4 H), 0.94 (t, 3 H), and 0.93 (s, 3 H); *m/e* calcd 240.1878, obsd 240.1882.

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# Stereoselective Bifunctional Catalysis of Dedeuteration of Cyclopentanone-*2,2,5,5-$d_4$* by (1*R*,2*S*,3*R*,4*R*)-3-Dimethylaminomethyl-1,7,7-trimethyl-2-norbornanamine[1]

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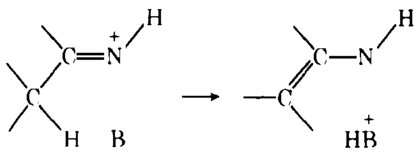
**Abstract:** The chiral diamine (1*R*,2*S*,3*R*,4*R*)-3-dimethylaminomethyl-1,7,7-trimethyl-2-norbornanamine (**2**) has been synthesized and found to be a very effective bifunctional catalyst for the dedeuteration of acetone-$d_6$. The Brønsted $\beta$ for dedeuteration of cyclopentanone-*2,2,5,5-$d_4$* in water at 35 °C is 0.57. The dedeuteration of cyclopentanone by **2** is rapid and stereoselective. The two *pro S* deuterium atoms are exchanged faster than the *pro R* deuterium atoms, by as much as 70-fold. Ketone containing >80% cyclopentanone-$d_2$ was isolated from the reaction mixture after partial exchange. This material showed a positive Cotton effect.

Certain primary amines containing basic substituents ($B\text{-}NH_2$) may act as bifunctional catalysts for removal of $\alpha$ hydrogen from aldehydes and ketones.[2-4] They transform the carbonyl compound to an iminium ion in which the basic group may remove the $\alpha$ hydrogen atom internally (eq I). To learn whether such hydrogen removal could be made strongly stereoselective with a simple model, the dedeuteration of cyclopentanone-*2,2,5,5-$d_4$* was studied in the presence of a chiral catalyst.[5] The enzyme acetoacetate decarboxylase, which is an effective bifunctional catalyst for the dedeuteration of acetone-$d_6$,[6] dedeuterates the methylene group of butanone stereoselectively.[7]


(I)

## Results and Discussion

**Synthesis of Chiral Catalyst.** The most effective bifunctional catalyst for the dedeuteration of acetone-$d_6$ that we had studied was 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine,[1b] which had been prepared from norcamphor.[8] Rather than resolving this diamine we thought it would be easier to make the analogous 1,7,7-trimethyl compound from natural chiral camphor. From (+)-camphor, which is known[9] to be 1*R*,4*R*, we obtained the 2-dimethylaminomethyl derivative (**1**) by reduction of the 2-dimethylaminomethylene derivative. The

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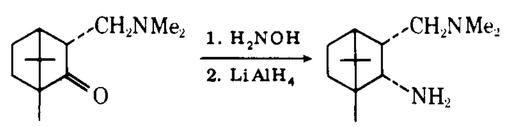
**Table I.** Kinetics of Dedeuteration of Acetone-$d_6$ in the Presence of **2**[a]

| pH | $10^5k_6$, $s^{-1}$ | $10^5k_p$, $s^{-1}$ | $q$ | $r$ | $10^5k_{im}$, $s^{-1}$ | $k_{ah}$, $M^{-1}$ $s^{-1}$ |
|---|---|---|---|---|---|---|
| 7.18 | 6.04 | 0.06 | 1.000 | | ≥6 | |
| 7.58 | 49.0 | 0.08 | 0.917 | 0.14 | 410 | 0.93 |
| 8.43 | 99.4 | 0.18 | 0.839 | 0.29 | 440 | 0.94 |
| 9.24 | 197 | 0.67 | 0.606 | 0.98 | 400 | 0.98 |
| 9.64 | 252 | 1.4 | 0.446 | 1.89 | 380 | 1.20 |
| 9.88 | 216 | 2.0 | 0.432 | 2.02 | 320 | 1.29 |
| 10.12 | 128 | 3.0 | 0.423 | 2.17 | 183 | 1.02 |

[a] Using 0.52 M ketone and 0.0050 M total **2** in water at 35 °C and ionic strength 0.002–0.008.

