction of *N*-Methylacridinium Iodide (ACI). The reduction of ACI was carried out with the five DHPs used to reduce TFA. The reductions showed clean second-order kinetics in dry acetonitrile and could be followed to >97% reaction. The reactivities of this series of reductions showed the same order as was found for the homolytic reduction of TFA: V > IV > III > II > I; see Table II. Small amounts (1–6%) of water affected the linearity of the plots; however, at 10% water/90% acetonitrile linear second-order kinetics were observed throughout the entire reaction (>97% reaction). We have shown that the reduction of TFA in dry acetonitrile proceeds by a free radical chain sequence. If the reduction of ACI involves a change in mechanism, the second-order kinetics observed for the ACI reductions must be consistent with a radical chain process. A homolytic sequence that is analogous to that proposed for the TFA reductions can be proposed for the reduction of ACI, Scheme II (for abbreviations see eq 3 and 4).

The kinetic expression that can be derived for this radical chain process is dependent upon the termination step; see eq 14. Under conditions where only cross ter-

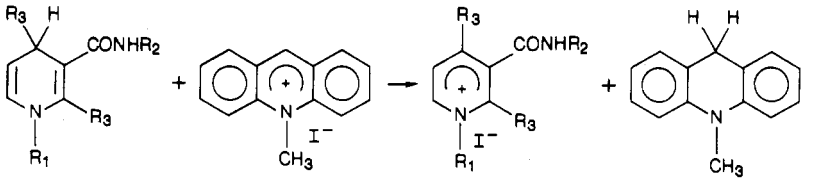
$$-\frac{d[Ac^+]}{dt} = R_i\left[\left(2 + \left(\frac{k_1k_2}{k_4k_i}\right)^{1/2}\right) + k_1\left(\frac{[D_iH]}{2k_ik_5[Ac^+]}\right)^{1/2} + k_2\left(\frac{[Ac^+]}{2k_3k_i[D_iH]}\right)^{1/2}\right] \quad (14)$$

where $R_i = k_i[D_iH][Ac^+]$

mination (eq 12) takes place, i.e. k_3 and $k_5 \ll k_4$, this rate expression requires the reaction to exhibit second-order kinetics, as is observed. In this case other criteria must be used to differentiate between the heterolytic and homolytic chain pathways. When the reductions were carried out in the presence of the inhibitors DNB, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[14] or di-*tert*-butyl nitroxide (DBNO), or with a low-temperature initiator di-*tert*-butyl peroxyoxylate (DBPO), no change in the second-order rate constant was observed; see Table II. The bimolecular rate of reduction by II, 71.7 ± 1.0 M^{-1} s^{-1}, (19

(14) A study of the oxidation of *N*-methylacridan has been reported with other quinone acceptors; however, the rate of reduction of DDQ would be >10^3 times slower than the formation of *N*-methylacridan and would not interfere with the kinetics of the reduction of ACI with added quinone (see Colter, A. K.; Saito, G.; Sharon, F. J. *Can. J. Chem.* **1977**, *55*, 2741.

Table II. Rate Constants for the Reduction of *N*-Methylacridinium Iodide by 1,4-Dihydronicotinamides (19 °C, Acetonitrile)



DHNA	$[D_iH]$	$[Ac^+]$	Additive	k_2, M^{-1} s^{-1}	$1/(A_0 - A_\infty)$
I	5×10^{-4}	5×10^{-4}		5.35 ± 0.05	0.60
	5×10^{-4}	5×10^{-4}	5% DNB	5.51 ± 0.17	0.62
	5×10^{-4}	5×10^{-4}	10% DBNO	5.56 ± 0.43	0.62
	5×10^{-4}	5×10^{-4}	20% DBNO	5.44 ± 0.29	0.63
	7.5×10^{-3}	5×10^{-4}		5.14 ± 0.05[a]	
	10^{-2}	5×10^{-4}		5.26 ± 0.02[a]	
	5×10^{-4}	5×10^{-4}	10% DBPO	5.88 ± 0.01	0.63
	5×10^{-4}	5×10^{-4}	20% DBPO	5.57 ± 0.06	0.63
			ave	5.44 ± 0.17	
II	5×10^{-4}	5×10^{-4}		73.5 ± 0.8	0.63
	5×10^{-3}	5×10^{-4}		71.7 ± 2.0[a]	
	5×10^{-4}	5×10^{-4}	5% DNB	69.4 ± 0.9	0.60
	5×10^{-4}	5×10^{-4}	10% DBNO	71.7 ± 1.4	0.64
	5×10^{-4}	5×10^{-4}	20% DBNO	72.2 ± 0.2	0.66
	5×10^{-4}	5×10^{-4}	10% DDQ	70.0 ± 1.0	0.63
	5×10^{-4}	5×10^{-4}	10% DBPO	73.1 ± 0.3	0.62
	5×10^{-4}	5×10^{-4}	20% DBPO	71.9 ± 0.3	0.62
			ave	71.7 ± 1.0	
III	5×10^{-4}	5×10^{-4}		316.2 ± 10.1	0.63
IV	5×10^{-4}	5×10^{-4}		467 ± 1.7	0.65
V	5×10^{-4}	5×10^{-4}		1640.5 ± 2.9	0.63

[a] Calculated from the pseudo-first-order rate constants.

