concentration only at amine concentrations >0.02 M in the pH increase experiments and >0.05 M in the pH decrease experiments (Figures 13 and 15, line c in Figure 18), (b) the buffer dilution plots for enolization (solid line) and dehydration (dashed line) intersect as shown in the inset to Figure 13a, (c) the enolization intercepts are more than 500-fold greater than can be accounted for by the general base catalyzed mechanism of eq 2 (Figure 11), (d) the enolization intercepts are about 10-fold greater than those determined for dehydration, and (e) the second-order rate constants for tertiary amine catalyzed keto–enol interconversion are more than 1000-fold greater than those for catalysis by oxygen bases of the same pK_a, too great a difference to be attributed to the enhanced ability of amines toward proton removal. We have proposed the nucleophilic addition–elimination mechanism of eq 18 to account for these experimental observations.

Registry No. HO^-, 14280-30-9; H_2O, 7732-18-5; PO_4^{3-}, 14265-44-2; HPO_4^{2-}, 14066-19-4; CO_3^{2-}, 3812-32-6; HCO_3^-, 71-52-3; $H_2PO_4^-$, 14066-20-7; oxaloacetic acid, 328-42-7; 2-(diisopropylamino)ethanol, 96-80-0; quinuclidine, 100-76-5; triethylamine, 121-44-8; trimethylamine, 75-50-3; 3-quinuclidinol, 1619-34-7; *N,N,N',N'*-tetramethylethylenediamine, 110-18-9; 1,4-diazabicyclo[2.2.2]octane, 280-57-9; 3-chloroquinuclidine, 42332-45-6; *N,N,N',N'*-tetramethylethylenediamine·H^+, 71889-99-1; *tert*-butyl 7-oxabicyclo[4.1.0]hepta-2,4-diene-3-carboxylate, 57078-21-4.

Directionality of Proton Transfer in Solution. Three Systems of Known Angularity

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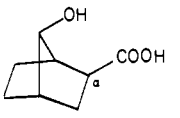
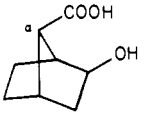
Abstract: Three compounds were synthesized each possessing rigid carbon frameworks that hold an oxygen base near a mobile C–H proton in well-defined angular and distance relationships; 2-iodo-4-hydroxyindan, *endo*-5-hydroxybicyclo[2.2.1]heptan-2-one, and *endo*-2-hydroxy-*exo*-6-bromomethyl[2.2.1]heptane. Effective proton transfer was detected with the second and third compounds but not the first. The data suggest that C-to-O proton transfer with severely bent O/H/C angles (106°) is permissible if the O–H distance is less than the sum of the van der Waals radii. "Long distance" catalysis at active sites of enzymes appears unlikely.

"Directionality" refers to the relationship between reactivity and spatial disposition. For example, the directionality of S_N2 substitutions is such that a linear Y/C/X geometry leads to reaction whereas an acute Y/C/X angle does not. Surprisingly, little is known about the directionality of organic reactions in solution. Thus, no information exists on how S_N2 reactivity depends on nucleophile trajectory within the domain of obtuse Y/C/X angles. Information of this kind is required to fully characterize organic pathways and to interpret structural data on enzymes. How can one evaluate a particular arrangement of catalytic groups surrounding a substrate at an active site without first understanding the connection between reactivity and alignment?

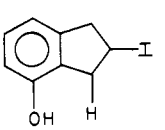
Theoretical methods provide one means for dealing with the directionality problem. For example, Stone and Erskine[1] used an intermolecular SCF perturbation theory to examine nucleophilic attack on carbonyl compounds. Energies were calculated as a function of attack angle and approach distance. Despite the considerable merit of such calculations, it must be emphasized (as do Stone and Erskine) that the results pertain only to isolated reactants and that reactants surrounded by solvent could behave quite differently. Nor does the widely quoted solid-state method of Dunitz[2] provide the necessary information. A series of X-ray structures may give an optimum trajectory, but they tell nothing about *other* concurrent trajectories and how they compare with the optimum. Collectively, an array of non-optimal geometries could well dominate a reaction pathway (similar to intermolecular hydrogen bonding where greater than half the population can deviate by 20° or more from the most stable linear structure[3]).

We recently studied the directionality of lactonization reactions with rigid hydroxy acids.[4] Compounds were constructed for which the HO/C=O/C_α angles differed by as much as 10° while other factors (such as the HO/C=O distances and ring strain in the lactones) remained constant. It was found that lactonization rates

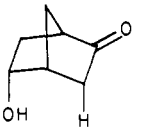




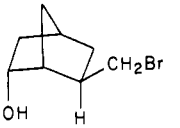
do *not* depend on the angularity differences. Carbonyl additions have, therefore, a "reaction window" of at least 10° (and perhaps much larger). In the present article, we continue the approach of examining reactive functionalities held in space at well-defined angles and distances by rigid carbon frameworks. Three compounds were synthesized each bearing an oxygen in proximity to a mobile C–H proton. The question arises as to whether or not the proton can effectively transfer from carbon to anionic oxygen in the course of an E2 elimination with compounds **1** and **3** or an enolization with compound **2**. The answer to this question



1



2



3

was of interest because proton transfer is fundamental to a host of organic and biochemical processes, because the directionality of proton transfer is unknown, and because the O^-/H/C angles in the three compounds are severely bent.

(1) Stone, A. J.; Erskine, R. W. *J. Am. Chem. Soc.* **1980**, *102*, 7185.
(2) Dunitz, J. D. "X-ray Analysis and the Structure of Organic Molecules"; Cornell University Press: Ithaca, N.Y., 1979.
(3) Jorgensen, W. L.; Ibrahim, M. *J. Am. Chem. Soc.* **1980**, *102*, 3309.
(4) Menger, F. M.; Glass, L. E. *J. Am. Chem. Soc.* **1980**, *102*, 5404.

