ion than at oxygen of the phenoxide ion and a consequent greater solvation of the substituent. It is noteworthy that the slope of this plot is close to unity, indicating that the ρ values for phenols and anilines are essentially identical despite a difference of 12.7 pK units, corresponding to 17.4 kcal/mol, in the basicities of $PhNH^-$ and PhO^- ions in Me_2SO.

Extrapolations with Aniline Acidities. A plot of the pK_a's of toluene bearing 4-NO_2, 4-F_3CSO_2, 4-$PhCO_2$, 4-$PhSO_2$, and 4-CN groups versus the pK_a's of like-substituted anilines is roughly linear and was used to obtain an extrapolated pK_a of 42 for toluene.[21] This correlation is suspect since we now recognize that it requires SSAR effects for toluenes and anilines to be comparable. Nevertheless, a pK_a for toluene in Me_2SO near 42 has been supported by other extrapolations. The CN function is best suited for extrapolations because it is a powerful electron-withdrawing group with minimal steric demands. Acidities in the gas phase for CH_4, CH_3CN, and $CH_2(CN)_2$ are 409, 364, and 330 kcal/mol, respectively.[22] Introduction of one CN group into methane thus causes an acidity increase of about 33 pK_a units and introduction of the second a 25 unit further increase. The 25% smaller second increment, which can be attributed to a saturation effect, is likely to be attenuated in solution. Starting with the 20.5 pK_a unit (per *hydrogen*) difference in acidity between $CH_2(CN)_2$ (pK_a = 11.0) and CH_3CN (pK_a = 31.5 on a per hydrogen basis) and assuming a 20% saturation effect gives a pK_a of 56 for methane: $CH_2(CN)_2$ (11.0) $\xrightarrow{20.5}$ CH_3CN (31.5) $\xrightarrow{24.6}$ CH_4 (56.2). A similar extrapolation gives a pK_a of 43 for toluene: $PhCH(CN)_2$ (4.2) $\xrightarrow{18}$ $PhCH_2CN$ (22.2) $\xrightarrow{21.6}$ $PhCH_3$ (43.8 on a per hydrogen basis; assigned pK_a = 43).

An extrapolation from the pK_a of cyanamide to that of NH_3 with use of the same CN increment as that from CH_3CN to CH_4 gives a pK_a of 41.8 for NH_3: H_2NCN (16.95) $\xrightarrow{24.6}$ 41.8. A plot of the pK_a's of anilines in Me_2SO versus the pK_a's of anilinium ions in water is linear with a slope of 1.8 (Figure 4). Extrapolation to the pK_a of NH_3 from that of NH_4^+ ion in water (9.27) gives a pK_a about 39.5 for NH_3 in Me_2SO. This extrapolation assumes that this point will fall on the line, i.e., that the ratio of α-phenyl effects will be proportional to the ratio of ρ values. This is not unreasonable since both the α-Ph effect and ρ reflect the sensitivity of the equilibrium toward substituent effects, as shown by the linear plot for α-phenyl effects versus ρ for the families $PhCH_2NO_2$, $PhCH_2COCH_3$, $PhCH(CN)_2$, PhOH, $PhCH_2CN$, and $PhCH_2Ph$ (slope = 2.4).[23] The average of this and another extrapolation leads to an estimate of 41 ± 1 for the pK_a of ammonia in Me_2SO.

Experimental Section

Materials. The anilines were for the most part commercial samples. The purity (and identity) of each sample was confirmed by spectral analyses (NMR, IR), by chromatography (VPC, TLC), and by the appropriate physical constants (bp, mp). NMR spectra were recorded on a Hitachi Perkin-Elmer R20-B spectrometer and IR were recorded on a Beckman IR-5. The purity of liquid samples was assessed on an analytical Hewlett-Packard F and M Model 5752A gas chromatograph equipped with a thermoconductivity detector. These analyses were performed with a 0.25 in. × 10 ft aluminum column packed with 3% or 5% Carbowax 20 M on acid-washed Chromasorb W. The analyses by TLC were performed with Eastman Chromagram sheets, No. 13181, silver-gel with fluorescent indicator. Purified samples of 4-fluoro- and 2,4-difluoroanilines were gifts from N. H. Andersen.