stereochemistry of the 2-dimethylaminomethyl group has not been reported. The endo isomer has been referred to briefly,[11] but its synthesis and structure proof not described. The exo isomer (whose hydrochloride melts 10 °C higher than that of our product) has been synthesized from trimethylsilyloxyborneol and *N*,*N*-dimethylmethyleneammonium chloride.[12] Reduction of the oxime of **1** gave our bifunctional chiral catalyst **2**. The stereochemistry of **2** was established by its $^1$H



**2**

NMR spectrum, especially the doublet of doublets ($J$ = 10.2, $J'$ = 1.8 Hz) arising from the hydrogen atom on C-2 ($\alpha$ to the primary amino group). If this hydrogen atom were endo there would be no detectable long range coupling.[13] The coupling constant of 10.2 Hz is much too large for a trans coupling constant in the bornane series.[13,14] Hence the hydrogen atoms on C-2 and C-3 are exo and cis and **2** is the 1*R*,2*S*,3*R*,4*R* isomer. Although $J$ is the range found for such exo-cis coupling constants, it is ~3 Hz larger than would be reasonable for an endo-cis coupling constant.[13,14]

**Dedeuteration of Acetone-$d_6$.** The rate of dedeuteration of acetone-$d_6$ in the presence of 0.005 M **2** at 35 °C was studied over the pH range 7.18–10.12. The first-order rate constants for disappearance of acetone-$d_6$ that would be expected if **2** and **2**H$^+$ acted as simple basic catalysts ($k_p$) were calculated from the Brønsted correlation and p$K_1$ (9.84) and p$K_2$ (6.59) for **2** as described previously for other diamines.[1b,15] Table I shows that the observed $k_6$ values are 40–600 times as large as the calculated $k_p$ values. This is strong evidence that **2** is a bifunctional catalyst. We assume that Scheme I, in which the bifunctional catalyst is B-NH$_2$, is operating. From the fraction of acetone present as acetone-$d_5$ at various times, the constant $q$ may be calculated in any given kinetic run.[1b,15] Equations 1 and 2 define $q$:

$$q = [2r(k_p/k_6) + 3]/(2r + 3) \qquad (1)$$

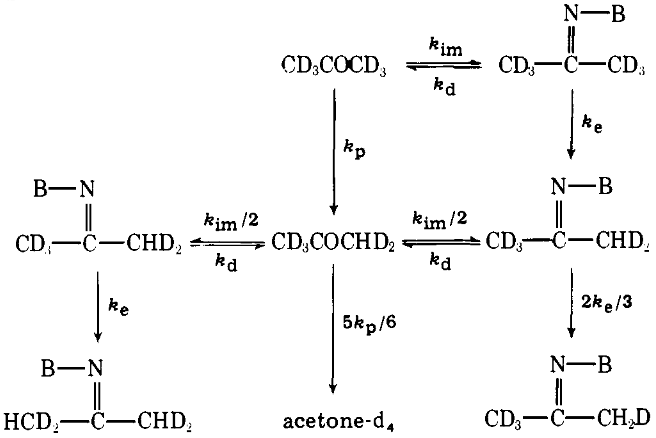
$$r = k_e/k_d \qquad (2)$$

If $k_5$, the first-order rate constant for disappearance of acetone-$d_5$ is equal to $5k_6/6$, as it will be if secondary deuterium kinetic isotope effects are negligible and either $k_{im}$ or $r$ is very small, $q$ will be equal to 1.0. Values of $q$ below ~0.8 require that much of the reaction goes via the imine ($k_{im} \geq k_p$) *and* that the rate of exchange of the imine is at least comparable with its rate of hydrolysis ($k_e \gtrsim k_d$). The values of $q$ obtained and the values of $r$ calculated from them are listed in Table I, as are the $k_{im}$ values that then result from

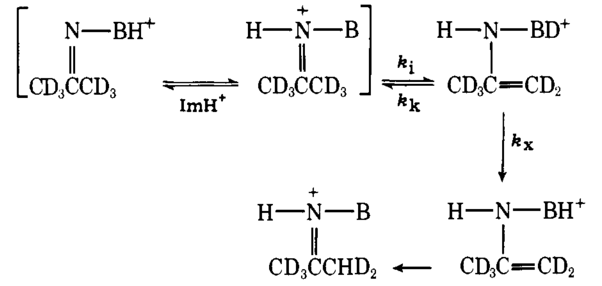
$$k_{im} = (k_6 - k_p)(1 + r)/r \qquad (3)$$