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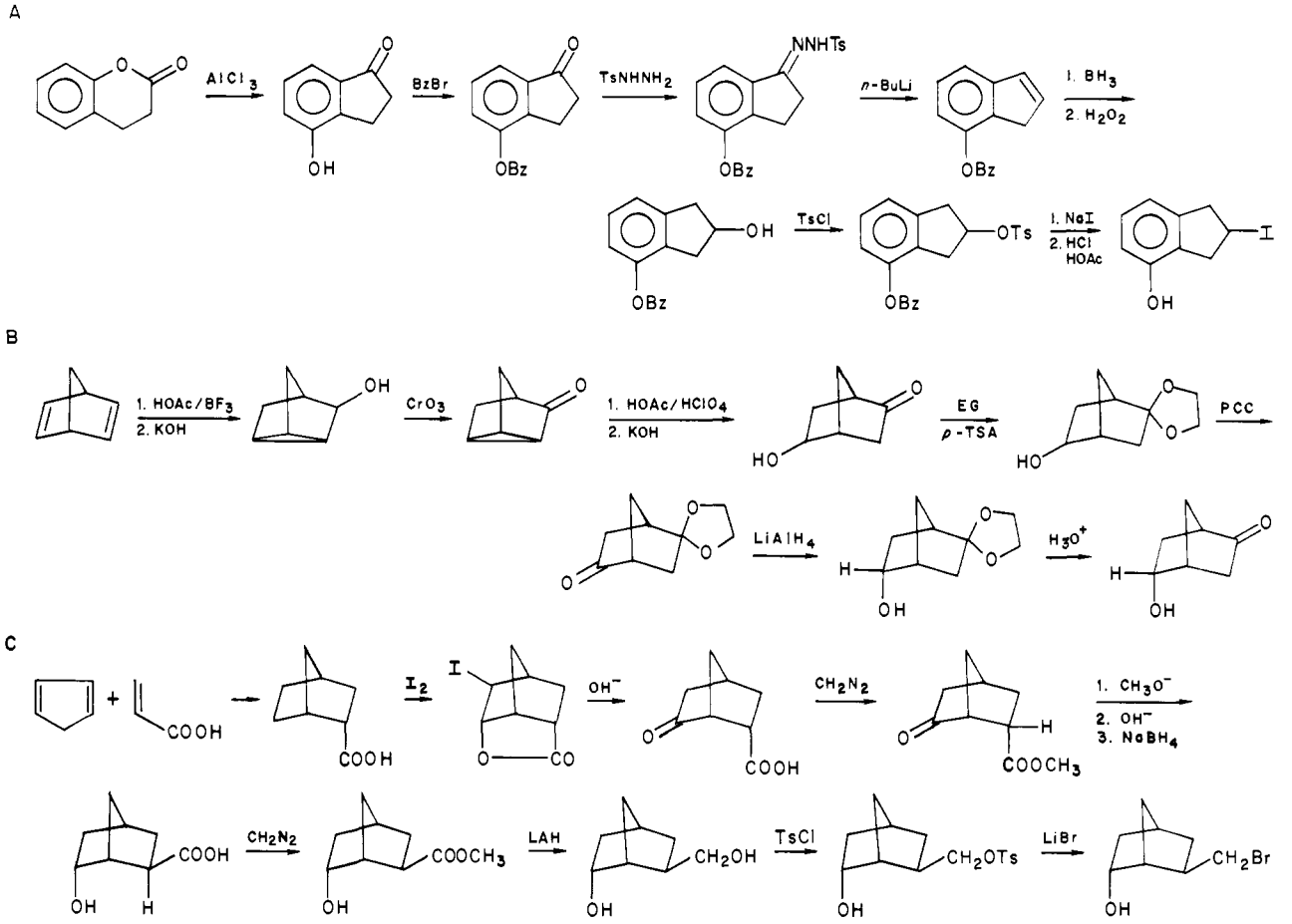
Scheme I



Experimental Section

All NMR spectra were recorded on a Varian EM-390 spectrometer. Mass spectra and UV work were performed on a Finnigan GC-MS Model 4000 and a Cary 14 spectrophotometer, respectively. Chromatographic separations were carried out with a size 25 glass column packed with 40–63-μm particle size LiChroprep Si60 (Merck) and operated under a pressure of about 45 psi.

The synthesis of 2-iodo-4-hydroxyindan (**1**), *endo*-5-hydroxybicyclo-[2.2.1]heptan-2-one (**2**), and *endo*-2-hydroxy-*exo*-6-(bromomethyl)bicyclo[2.2.1]heptane (**3**) are shown in Scheme I. Specific details follow. Spectral data were always consistent with the cited product.

A, 4-Benzyloxyindanone. Dihydrocoumarin (Aldrich) was converted into 4-hydroxyindanone (60% yield) by fusion with $AlCl_3$ according to the procedure of Bruce et al.[5] A solution of 7.0 g (0.047 mol) of 4-hydroxyindanone and 8.1 g (0.047 mol) of benzyl bromide in 250 mL of acetone over 6.8 g (0.049 mol) of potassium carbonate was heated under reflux for 4 h. The solvent was removed leaving a residue which was extracted with ether; evaporation of the ether gave a quantitative yield of product which, after recrystallization from hexane, melted at 66–67 °C. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.61; H, 5.99.

4-Benzyloxyindanone Tosylhydrozone. Following the procedure of Bose and Steinberg,[6] we added Aldrich *p*-toluenesulfonyl hydrazide (6.3 g, 0.034 mol) and three drops of concentrated sulfuric acid to a solution of 4-benzyloxyindanone (8.0 g, 0.034 mol) in 500 mol of absolute methanol and refluxed for 3 h under nitrogen. Solvent was then largely removed with the aid of a rotary evaporator; material which crystallized from the remaining solvent was collected by filtration and dried to give the tosylhydrazone with a melting point of 158–159 °C (methanol) in 91% yield. Anal. Calcd for $C_{23}H_{22}N_2O_3S$: C, 67.95; H, 5.46; N, 6.89. Found: C, 67.34; H, 5.48; N, 6.76.

4-Benzyloxyindene. After a solution of 8.5 g (0.021 mol) of 4-benzyloxyindanone tosylhydrazone in 250 mL of dry tetrahydrofuran was cooled to 0–5 °C, it was mixed with 40 mL of 1.6 M *n*-butyllithium in hexane (Aldrich), stirred at room temperature for 48 h, cooled to 0 °C, diluted with ice water, acidified with dilute hydrochloric acid, and extracted several times with ether. The organic layers were combined, washed successively with 10% aqueous sodium bicarbonate and water saturated with sodium chloride, and dried over anhydrous sodium sulfate. The solvent was removed and the residue chromatographed using hexane as the eluant to give the desired indene as a pale yellow oil in 70% yield. Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.41; H, 6.59.

We were not successful in synthesizing 4-benzyloxyindene by reducing 4-benzyloxyindanone to the alcohol and then dehydrating the alcohol. Polymerization during a variety of dehydration procedures precluded good yields of olefin.

4-Benzyloxyindan-2-ol. A dry flask equipped with a thermometer, reflux condenser, and septum was flushed with dry nitrogen and maintained under positive nitrogen pressure. The flask was charged with 2.2 g (0.010 mol) of 4-benzyloxyindene and 10 mL of dry tetrahydrofuran and then cooled in ice. Hydroboration was achieved by dropwise addition of 3.6 mL of Aldrich borane–methyl sulfide complex (2 M in tetrahydrofuran) followed by 3 h of stirring at room temperature. Ethanol (6 mL) and 3 N aqueous sodium hydroxide (2.2 mL) were added, the mixture cooled to 0–5 °C, and hydrogen peroxide (2.2 mL of 30% aqueous solution) added at such a rate that the reaction mixture warmed to about 25 °C. After 1 h of refluxing, the reaction mixture was cooled and poured into 25 mL of ice water. The product was extracted into ether (2 × 25 mL) and obtained as a clear oil upon removal of the ether. Yields of unpurified but spectrally satisfactory material were almost quantitative. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.92; H, 6.73.

4-Benzyl-2-hydroxyoxyindyl Tosylate, 4-Benzyloxyindan-2-ol was tosylated following standard procedures.[7] The tosylate was obtained as a yellow oil which was not further purified.