°C) was in excellent agreement with the value reported in the literature, 79.9 ± 0.9 M^{-1} s^{-1} for the same reduction (30 °C).[8c] Since no initiation or inhibition was observed, it is doubtful that a chain reduction similar to that found for the TFA reductions was operative in the ACI reductions. Since the evidence for the proposed nonchain homolytic reduction has been shown to be doubtful,[8c] the heterolytic hydride-transfer mechanism is left as the most likely sequence of reactions leading to reduced acridan.

Conclusion

The model DHNAs used as biomimetic models for enzyme-controlled reductions by NADH appear to reduce TFA and ACI by different mechanisms. In dry acetonitrile the homolytic chain reduction of TFA was the product-controlling sequence, while under the same conditions ACI did not undergo homolytic chain reduction. The kinetics of ACI reduction are consistent with bimolecular hydride transfer.

Both solvent and choice of substrate can influence the mechanism of reduction, and enzymatic mechanistic conclusions reached from model studies must be viewed with reservation.

Experimental Section

Materials. Reagent acetonitrile (Caledon, HPLC grade) was purified by successive distillations over potassium permanganate and sodium carbonate. The distillate was treated with several drops of concentrated sulfuric acid and redistilled. Finally it was distilled again from calcium hydride.

The internal standard *p*-di-*tert*-butylbenzene (Aldrich), mp 78–79 °C (lit.[15] mp 80 °C) was recrystallized from ethanol and dried under vacuum over P_2O_5.

α,α'-Azobis(isobutyronitrile) (Aldrich) was recrystallized from ethanol–water and dried under vacuum over P_2O_5, mp 101–102 °C (lit.[14] mp 103 °C).

m-Dinitrobenzene (Fisher) was recrystallized from ethanol, mp 89 °C (lit.[15] mp 88–90 °C).

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone and di-*tert*-butyl nitroxide (Aldrich) were used as supplied.

Di-*tert*-butyl peroxyoxalate was prepared according to the literature procedure.[16]

N-Methylacridinium iodide was prepared by the procedure previously reported,[17] mp 228–230 °C dec (lit.[18] mp 215–222 °C dec).

α,α,α-Trifluoroacetophenone (Aldrich) was redistilled, bp 69–70 °C (30 mm) (lit.[15] bp 165–166 °C). The purity of the distillate was confirmed by GLC (see analytical procedure).

α-(Trifluoromethyl)benzyl alcohol was prepared by the procedure previously reported.[4]

1-Phenyl-1,4-dihydronicotinamide was prepared by an exchange reaction with 1-(2,4-dinitrophenyl)-3-carbamoylpyridinium chloride and aniline followed by reduction,[19] mp 100 °C dec (lit.[19] mp 100 °C dec): NMR ($CDCl_3$) δ 3.20 (m, 2 H), 4.90 (m, 1 H), 5.61 (s, 2 H), 6.32 (m, 1 H), 7.20 (m, 5 H), 7.51 (d, 1 H).

1-Benzyl-1,4-dihydronicotinamide was prepared according to the literature procedure,[20] mp 119–121 °C dec (lit.[20] mp 120–122 °C dec): NMR ($CDCl_3$) δ 3.05 (m, 2 H), 4.30 (s, 2 H), 4.72 (m, 1 H), 5.60 (s, 2 H), 5.86 (m, 1 H), 7.0 (d, 1 H), 7.25 (m, 5 H).

1-Propyl-1,4-dihydronicotinamide was prepared according to the literature procedure,[7e] mp 87 °C dec (lit.[7e] mp 86 °C dec): NMR ($CDCl_3$) δ 0.92 (t, 3 H), 1.61 (q, 2 H), 3.14 (m, 4 H), 4.76 (m, 1 H), 5.60 (s, 2 H), 5.75 (m, 1 H), 6.92 (d, 1 H).

N-[α-Methylbenzyl]-1-propyl-1,4-dihydronicotinamide was prepared by the literature procedure[7e] from α-methylbenzylamine (Aldrich) and nicotyl chloride hydrochloride followed by alkylation and reduction, mp 111 °C dec (lit.[7e] mp 110 °C dec): NMR ($CDCl_3$) δ 0.91 (t, 3 H), 1.55 (m, 5 H), 3.05 (t, 2 H), 3.15 (m, 2 H),

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4.70 (d, 1 H), 5.4 (s, 2 H), 5.75 (d, 1 H), 6.78 (d, 1 H), 7.30 (m, 5 H).

N-[α-Methylbenzyl]-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide was prepared from the α-methylbenzylamine (Aldrich) and the 2,4-dimethylnicotyl chloride hydrochloride followed by alkylation and reduction according to the literature procedure,[7a] mp 119–120 °C dec (lit.[7a] mp 119.5 °C dec): NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.05 (d, 3 H), 1.45 (m, 2 H), 1.55 (d, 3 H), 2.05 (s, 3 H), 3.1 (t, 2 H), 3.25 (d, 1 H), 4.75 (d, 1 H), 5.25 (m, 1 H), 5.65 (s, 1 H), 5.75 (d, 1 H), 7.30 (m, 5 H).