Judging from the rate constants for imine formation by other unprotonated tertiary-primary diamines,[16,17] imine formation by unprotonated **2** should not be fast enough to contribute significantly to the $k_{im}$ values in Table I. Since imine formation by diprotonated **2** is also not expected, second-order rate constants for imine formation from **2**H$^+$ and acetone ($k_{ah}$) were obtained by dividing $k_{im}$ by the concentration of **2**H$^+$. The resulting values of $k_{ah}$ in Table I are sufficiently constant to support the assumptions made. The average value 1.06 M$^{-1}$ s$^{-1}$ is more than twice as large as the largest $k_{ah}$ value obtained previously, which was for monoprotonated 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine, which is just **2** without its three carbon-bound methyl groups. We are not sure why these methyl substituents make the imination, which must involve an internal acid-catalyzed dehydration of the intermediate carbinolamine,[16,17] so much faster.

Scheme I



Scheme II



Decreases in $r$ with decreasing pH have been observed before[1b,15] and explained in terms of Scheme II, which details the exchange step governed by $k_e$ in Scheme I. If essentially all the imination arises from **2**H$^+$, as suggested by the constancy of the $k_{ah}$ values in Table I, then hydrolysis back to the ketone must be a first-order reaction of the iminium ion:

$$k_d = k_{ah}[\mathrm{ImH}^+] \qquad (4)$$

According to Scheme II, $k_e$ in Scheme I may be expressed as

$$k_e = [\mathrm{ImH}^+]k_ik_x/(k_x + k_k) \qquad (5)$$

Combination of eq 2, 4, and 5 gives

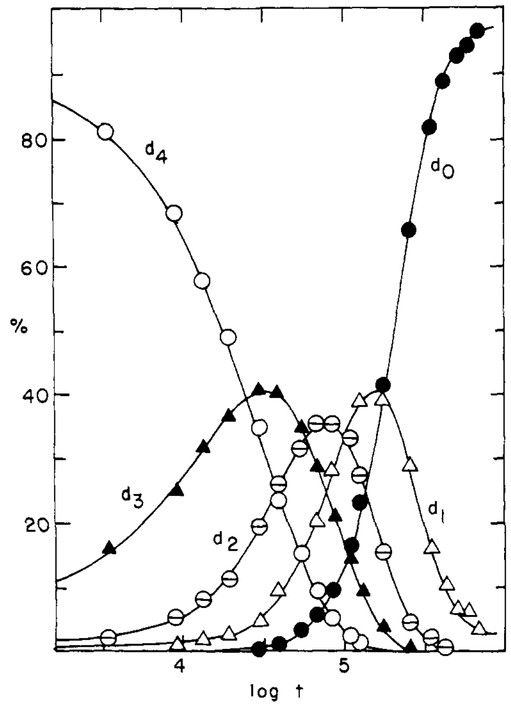


**Figure 1.** Dedeuteration of aqueous 0.206 M cyclopentanone-*2,2,5,5*-$d_4$ containing 0.0986 M total 3-dimethylaminopropionitrile at pH 7.63 and 35 °C. The curves are based on Scheme III, eq 8, and initial fractions of deuteration of 0.9050, 0.0747, 0.0102, 0.0101, and 0.000 for $d_4$ through $d_0$, respectively; $z$ = 1.043, and $k_4 = 3.30 \times 10^{-5}\ s^{-1}$.

**Table II.** Kinetics of Dedeuteration of Cyclopentanone-*2,2,5,5*-$d_4$[a]

| catalyst | $10^4k$,[b] $M^{-1}\ s^{-1}$ | $pK_a$[c] |
|---|---|---|
| HCl | 0.33 | |
| NaOH | 2150 | |
| $n$-BuNMe$_2$ | 166 | 9.80 |
| $MeOCH_2CH_2NMe_2$ | 38.3 | 8.96 |
| $(EtO)_2CHCH_2NMe_2$ | 6.79 | 7.96 |
| $NCCH_2CH_2NMe_2$ | 4.12 | 6.89 |

[a] Using 0.206 M ketone in water at 35 °C. [b] For transformation of the $d_4$ to the $d_3$ ketone. [c] For the conjugate acid of the base.

$$r = k_i k_{dh} k_x/(k_x + k_k) \tag{6}$$

in which the values of $k_i$, $k_{dh}$, and $k_k$ should all be independent of the pH. However, since $k_x$ must involve attack by bases, its value should decrease with decreasing pH at constant total buffer concentration. Although the ratio $k_x/k_k$ was analyzed in more detail with other catalysts,[1b,15] we did not use enough different concentrations of **2** to make that practical here.