2-Iodo-4-benzyloxyindan. 4-Benzyl-2-hydroxyoxyindyl tosylate (2.8 g, 7.1 mmol) was dissolved in 50 mL of acetone containing 3.4 g of sodium iodide. The mixture was boiled under reflux overnight,[8] cooled,

(5) Bruce, D. B.; Sorrie, A. J. S.; Thomson, R. H. *J. Chem. Soc.* **1953**, 2403.
(6) Bose, A. K.; Steinberg, N. G. *Synthesis* **1970**, 595.
(7) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. I, p 1180.
(8) Gibson, T. W.; Erman, W. F. *J. Am. Chem. Soc.* **1969**, *91*, 4771.

and filtered. Solvent was removed from the resulting filtrate under reduced pressure leaving a residue which was dissolved in ether and then washed with 5% aqueous sodium thiosulfate, water, and saturated aqueous sodium chloride. The ether was dried over sodium sulfate and stripped to give crude product (mp 66–68 °C) in 85% yield. No attempt was made to purify the material.

2-Iodo-4-Hydroxyindan (1), 2-Iodo-4-benzyloxyindan (0.60 g, 1.7 mmol) was dissolved in a mixture of glacial acetic acid (15 mL) and concentrated hydrochloric acid (5 mL). The solution was stirred at 70° for 30 min (similar to a literature procedure[9]) and then poured onto ice and extracted with ether repeatedly. The ether was washed with water, dried, and evaporated. The residue was subjected to medium pressure liquid chromatography with hexane–chloroform as the eluant. The product was obtained as a white solid in 60% yield. Further purification was affected by means of sublimation to give white crystals (mp 105–106 °C). Anal. Calcd for C_9H_9IO: C, 41.56; H, 3.49. Found: C, 41.61; H, 3.51. TLC R_f values (precoated sheets, Silica Gel 60 F_{254}, EM reagents): 0.33 (chloroform); 0.77 (4:1 chloroform–ether). IR (Nujol) 3300 (b), 1630 (w), 1590 (s), 1420 (s), 1300 (vs), 1280 (m), 1255 (s), 1210 (vs), 990 cm^{-1} (s). MS 260 (32%), 133 (100%), 115 (13%), 105 (57%), 77 (38%). ^1H NMR (acetone-d_6) δ 3.46 (m, 4 H), 4.93 (m, 1 H), 6,8–7.4 (m, 3 H), 8.5 (s, 1 H).

2-Iodoindan, 2-Hydroxyindan (Aldrich) was converted into the tosylate using standard procedures.[7] The tosylate was in turn converted into the iodide in 80% yield (based on 2-hydroxyindan) by using the same method as described above for compound **1**; mp 51–52 °C (lit.[10] mp 52–53 °C).

B, *exo*-5-Hydroxybicyclo[2,2,1]heptan-2-one, *exo*-5-Acetoxybicyclo[2.2.1]heptan-2-one was prepared from norbornadiene via nortricyclanone according to the procedures of Meinwald and Crandall.[11] Basic hydrolysis of the acetate gave *exo*-5-hydroxybicyclo[2.2.1]heptan-2-one which was ketalized directly, as described below, without careful purification.

exo-5-Hydroxy-2-(ethylenedioxy)bicyclo[2,2,]heptane, The ketalization procedure was based on a literature method.[12] Thus, *exo*-5-hydroxybicyclo[2.2.1]heptan-2-one (5.0 g, 0.040 mol), ethylene glycol (25 mL), and *p*-toluenesulfonic acid (0.50 g) were boiled under reflux for 24 h with 130 mL of benzene in an apparatus equipped with a Dean-Stark trap. The reaction mixture was then washed with saturated aqueous bicarbonate and dried over magnesium sulfate. Removal of the solvent left an oil with no C=O band in the IR and a single spot on a TLC plate.

2-(Ethylenedioxy)bicyclo[2,2,1]heptan-5-one, The hydroxyl of the previous compound was oxidized to a carbonyl by means of pyridinium chlorochromate.[13] Pyridine (11.2 g, distilled over barium oxide) was added to methylene chloride (88 mL, purified by shaking with concentrated sulfuric acid, washing with brine, drying over calcium chloride, distilling, and storing over molecule sieve) in a stirred flask purged with nitrogen. Chromium trioxide (7.0 g, dried in oven at 140 °C) and *exo*-5-hydroxy-2-(ethylenedioxy)bicyclo[2.2.1]heptane (2.0 g, 0.012 mol) were added in one portion each and the mixture stirred for 15 min at room temperature. The solvent was decanted and combined with an ether extract of the residue. This was washed three times with 5% sodium hydroxide and once with 5% hydrochloric acid, 5% aqueous bicarbonate, and brine. Removal of the dried solvent left a yellow oil with a strong carbonyl band and no hydroxyl peak in the IR. It was used in the last step of the sequence without purification.

***endo*-5-Hydroxybicyclo[2,2,1]heptan-2-one (2),** Lithium aluminum hydride (0.040 g, 1.0 mmol) was added to 20 mL of anhydrous tetrahydrofuran. 2-(Ethylenedioxy)bicyclo[2.2.1]heptan-5-one (0.34 g, 2.0 mmol) in 20 mL of tetrahydrofuran was added dropwise to maintain a gentle reflux. The mixture was subjected to an additional 5 h of reflux after which it was cooled, quenched with ethanol, and reduced in volume on a rotary evaporator. The residue was extracted with an ether/water mixture followed by washing, drying, and stripping of the ether layer. The resulting oil, which solidified on cooling, was recrystallized from hexane to give white needles of hydroxy ketal in 50% yield with mp 65–66 °C and one spot on a TLC plate. The product was next subjected to acid hydrolysis: hydroxy ketal, 100 mg; concentrated hydrochloric acid, 0.040 mL; acetone, 1.5 mL; water, 0.070 mL. The procedure involved 4 h of refluxing, solvent removal, ether extraction, bicarbonate and water washes, drying over $MgSO_4$, and ether stripping to give crude *endo*-5-hydroxybicyclo[2.2.1]heptan-2-one. This was washed with hexane and sublimed to give white needles, mp 156–158.5 °C. Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.43; H, 8.05. M^+ 126; NMR (D_2O) δ 1.2 (m, 1 H), 1.8 (b s, 2 H), 2.2–2.5 (m, 3 H), 2.5–2.8 (m, 2 H), 4.2 (m, 1 H).