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Communications to the Editor

Free-Radical Reduction Reactions of Chiral Dihydronicotinamides. Enantioselective Hydrogen Atom Transfer and Electron-Transfer Processes during the Reduction of Ketones

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We wish to report that the enantioselective reductions of α,-α,α-trifluoroacetophenone (TFA) by enantiomerically enriched DHNA **1** and **2** involve the enantioselective transfer of a hydrogen atom. Furthermore, the reduction of *d,l*-fenchone by **2** demonstrate enantioselective transfer of a single electron from the 4-hydropyridyl radical.

The reduction of TFA by five dihydronicotinamides (DHNA's) proceeds by a free-radical chain mechanism containing initiation and propagation steps involving single electron transfer (SET).[2] The ketyl intermediate in these reductions abstracts a hydrogen atom from the DHNA and forms a 4-hydropyridyl radical, which carries the chain by subsequent electron transfer to another molecule of TFA. Hydrolysis of the pyridinium alkoxide forms the alcohol, 1-phenyl-2,2,2-trifluoroethanol.

The enantioselective reduction of ketones by chiral 1,4-dihydropyridines (DHP's) in the presence of divalent metal ions (Mg^{2+} and Zn^{2+}) has been reported.[3-6] Metal ions were added to mimic the action of metal ions contained in NADH reductase enzymes. The metal ions catalyze the reactions and presumably help control the stereochemistry of reduction by the formation of a complex between the DHP and the ketone. Little detailed mechanistic investigation has been reported, i.e., intermediates involved, for these intermolecular biomimetic reductions; however, in the case of a covalently bonded intramolecular reduction of a benzoylformyl ester a transition state model for a hydride transfer process was proposed.[6b]

Chiral DHNA's (**1**, and **2**) used by Ohno[3a] react with TFA to

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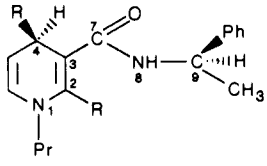
Table I. The Reduction of TFA by **1** and **2** (Acetonitrile, 61 °C)[a]

reaction reagent				product $PhCH(OH)CF_3$[b]		
		$[\alpha]^{20}_D$	additives (%)	yield (%)	$-\alpha^{20}_D$	ee (%)
1–2	**1**, (9*R*)-(−)	−173.2		28.3 ± 2.6	0.450	21.9 ± 0.2
3–4			DNB (4)	10.8 ± 0.2	0.240	21.0 ± 1.0
5–6			AIBN (3)	69.1 ± 0.9	0.751	22.1 ± 1.0
7–8	**2**, (4*R*,9*R*)-(−)	−172.3		42.7 ± 1.5	0.721	65.8 ± 1.8
9–10			DNB (4)	12.8 ± 0.3	0.229	66.2 ± 0.7
11–12			AIBN (3)	82.3 ± 2.1	1.377	68.2 ± 0.3

[a] Duplicate reactions, degassed ampules, 94 h; DHP:ketone (0.1 M:0.2 M). [b] $[\alpha]^{23}_D = +13.7$.[7]

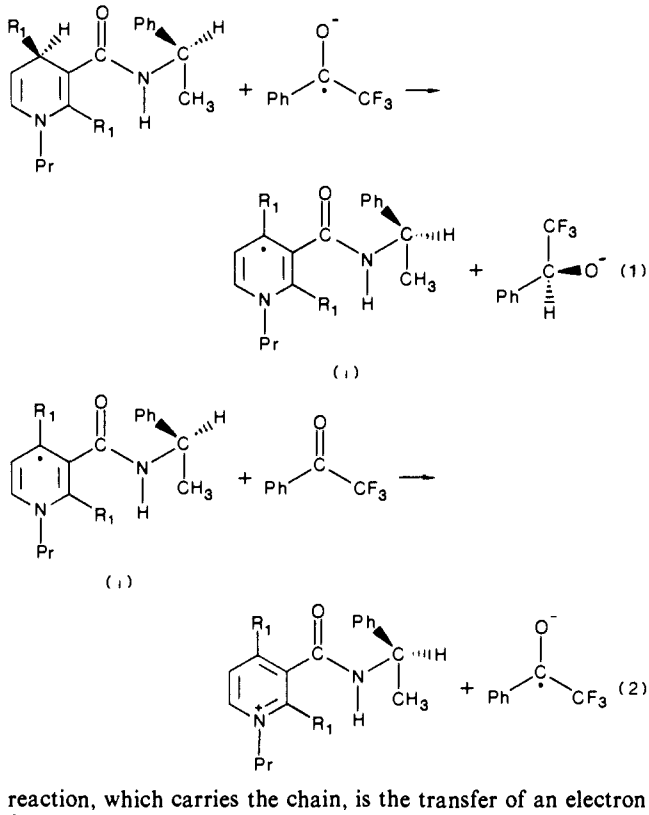
yield enantiomerically enriched (*S*)-(+)-1-phenyl-2,2,2-trifluoroethanol (see Table I). It has been reported[3a] that **2** yields