**Dedeuteration of Cyclopentanone-*2,2,5,5*-$d_4$ by Monofunctional Catalysts.** To estimate how effective a catalyst **2** would be if it could not act bifunctionally, the rate of dedeuteration of cyclopentanone-*2,2,5,5*-$d_4$ was studied in the presence of hydrochloric acid, sodium hydroxide, and four amines of the type $RCH_2NMe_2$. In aqueous solution these reactions follow Scheme III, in which reversibility needs to be allowed

**Scheme III**

$$d_4 \xrightarrow{k_4} d_3 \xrightarrow{k_3} d_2 \xrightarrow{k_2} d_1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} d_0$$

for only in the last step. If secondary deuterium kinetic isotope effects are ignored,

$$k_1 = k_2/2 = k_3/3 = k_4/4 \tag{7}$$

results. A plot of the $d_4$, $d_3$, etc., contents of the ketone vs. log $t$, where $t$ is the time, is shown in Figure 1 for a typical kinetic run. As shown in the Appendix, if the $\gamma$ secondary deuterium isotope effect is independent of whether the deuterium atom being removed is cis or trans, if this effect and the $\alpha$ secondary deuterium isotope effect are multiplicative when expressed as $k^H/k^D$ ratios, and if these ratios are fairly near 1.0, we obtain

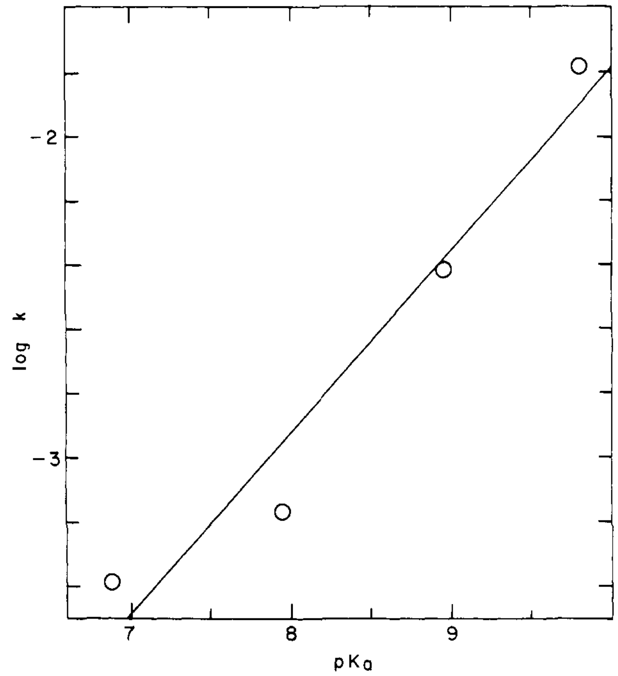


**Figure 2.** Brønsted plot for dedeuteration of cyclopentanone-*2,2,5,5*-$d_4$ by the $RNMe_2$ amines of Table II in water at 35 °C.

$$k_1 = k_2z/2 = k_3z^2/3 = k_4z^3/4 \tag{8}$$

in which $z$ is equal to $(a + 2g)/3$, where $a$ is the $k^H/k^D$ $\alpha$ secondary isotope effect and $g$ is the $\gamma$ effect. The solid line in Figure 1 is based on eq 8. From the data on runs whose $k_4$ and $z$ values are listed in the Appendix (Table IV), second-order rate constants for removal of deuterium from the $d_4$ ketone are obtained; these are listed in Table II. The Brønsted plot for the four amines (Figure 2) has a slope of 0.57, which is near the value (0.60) found for the reaction of acetone-$d_6$ with amines of the type $RCH_2NMe_2$.[15] The rate constants in Table II are 1.2-3 times as large as the corresponding rate constants for acetone-$d_6$.[15,18] The $z$ values obtained ranged from 0.99 to 1.09, with all but two of them exceeding 1.0 by more than the estimated standard deviation.