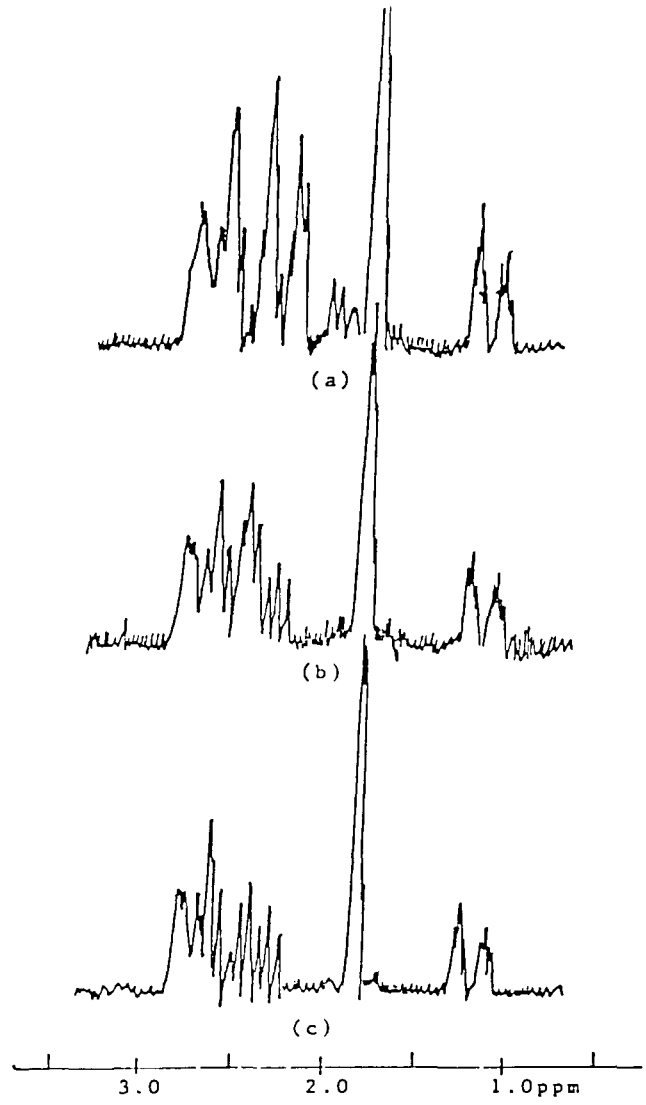


Figure 1. Proton NMR spectra of *endo*-5-hydroxybicyclo[2.2.1]heptan-2-one: (a) initial; (b) monodeuterated; (c) dideuterated. EM-390 spectrometer.

***endo*-5-Methoxybicyclo[2,2,1]heptan-2-one,** The hydroxy ketal synthesized above (0.50 g, 2.9 mmol) was stirred with dry dimethylformamide (1.5-mL) in a three-necked flask equipped with nitrogen inlet, condenser, and thermometer. Methyl iodide (0.20 mL) was added to the flask and the system cooled to −5 °C. Sodium hydride (0.14 g of 60% dispersion in mineral oil, 3,5 mmol) was added over a period of 10 min during which the temperature rose to 35 °C. After the reaction mixture was permitted to cool down again, about 0.1 mL of additional methyl iodide was added and stirring continued for 2 h more at room temperature. Acidification with 10% hydrochloric acid, extraction with ether, washing of the ether with water, treatment with magnesium sulfate and Norit, and removal of the ether gave a yellowish oil. This was purified on medium-pressure liquid-chromatography apparatus with chloroform: hexane (1:1) as the eluant. The product, *endo*-5-methoxybicyclo-[2.2.1]heptan-2-one, was obtained as a straw-colored oil. Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.31; H, 8.75. M^+ 140; ^1H NMR (D_2O) δ 3.1 (s, 3 H).

***endo*-6-Carbomethoxybicyclo[2,2,1]heptan-2-one,** This intermediate in the third pathway of Figure 1 was prepared from *endo*-2-carboxybicyclo[2.2.1]hept-5-ene which in turn was prepared by a Diels–Alder reaction.[14] The procedure followed closely that used by Nakazaki et al.[15]

(9) Dreyer, D. L. *J. Org. Chem.* **1970**, *35*, 2294.
(10) Bowman, R. M.; McCullough, J. J.; Swenton, J. S. *Can. J. Chem.* **1969**, *47*, 4503.
(11) Meinwald, J.; Crandall, J. K. *J. Am. Chem. Soc.* **1966**, *88*, 1292.
(12) Brown, J. J.; Lenhard, R. H.; Bernstein, S. *J. Am. Chem. Soc.* **1964**, *86*, 2183.
(13) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.
(14) Alder, K.; Stein, G. *Ann.* **1934**, *514*, 185.
(15) Nakazaki, M.; Naemura, K.; Kondo, Y. *J. Org. Chem.* **1976**, *41*, 1229.

***endo*-2-Hydroxy-*exo*-6-(carbomethoxy)bicyclo[2,2,1]heptane.** Epimerization of *endo*-6-(carbomethoxy)bicyclo[2.2.1]heptan-2-one in base, ester saponification, and borohydride reduction of the ketone were carried out according to Beckmann et al.[16] The resulting *endo*-2-hydroxy-*exo*-6-carboxybicyclo[2.2.1]heptane was converted into the methyl ester with Aldrich *N*-[(methylnitrosoamino)methyl]benzamide and a procedure based on the work of Sekiya et al.[17] The product was purified by medium-pressure liquid chromatography with 40% methanol in chloroform as the eluant. Fischer et al. prepared this compound by another route.[18]

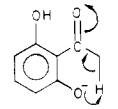
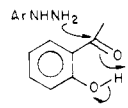
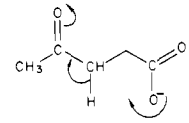
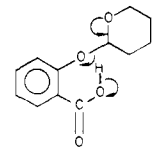
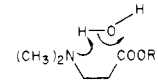
***endo*-2-Hydroxy-*exo*-6-(tosyloxymethyl)bicyclo[2,2,1]heptane.** Lithium aluminum hydride (3.2 g, 0.084 mol) in anhydrous ethyl ether (50 mL) was added slowly with stirring to a cooled (0 °C) solution of *endo*-2-hydroxy-*exo*-6-(carbomethoxy)bicyclo[2.2.1]heptane (6.5 g, 0.038 mol) in anhydrous tetrahydrofuran (150 mL) under a blanket of nitrogen. After the addition was complete, the reaction mixture was brought to reflux and left in this state overnight. When 8 mL of 4% aqueous sodium hydroxide was added to the cooled (25 °C) reaction mixture, aluminum hydroxide precipitated which was removed by filtration. The filtrate was stripped under reduced pressure, leaving the diol product which was treated directly with 1 equiv of *p*-toluenesulfonyl chloride in 15 mL of dried pyridine. The reaction mixture was stirred for 2 days and then poured into ice water. An ether extract of the water was washed with 10% hydrochloric acid until no pyridine was evident by NMR. The ether was removed and the residue chromatographed on silica with chloroform as the eluant. The ditosylate eluted first as a minor component. The desired monotosylate, an oil, eluted as the major component (41% yield for the two steps). Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.78; H, 6.80; S, 10.82. Found: C, 60.51, H, 6.83; S, 10.65. M^+ 296; ^1H NMR ($CDCl_3$) δ 0.65–2.9 (13 H), 3.6–4.0 (m, 2 H), 4.1–414 (m, 1 H), 7.2–8.0 (AA'BB', 4 H); ^{13}C NMR ($CDCl_3$) δ 21.60, 31.01, 34.03, 34.53, 36.62, 37.07, 38.05, 71.92, 73.51, 127.8, 129.9, 133.2, 144.8; IR (film) 3500, 1450, 1360, 1195, 1180, 1100, 950 cm^{-1}.