General Procedure for Determination of the Kinetics of Reduction of *N*-Methylacridinium Iodide. Acetonitrile solutions containing either 0.015 mmol of *N*-methylacridinium iodide or 0.3 mmol of 1,4-dihydronicotinamide were deoxygenated by bubbling argon through each solution protected from the atmosphere with a septum. After the solution was deoxygenated the concentration of each solution was readjusted by the syringe addition of a few drops of acetonitrile. An aliquot of the 1,4-dihydronicotinamide solution (10^{-3}–2×10^{-2}) and an aliquot of the acridinium salt (10^{-3}) (with or without additives) were transferred by syringe to the two compartments of the stop–flow apparatus. Upon mixing at 19 °C the reactions were monitored for >5 half-lives (10–3000 s); see Table II).

A Hi-Tech stop–flow accessory (Hi-Tech Scientific Limited) was used to mix the two solutions. As a general procedure the decrease in the concentration of *N*-methylacridinium iodide was monitored by observing the decrease in the intensity of absorption at 420 nm ($\epsilon = 3620$); a constant infinity value was observed after a period between 1 and 12 h.

The UV spectrometer used is a HP 8450A diode array spectrophotometer connected to a HP 7470A plotter and a HP 82901M flexible disc drive.

General Procedure for the Reduction of α,α,α-Trifluoroacetophenone. An aliquot solution of DHNA (0.10 M), the ketone (0.050 M), and the additive was placed in a Pyrex reaction ampule, degassed, and sealed under vacuum. The ampule was thermostated in the dark in an oil bath at 61 °C for 96 h. The ampule was opened and an aliquot solution of the internal standard (0.04 M) was added. The product mixture was analyzed by GLPC using a 20 ft × $^1/_4$ in. glass column packed with 5% OV-101 on Chromosorb WAW DMCS, 100/120 mesh.

GLPC analyses were carried out on an HP 5840A gas chromatograph interfaced to a HP 5840A integrator. The area ratios were converted to mole ratios for quantitative determinations by using standard calibration curves constructed from known mixtures.

Products were identified by a comparison of their retention times, GLPC–mass spectra, and GLPC–IR and ^1H NMR spectra with those of authentic samples. Duplicate experiments were run with each ketone.

Cyclic Voltammetry. Electrochemistry was performed on a Princeton Applied Research EG & G Parc Model 175 universal programmer wave form generator equipped with a Amel Model 551 potentiostat that provided feedback compensation for ohmic drop between the working and reference electrodes. Voltammograms were recorded on a Tektronix 2430 digital oscilloscope equipped with a Hewlett-Packard Thinkjet printer. Electrochemical measurements were carried out at 25 °C in an anhydrous acetonitrile solution containing 5×10^{-3} M TFA and 0.1 M tetrabutylammonium perchlorate on a hanging mercury drop electrode. The voltammograms show a wave ($E_{1/2} = -1.69$ V vs $Ag/AgClO_4$, 10^{-3} M) which is completely reversible at sweep rates >1 V/s. A second irreversible wave at more negative potential is observed.

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On the Relationship between Proximity and Reactivity. An ab Initio Study of the Flexibility of the OH• + CH_4 Hydrogen Abstraction Transition State and a Force-Field Model for the Transition States of Intramolecular Hydrogen Abstractions

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Ab initio transition structures with various distance and angular constraints have been located for the hydrogen abstraction from methane by the hydroxyl radical. Some exemplary results are as follows: (1) when the CO distance in the transition state is constrained to be 0.1 Å longer than optimum, the predicted activation energy increases by 1.2 kcal/mol, which corresponds to a sevenfold decrease in rate at 25 °C; (2) a 20° change in the C···H···O angle from the optimum increases the activation energy by only 1 kcal/mol, which would result in only a sixfold decrease in rate. A force field has been developed to model the transition states of hydrogen abstraction by alkoxy radicals. Allinger's MM2 force field has been modified to incorporate force constants for atoms involved in bonding changes. Relative activation energies are calculated for intramolecular hydrogen abstractions by a variety of alkoxy radicals. The results agree with the experimental data which are available, and predictions of relative rate constants have been made for these and related reactions. The results also show that there is no simple relationship between calculated reaction rates and distances between the reacting atoms in the starting materials. The force-field model and ab initio calculations show that the preference for six-membered transition states over seven-membered is a result of a large entropic preference for the six-membered transition structure.

Introduction

There has been intense interest in the relationship between the proximity of reacting centers and the rate of reaction.[1-6] This issue is of particular importance for understanding how enzymes catalyze bimolecular reactions with astonishing efficiency. Prompted by a recent stimulating review of the subject by Menger,[7] we have undertaken theoretical studies[8] which we believe will lead

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