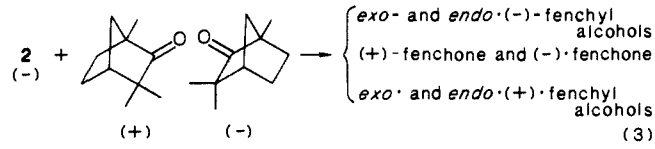
1, (9*R*), R = H
2, (4*R*, 9*R*), R = CH_3

the active alcohol, with and without added magnesium (70.3 and 63.1% ee, respectively), and that **1** gives only 16% enantiomeric selectivity with added magnesium.

The enantioselectivities we obtained agreed with those previously reported.[3a] The chain reduction was inhibited by the addition of an efficient electron acceptor *m*-dinitrobenzene (DNB, 4%) and initiated by AIBN (3%). Under all conditions (reactions 1–6 and 7–12) the enantiomeric excess with each DHNA remained the same. The uninitiated, the partially inhibited, and the initiated reactions all give alcohol with the same optical purity, albeit in different yields. It is reasonable to conclude that all of these reductions proceed by the same mechanism, a stereoselective free-radical chain reduction. The first propagation step is the transfer of a hydrogen atom from the chiral DHNA to the ketyl, eq 1. Although it has lost its stereocenter at C-4, the new radical i still maintains a stereocenter at C-9. The second propagation



reaction, which carries the chain, is the transfer of an electron from the chiral radical, i, to a ketone to form a new ketyl, eq 2. Since the electron donor is chiral, the possibility exists, if electron transfer is a contact phenomenon, that enantiomeric ketones will undergo enantioselective electron transfer. This process will only be observable if the radical intermediate retains asymmetry. This suggestion was tested by carrying out the partial reduction of (±)-*d*,*l*-fenchone (α = 0.000) with **2** (eq 3). Although the

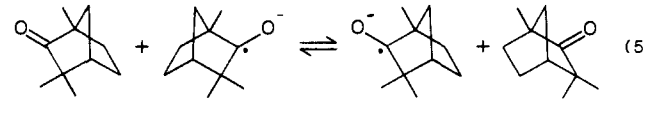


substrate was unreactive thermally, it could be initiated (6%, *tert*-butyl perbenzoate). The yield of each product was determined by using a combination of capillary GLPC, high resolution NMR (400 MHz) spectroscopy, NMR spectroscopy using a chiral shift reagent, and polarimetry on both the reisolated unreacted starting material and the isolated mixture of alcohols. GLPC analysis (50 m, 0.2 mm i.d.; carbowax 20 M fused quartz capillary column) of duplicate reaction mixtures which contained an internal standard (*p*-di-*tert*-butylbenzene) showed that the reaction had proceeded to 31.5 ± 3.2% completion and contained starting material (60.8 ± 4.0%) and both *endo*- and *exo*-fenchyl alcohol (28.1 ± 2.9 and 3.37 ± 0.34%, respectively). The unreacted starting material was reisolated (preparative GLPC), and its polarimetric rotation showed it to be 10.6% enriched in (*R*)-(−)-fenchone ($[\alpha]^{20}_D$ (C_2H_5OH) = −35.1°).[8] NMR determination ($CDCl_3$) using the tris[3-(heptafluoropropylhydroxymethylene)-(−)-camphorato]praseodymium(III) shift reagent confirmed the polarimetric results and showed a 10.0% ee for the recovered ketone.

Polarimetric analysis of the preanalyzed (GLPC) mixture of *endo*- and *exo*-alcohols allowed the determination of the enantiomeric excess for both epimers produced in the reduction. The optical purity calculated with eq 4 was 16.0% ee. The 10.6% ee

$$\%ee = (\alpha_{obsd} \times 100)/([\alpha]_{endo}\cdot[\%\ endo] + [\alpha]_{exo}\cdot[\%\ exo]) \quad (4)$$

found in the recovered starting material was a result of the preferential enantioselective reduction of (+)-fenchone to a mixture of *exo*- and *endo*-(−)-fenchyl alcohols. A control experiment was carried out that excluded the possibility of a dynamic equilibrium involving electron transfer between enantiomeric ketyls (eq 5).