***endo*-2-Hydroxy-*exo*-6-(bromomethyl)bicyclo[2,2,1]heptane (3).** This compound was prepared in 61% yield from the corresponding tosylate in an acetone solution of lithium bromide according to a procedure published by Fischer et al.[18] The latter prepared the compound **3** by a somewhat different route to obtain a material with a melting pont of 32–33 °C. Our material, on the other hand, was isolated as a colorless oil after medium-pressure liquid chromatography. Owing to the existance of this discrepancy and to the fact that compound **3** was a final synthetic objective on which experiments were to be performed, we characterized the material as one would with a new compound. A small amount of impurity (≤5%) was evident from the spectra, but there was no question as to the identity of the major component. Nor was there any indication that the small amount of impurity affected our results described in the next section. Anal. Calcd for $C_8H_{13}BrO$: C, 46.85; H, 6.39; Br, 38.97. Found: C, 48.07; H, 6.37; Br, 37.60. ^1H NMR ($CDCl_3$) δ 0.7–3.9 (10 H), 3,1–3.6 (m, 2 H), 4.1–4.6 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 34.4, 35.0, 37.7, 37.8, 37.9, 38.7, 46.9, 72.1; IR (film) 3180, 1450, 1220, 1090, 1050 cm^{-1}.

Results and Discussion

Modern investigators of proton-transfer reactions have concerned themselves with topics such as tunneling, the significance of Brönsted exponents, gas-phase behavior, isotope effects, the influence of micelles and neighboring groups, potential energy surfaces, and heterogeneous systems. Many of these subjects are discussed in two books, "Proton Transfer Reactions" and "Transition States of Biochemical Processes".[19,20] Amidst this wealth of information, one finds little on a particularly important aspect of proton transfer: its geometry. The tendency has been to assume linear transition states for intermolecular proton transfers. For example, it is stated that "deviations from linearity for most intermolecular program transfers are probably not very great".[21] Recent ab initio calculations on proton-transfer energetics utilize linear geometries exclusively.[22] A case has been made that linear relationships are a necessity for facile proton transfer.[23] This predilection for linearity dates back decades. Thus, the Westheimer analysis of primary hydrogen isotope effects[24] depends on the transition state being linear. Traditional hydrogen bonding theory has also influenced our preception of proton transfer. Since intermolecular hydrogen bonds are often regarded as linear,[25,26] and since hydrogen bonds may lie on the reaction coordinate for proton transfer,[27,28] it has been presumed that the transition states for intermolecular proton transfer are likewise linear. Linearity in hydrogen bonding is, however, by no means a stringent requirement,[3] and to the authors' knowledge there exists no convincing evidence demanding it for proton transfer. The fact of the matter is that the geometry of proton transfer has never been adequately defined.

Table I, Intramolecular Proton Transfers and Effective Molarities[a]

reaction	EM	reaction	EM
	0.025		0.1
	0.1		6500
	>20		

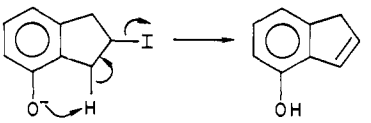
[a] Data taken from ref 29.

The literature contains, of course, many examples of intramolecular proton transfers which presumably involve nonlinear transition states; some of these are given in Table I along with their so-called "effective molarities" (EM).[29] EM values are calculated from the first-order rate constant for an intramolecular reaction divided by the second-order rate constant for the corresponding intermolecular process. Table I merits a few comments. (a) The efficiency of intramolecular reactions, as judged by their EM values, varies widely for reasons that are not well understood. Small EM's can be in principle arise when "loose" transition states prevail.[30] But there is no simple way of predicting whether a given reaction should have a "loose" or "tight" transition state. As seen from Table I, general acid/general base-catalyzed reactions display *both* loose and tight transition states (i.e., low and high EM values). At present we do not know why this is nor what role directionality plays in determining EM values. (b) The transition states for proton transfer such as shown in Table I are "bent" provided, of course, that solvent molecules do not intervene. Since solvent bridging has seldom been proved,[31] nonlinear transition states are generally accepted for intramolecular proton transfers. Nonlinear trajectories should, therefore, contribute to intermolecular processes, literature assertions not to the contrary. (c) Most of the intramolecular reactions studied in the past utilize flexible molecules, thereby making it difficult to specify the reaction trajectory, In order to examine directionality unambiguously, one requires rigid systems in which a basic atom is fixed in space relative to a mobile proton. Such is the case with compounds **1**, **2**, and **3** mentioned in the introduction. We will now discuss the properties of each.

A. 2-Iodo-4-hydroxyindan. The central question here is whether or not the oxygen anion of 2-iodo-4-hydroxyindan can participate

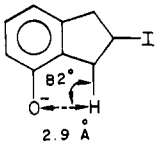
(16) Beckmann, S.; Eder, G.; Geiger, H. *Chem. Ber.* **1969**, *102*, 815.
(17) Sekiya, M.; Ohashi, Y.; Terao, Y.; Ito, K. *Chem. Pharm. Bull.* **1976**, *24*, 369.
(18) Fischer, W.; Grob, C. A.; von Sprecher, G.; Waldner, A. *Helv. Chim. Acta* **1980**, *63*, 816.
(19) Caldin, E. F.; Gold, V. Eds. "Proton-Transfer Reactions"; Wiley: New York, 1975.
(20) Gandour, R. D.; Schowen, R. L., Eds. "Transition States of Biochemical Processes"; Plenum: New York, 1978.
(21) Reference 20, p 171.
(22) Kollman, P. A.; Hayes, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 2955.
(23) Gandour, R. D. *Tetrahedron Lett.* **1974**, 295.
(24) Westheimer, F. H. *Chem. Rev.* **1961**, *61*, 265.
(25) Adam, W.; Grimison, A.; Hoffmann, R.; Zuazaga de Ortiz, C. *J. Am. Chem. Soc.* **1968**, *90*, 1509.
(26) Jones, R. E.; Templeton, D. H. *Acta Crystallogr.* **1958**, *11*, 484.
(27) Strohbusch, F.; Marshall, D. B.; Eyring, E. M. *J. Phys. Chem.* **1978**, *82*, 2447.
(28) Scott, R.; Vinogradov, S. *J. Phys. Chem.* **1969**, *73*, 1890.
(29) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.
(30) Page, M. I. *Chem. Soc. Rev.* **1973**, *2*, 295.
(31) For examples of solvent involvement see: Grunwald, E.; Meiboom, S. *J. Am. Chem. Soc.* **1963**, *85*, 2047.

in an intramolecular base-catalyzed elimination,



(1)

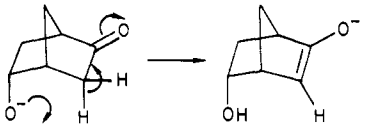
An oxygen anion is held beside the reactive proton at a distance of 2.9 Å (somewhat longer than the sum of the van der Waals radii[32]) and at an acute $O^-/H/C$ angle of 82° as judged from Dreiding models;



Since indan systems prossess only a minor degree of torsional freedom, the geometric parameters cannot fluctuate significantly from those cited. Presumably the removable proton is the one cis to the iodine,[33] but this was not a point of major concern, The H/I relationship should be the *same* for both the intramolecular-catalyzed elimination and its bimolecular counterpart; comparison of the two reaction modes would thus accurately reflect the efficiency of the intramolecular proton transfer and its "bent" trajectory. Iodine, incidentally, was selected as the leaving group for practical reasons. We needed a good leaving group to ensure an observable elimination under reasonable reaction conditions, This consideration runs counter to the desirability for substantial C–H cleavage in the transition state,[34] On the other hand, the presence of an aromatic ring favors C–H cleavage in the transition state[34] so that a true E2 mechanism with our secondary iodide seems assured,

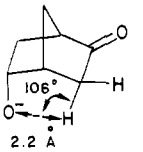
NMR and UV experiments gave no indication of intramolecular oxygen anion participation. Thus, dehydrohalogenation of 0.016 M 2-iodo-4-hydroxyindan at 70 °C in aqueous pH 10.13 buffer (selected to generate the phenolate but minimize hydroxide ion levels) was followed by an absorbance increase at 230 nm, The reaction time was roughly two times faster than that for the dehydrohalogenation of 2-iodoindan under the same conditions, This difference is not considered significant[35] or indicative of intramolecular catalysis. Reactions were also carried out in an aprotic solvent (THF) and followed by using the aromatic region of the NMR (6–8 ppm). 2-Iodo-4-hydroxyindan (0.10 M in THF) was converted into its conjugate base with a small excess of sodium hydride. Elimination required 4 h at 60 °C for completion compared to only 1 h for the reaction between 0.05 M 2-iodoindan and 0,05 M phenolate in THF, When the concentration of 2-iodo-4-hydroxyindan conjugate base in THF was very low (1×10^{-4} M), there was no reaction observable by UV after several hours at 60 °C. Both the concentration-dependent reactivities plus rather prosaic rates demonstrate the absence of anchimerically assisted proton removal; reaction is exclusively intermolecular. Either the oxygen anion of 2-iodo-4-hydroxyindan is too far removed from the proton or else the $O^-/H/C$ angle is too nonlinear to permit a facile intramolecular proton transfer.

B. *endo*-5-Hydroxybicyclo[2.2.1]heptan-2-one. *endo*-5-Hydroxybicyclo[2.2.1]heptan-2-one should undergo, geometric factors permitting, an intramolecular catalyzed enolization,

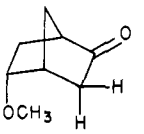


(2)

The O^-/H distance is shorter and the $O^-/H/C$ angle larger than with the indan system:

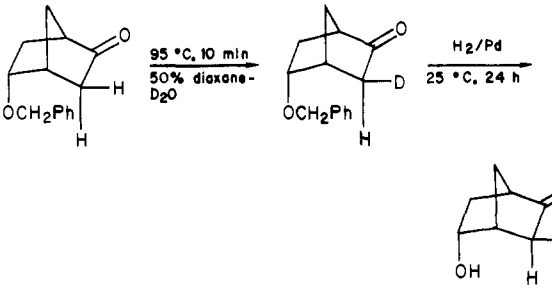


Intramolecular proton transfer is thus favored on both counts. Our plan was to test for such a reaction by comparing the rate of base-catalyzed deuterium exchange in D_2O with that of corresponding methoxy compound where intramolecular catalysis is not possible:



Tidwell and co-workers[36] showed that the parent ketone, norcamphor, exchanges its *exo*-3-H 650 times faster than the *endo*-3-H, Therefore, the hydroxyl of *endo*-5-hydroxybicyclo-[2,2.1]heptane lies contiguous to the more inert proton with respect to intermolecular catalyzed exchange,

Proton exchange with *endo*-5-hydroxybicyclo[2,2.1]heptane in basic D_2O was monitored by NMR. As seen from Figure 1, monodeuteration simplifies the 2,2–2.5-ppm region containing the *exo*-3-H and *endo*-3-H (as well as *exo*-6-H),[37] In addition, the upfield portion of the 2.2–2.5-ppm region experiences a one-proton reduction in amplitude, Dideuteration generates another one-proton reduction within the 2.2–2,5-ppm region, but the change is downfield from the first. Is the upfield proton that exchanges initially *exo*-3-H or *endo*-3-H? Norcamphor itself is known to have its *endo*-3-H upfield from the *exo*-3-H,[37] and on this basis one might conclude that *endo*-5-hydroxybicyclo[2.2,1]heptane exchanges its *endo*-3-H first. If this is true, then intramolecular catalysis overcomes the 650;1 rate disadvantage mentioned above. However, such is not the case. We were able to prove that the presence of the *endo*-5-hydroxyl reverses the chemical shifts of the 3-protons from those found in norcamphor. Thus, monodeuteration of benzylated hydroxy ketone (eq 3) was readily accomplished in basic dioxane–D_2O (50:50 v/v) at pK −13,6 and 94 °C. Subsequent removal of the benzyl group by hydrogenolysis gave a material whose NMR spectrum was identical with that shown in Figure 1b for the monodeuterated compound. Since the benzylated derivative lacks an intramolecular catalyst, it should deuterate preferentially at the exo site (similar to norcamphor); hence *endo*-5-hydroxybicyclo[2.2.1]heptane does likewise. With the assignments in hand, we were then able to investigate exchange rates at the 3-position.



(3)

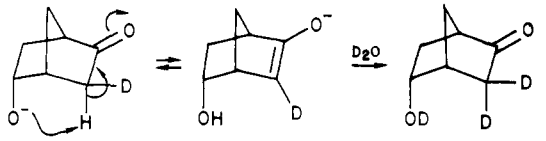
Solutions of *endo*-5-hydroxybicyclo[2.2.1]heptane and *endo*-5-methoxybicyclo[2.2,1]heptane in D_2O (0.10–0.33 M, pD −13.9) were incubated side-by-side at 70 °C and 89 °C. Aliquots were periodically removed from NMR analysis of the 2.2–2.6-ppm region. Two factors prompted us to focus exclusively on the monodeuteration-to-dideuteration process: (a) *exo*-3-H exchange

(32) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
(33) Kwart, H.; Takeshita, T.; Nyce, J. L. *J. Am. Chem. Soc.* **1964**, *86*, 2606.
(34) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274.
(35) Menger, F. M. *J. Chem. Educ.* **1980**, *57*, 351.
(36) Abad, G. A.; Jindal, S. P.; Tidwell, T. T. *J. Am. Chem. Soc.* **1973**, *95*, 6326.
(37) Marshall, J. L.; Walter, S. R. *J. Am. Chem. Soc.* **1974**, *96*, 6358.