If enantioselective hydrogen atom transfer had occurred preferentially with one of the chiral ketyls, then an enantioselective SET would appear to have taken place. However, in the proposed chain reduction mechanism the stereocenter of **2** at C-4 loses its asymmetry during hydrogen atom transfer. The chirality of the resultant radical i will be the same whether it was formed from **2** or from its (4*S*,9*R*)-(+)-epimer, and its SET reactions will show the same enantioselectivity. On the other hand, the selectivity for hydrogen atom transfer will be determined by the configuration at C-4.[4] When *d*,*l*-fenchone was reduced by using a (60/40)

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(8) The rotation of the ketone was measured by using an ethanol solution of 98% commercially available (Fluka) (*R*)-(−)-fenchone.

mixture of (4*R*,9*R*)-(−)- and (4*S*,9*R*)-(+)-epimers, the same enantioselective reduction takes place. Alcohol enriched in the (−)-epimers was formed in an endo/exo ratio of 8.5/1 and had an optical purity of 13.1% ee, while the recovered ketone was enriched in the (−)-epimer by 10.3% ee. Within experimental error, these results were identical with those obtained with the pure diastereoisomer.

To our knowledge, these results constitute the first experimental evidence for a free-radical chain reaction whose propagation step contains an enantioselective hydrogen atom transfer, while the enantioselective reduction of *d,l*-fenchone constitutes the first example of an enantioselective electron-transfer reaction.

Synthesis, Coloration, and Crystal Structure of the "Dibasic" Chromoacerand–Piperazine 1:1 Salt Complex

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In spite of the explosive development of host–guest complexes,[1] much less attention has been focused on so-called salt complexes[2] where anionic hosts and cationic guests interact complementarily or vice versa. The *saltex*[3] is distinct from the major complexes of ligands such as crowns,[4] cryptands,[5] spherands,[6] cavitands,[7] cyclophane onium salts,[8] cyclodextrins,[9] and ionophores[10] in the following respect. Both the host and guest components in the saltexes are real ions which are held together by coulombic attraction of the opposite charges, and they are generated by neutralization or proton-transfer reactions from their ionizable precursors, acids and bases, before or during *saltexation*.[3] The unique characters of the saltexes would be advantageous to host–guest complexing in more bulky systems involving secondary and tertiary amines. Here, we propose the class name *acerands*[11] for acidic ligands as saltex precursors.

"Dibasic" chromoacerand **2a** constructed by incorporating a benzoic acid unit into "monobasic" acerands **1**[12] provides a good

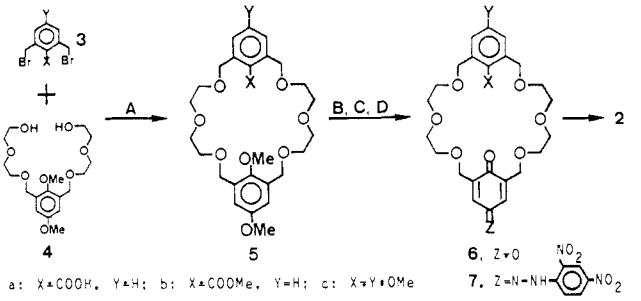

Figure 1. Synthetic scheme: (A) NaH, THF; (B) aqueous KOH, reflux; (C) $Ce(NH_4)_2(NO_3)_6$, $MeCN-H_2O$; (D) 2,4-dinitrophenylhydrazine, H_2SO_4, $EtOH-CH_2Cl_2$.

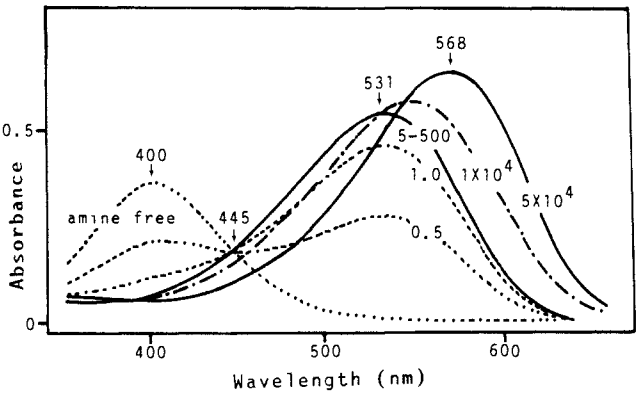

Figure 2. Visible spectra of **2a**–piperazine systems in $CHCl_3$. The numbers on the curves mean the molar ratio, piperazine:**2a**.

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