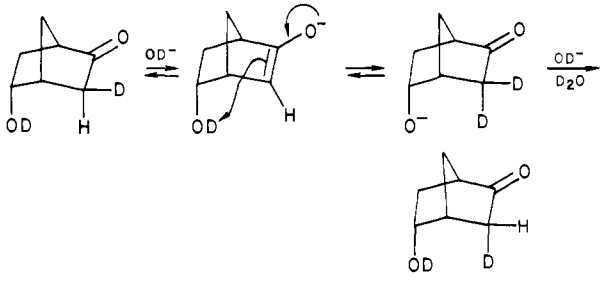
is dominated by an uninteresting hydroxide-catalyzed reaction and (b) *exo*-3-H and *endo*-3-H of the methoxy "model" cannot be clearly differentiated by NMR, Dideuteration of the hydroxy compound at 70 °C required 2,5 min compared with 70 min for the methoxy analogue. At 89 °C the reactions were complete in 0.75 min and 20 min, respectively. The rates did not vary over a 0,15–0.33 M concentration range of substrate, precluding an alcohol/alcohol reaction, Crude though the "kinetic" experiments might be, it is clear that *endo*-5-hydroxybicyclo[2,2.1]heptane exchanges its *endo*-3-H significantly faster (roughly 27-fold at pD = 13.9) than does the methoxy derivative under identical conditions.

In order to evaluate the magnitude of an intramolecular catalysis, one must estimate reactivities in the absence of such an effect.[38] This demands the study of a model compound. No model is ideal since removal of intramolecular catalysis necessarily perturbs steric and electronic properties as well. Although the size and polar effect of hydroxy and methoxy groups are not identical, neither difference sufficies to explain the 27-fold faster rate of *endo*-3-H exchange in the hydroxy compound, Both substituents provide an oxygen near the reactive center. The methyl of the methoxy group adds little to the steric bulk, This is seen, for example, in biphenyl systems where an *o*-CH_3 or *o*-Cl offers much more interference to internal rotation than does an *o*-OCH_3.[39] Steric inhibition in the methoxy model therefore seems unlikely. Indeed, one could argue that the hydroxyl is solvated in D_2O and thus actually *larger* than the methoxy,[40] Polar effects also seem unimportant. Hydroxy and methoxy groups have similar σ_I values (0.25 and 0.27, respectively[41]), and the oxygen anion should be *less* electron withdrawing than the methoxy group. "Through-bond" inductive effects are, in any event, attenuated by three intervening carbons, We conclude that the rapid *endo*-3-H exchange represents a true intramolecular catalysis by the *endo*-5-hydroxyl.

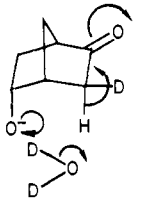
Anchimeric assistance by the *endo*-5-hydroxyl could occur by two interrelated mechanisms.[41] (a) Alkoxide participates in an intramolecular removal of the *endo*-3-H from the monodeuterated compound; this is followed by rapid deuteration (eq 4). (b) An


(4)

OD group delivers a deuterium from the endo side; the resulting intermediate is never detected by NMR since exo exchange is fast under the reaction conditions (eq 5), If the general base

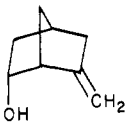

(5)

mechanism is correct, then the observed enhancement must be adjusted upward to account for the low levels of alkoxide present at pD = 13.9. Assuming a pK_a of 18 for our secondary hydroxyl in water,[42] one calculates an actual catalysis of 10^5. On the other hand, if dideuterated material is formed by an internal transfer from the *endo*-OD, then the catalysis is only one order of magnitude. Ambiguity of this type appears frequently in the literature,[43] and unfortunately our NMR experiments cannot differentiate the alternatives. Another complication relates to the possibility that an intervening D_2O molecule participates in the reaction:

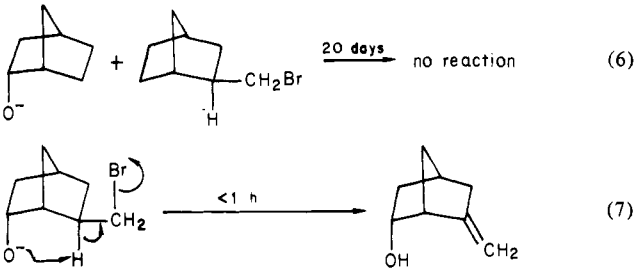


Although to our knowledge there does not exist a single proven case of such a "double general base" mechanism, it cannot be excluded. (Catalysis through a solvent molecule certainly did *not* occur with our 2-iodo-4-hydroxyindan even though the angular relationships would be benefited substantially.) Whatever the detailed mechanism of the norboranone reaction, the data prove that an intramolecular catalysis (worth 10^5 if alkoxide is the catalyzing entity) can arise despite a ground-state $O^-/H/C$ geometry deviating 74° from linearity. Data on the third system of this study, described below, confirm the efficacy of the transfer.

C. *endo*-2-Hydroxy-*exo*-6-bromomethyl[2.2.1]heptane. The title compound (0.050 M) and freshly prepared potassium *tert*-butoxide (0,050 M) in *tert*-butyl alcohol-*d* were warmed to 53 ± 1 °C. Dehydrobromination was apparent in the NMR from the appearance of a vinyl doublet concomitant to the disappearance of the $-CH_2Br$ multiplet. The time dependence of the vinyl peak area (relative to the peak area of benzene added as an internal standard) provided a semiquantitative measure of the reaction time. Thus, 15 min were required for 3 half-lives to form the expected olefin whose structure was confirmed by ^{13}C NMR:

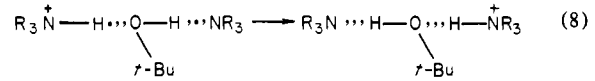


When *exo*-2-(bromomethyl)bicyclo[2.2,1]heptane (0.050 M), *endo*-norborneol (0.050 M), and potassium *tert*-butoxide (0.090 M) were incubated at 53 °C, no intermolecular base-catalyzed elimination was observed after 20 days (eq 6). Fast *intramolecular* elimination in *endo*-2-hydroxy-*exo*-6-(bromomethyl)bicyclo-[2,2.1]heptane (eq 7) is clearly indicated,


(6)

(7)

Note that the possibility of *tert*-butyl alcohol involvement in the elimination mechanism (similar to that mentioned in the enolization studies) cannot be excluded, Examples of a solvent molecule acting simulataneously as a donor and acceptor in proton transfers are well documented (eq 8).[45] Nonetheless, the pos-


(8)

sibility seems remote here since all known cases allow for strong hydrogen bonding interactions. When hydrogen bonding is weak, as with sulfur bases, direct proton transfer predominates over a

(38) Capon, B. *Q. Rev., Chem. Soc.* **1964**, *18*, 45.
(39) Förster, H.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 429.
(40) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199.
(41) Hine, J. "Structural Effects on Equlibria in Organic Chemistry"; Wiley: New York, 1975.
(42) Banerjee, S.; Werstiuk, N. H. *Can. J. Chem.* **1975**, *53*, 1099.
(43) McEwen, W. K. *J. Am. Chem. Soc.* **1936**, *58*, 1124.
(44) Bender, M. L.; Kézdy, F. J.; Zerner, B. *J. Am. Chem. Soc.* **1963**, *85*, 3017.
(45) Grunwald, E.; Eustace, D., ref 19, Chapter 4.

"solvent-intervention" process.[45] Hence the inability of our C-H linkage to hydrogen bond mitigates against solvent participation. But whether or not solvent intervenes, it is clear that the sharp $O^-/H/C$ angle of 106° in the norbornyl system (and by inference also at the active sites of enzymes) need not preclude rapid reaction.

The 106° $O^-/H/C$ angle represents, of course, a ground-state value. Bending and stretching distortions of the C-H bond change this angle for the transition state and contribute substantially to the activation energy for the elimination. We are currently investigating by theoretical methods the relative timing of C-H bending and stretching as the proton transfers from one heavy atom to another.

Conclusion

Proton-transfer rates between B and HA depend on the B/H/A angle and the B/HA distance. Ideally one would like to construct a three-dimensional map having reactivity, angularity, and distance as its axes. Each point on the map would represent a rate constant from a rigid molecule in which B and HA are fixed in a particular ground-state geometry. We have synthesized three such systems, and the data on them are easily summarized; The indane compound with a B/H/A angle of 82° and B/HA distance of 2.9 Å manifests no detectable intramolecular proton transfer; on the other hand, the norbornyl compounds with a B/H/A angle of 106° and B/H distance of 2,2 Å are capable of effective intramolecular transfer, A paltry harvest one might think! Yet there are important aspects to our initial results that should be emphasized in conclusion. (a) One suspects that distance is the critical geometric factor here because the indan and norbornyl systems, although behaving differently, both have severely bent B/H/A angles. Reducing the distance from 2.9 Å (greater than the van der Waals distance) to 2.2 Å (less than the van der Waals distance) probably accounts for much of the reactivity difference. If this is true, then "long distance catalysis" appears unlikely in organic molecules and at the active sites of enzymes. (b) Little doubt now exists that intramolecular proton transfers can take place via severely bent ground-state geometries. Assumptions of linearity in intermolecular transfers[21-24] are therefore suspect. More likely, there exists a "reaction window"[46] encompassing a range of trajectories; each trajectory, we believe, is associated with a particular degree of proton transfer at the transition state. Ramifications of this "multidirectional transition-state theory" are discussed elsewhere.[47] (c) The work herein, along with that published previously,[4] represents our initial effort at an approach that merits further exploitation in the future. The main difficulty lies in synthesizing sets of compounds with subtle variations in the spatial relationships among intramolecular functionalities supported on rigid frameworks. As the synthetic problems are overcome, chemistry will be rewarded with an understanding of reactivity in solution far more detailed than now available.[48]

Acknowledgment. This work was supported by the National Science Foundation and the National Institutes of Health.

Registry No. **1**, 86045-81-0; **2**, 58029-23-5; **3**, 75364-33-9; 4-hydroxyindanone, 40731-98-4; 4-benzyloxyindanone, 86045-82-1; 4-benzyloxyindanone tosylhydrozone, 86045-83-2; 7-benzyloxyindene, 86045-84-3; 4-benzyloxyindan-2-ol, 86045-85-4; 4-benzyloxy-2-hydroxyindan tosylate, 86045-86-5; *exo*-5-hydroxybicyclo[2.2.1]heptan-2-one, 58029-22-4; *exo*-5-hydroxy-2-(ethylenedioxy)bicyclo[2.2.1]heptane, 67594-60-9; 2-(ethylenedioxy)bicyclo[2.2.1]heptan-5-one, 67594-61-0; *endo*-5-hydroxy-2-(ethylenedioxy)bicyclo[2.2.1]heptane, 86116-71-4; *endo*-2-hydroxy-*exo*-6-(tosyloxymethyl)bicyclo[2.2.1]heptane, 86045-87-6; 2-iodoindane, 24329-96-2; 2-iodo-4-benzyloxyindane, 86045-88-7; *endo*-5-methoxybicyclo[2.2.1]heptan-2-one, 85164-48-3; *endo*-5-deuteroxy-*exo*-3-deuterobicyclo[2.2.1]heptan-2-one, 86045-89-8; *endo*-5-deuteroxy-3,3-dideuterobicyclo[2.2.1]heptan-2-one, 86045-90-1.

(46) Menger, F. M.; Williams, D. Y. *Tetrahedron Lett.* **1982**, *23*, 3879.
(47) Menger, F. M. *Tetrahedron* **1983**, *39*, 1013.
(48) **Note Added in Proof**: Recent unpublished data indicate that not only is distance important but also the *residence time* within the reaction window plays a critical role.

Catalytic Alkyl Group Exchange Reaction of Primary and Secondary Amines

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Abstract: It has been shown that primary and secondary amines undergo alkyl group exchange reactions upon treatment with palladium catalyst as depicted in the following equation: $R^1R^2CHNHR^3 + R^4R^5NH \xrightarrow{Pd} R^1R^2CHNR^4R^5 + R^3NH_2$. The reaction is operationally simple and highly efficient and hence provides a convenient method for synthesis of unsymmetrical amines. The application of the reaction for the preparation of various substituted amines and heterocyclic compounds such as hexahydropyrimidine **12**, tetrahydropyrimidine **13**, imidazolidine **14**, and imidazoles **15** and **16** is described. The preparation of polyamines such as $H_2N(CH_2)_mNH(CH_2)_nNH_2$ (**10**) and $H_2N(CH_2)_lNH(CH_2)_mNH(CH_2)_nNH_2$ (l-n, = 2,3; **11**) is readily performed by the palladium-catalyzed reactions of azetidine (**6**) and aziridine (**7**) via azetine (**9**) and azirine intermediates. The mechanism of the palladium-catalyzed reaction has been extensively studied on the carbonylation, racemization, and deuterium-exchange reaction of (*S*)-(−)-α-phenylethylamine (**17**). Insertion of palladium into the N-H bond of an amine followed by β-elimination of PdH species gives imine complex intermediate **33**, which is in rapid equilibrium with enamine complex **34**. Addition of a second amine to **33** gives aminal **35**, which subsequently undergoes reductive cleavage to form the product amine. The results of the reaction of **17** with (*S*)-(+)-*sec*-butylamine (**23**) and the reductive cleavage of *N*-phenylbenzamidine (**31**) support the mechanism.

On many methods available for preparation of unsymmetrical secondary and tertiary amines, Hoffmann alkylation,[1] reductive alkylation of carbonyl compounds,[2] and their improved methods[3] are central methods. Recently, catalytic alkylation and allylation of amines by the activation of alcohols[4] and their derivatives[5] have been explored, In relation to the study of the metabolism of

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(1) Gibson, M. S. "The Chemistry of the Amino Group"; Patai, S.; Ed.; Interscience: New York, 1968; p 37.
(2) Emerson, W. S. *Org. React.* **1948**, *4*, 147.

0002-7863/83/1505-5002$01.50/0