**Dedeuteration of Cyclopentanone-*2,2,5,5*-$d_4$ by (1*R*,2*S*,3*R*,4*R*)-3-dimethylaminomethyl-1,7,7-trimethyl-2-norbornanamine (2).** Because the value of $z$ for the plot in Figure 1, like those for all the runs we made, is near 1.00, the plot very nearly follows Scheme II and eq 7, i.e., one-at-a-time random exchange of deuterium. Any reaction of this type will give a plot with the same shape.[19] By adding a constant to the abscissa the plot would become applicable to any other such reaction. In any such process, for example, the $d_1$ concentration will reach a maximum after 8 half-lives for the disappearance of $d_4$.[20] A typical plot for dedeuteration in the presence of **2** (Figure 3) shows markedly different behavior. The $d_1$ concentration does not reach its maximum until after >100 half-lives for the disappearance of $d_4$. This is not consistent with Scheme III and eq 7 or 8, but is explained by Scheme IV, in which the exchange is assumed to be stereoselective. Table III lists values of $k_4$ (first-order rate constants for disappearance of $d_4$), $k_d$ and $k_l$ (calculated as described in the Appendix), and $k_p$ (the values that would be expected for $k_4$ if only simple basic catalysis were occurring)[21] for the exchange in

**Table III.** Dedeuteration of Cyclopentanone-*2,2,5,5*-$d_4$ in the Presence of **2**[a]

| pH | $10^4k_4$, $s^{-1}$ | $10^6k_p$, $s^{-1}$ | $10^6k_d$, $s^{-1}$ | $10^4k_l$, $s^{-1}$ | $k_l/k_d$ | $k_{ah}r/(1+r)$, $M^{-1}$ $s^{-1}$ |
|---|---|---|---|---|---|---|
| 6.57[b] | 1.96 | 0.46 | 1.36 | 0.97 | 71 | 0.18 |
| 6.68[c] | 4.48 | 1.0 | 3.23 | 2.21 | 68 | 0.19 |
| 7.16[c] | 12.4 | 1.6 | 9.69 | 6.12 | 63 | 0.34 |
| 8.03 | 54.1 | 3.1 | 47.7 | 26.6 | 56 | 1.13 |
| 8.76 | 57.5 | 7.6 | 62.1 | 28.1 | 45 | 1.25 |
| 9.87 | 40.7 | 57 | 70.2 | 19.7 | 28 | 1.60 |
| 10.03[d] | 18.0 | 62 | 28.8 | 8.70 | 30 | 1.68 |
| 10.19 | 29.0 | 99 | 81.4 | 13.7 | 17 | 1.74 |

[a] Using 0.206 M ketone and 0.00509 M total **2** in water at 35 °C unless otherwise noted. [b] 0.00245 M **2**. [c] 0.00500 M **2**. [d] 0.00250 M **2**.

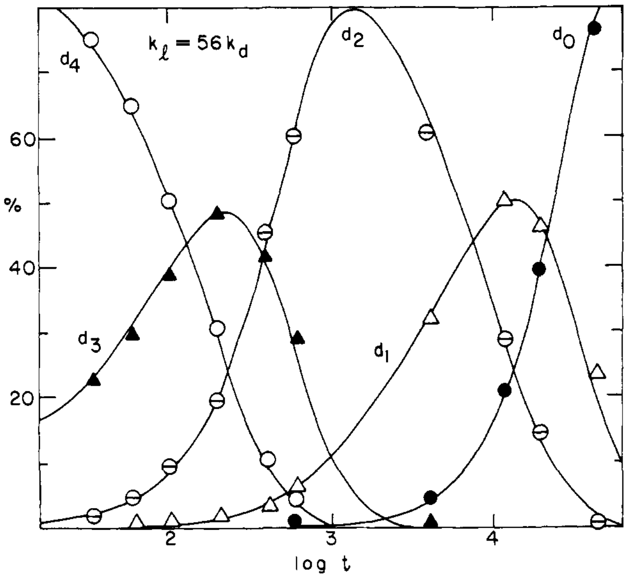


**Figure 3.** Dedeuteration of aqueous 0.206 M cyclopentanone-*2,2,5,5*-$d_4$ containing 0.00509 M total **2** at pH 8.03 and 35 °C. The curves are based on Scheme IV, with $k_d$ and $k_l$ values of $4.77 \times 10^{-5}$ and $266 \times 10^{-5}$ $s^{-1}$, respectively.

**Scheme IV**

$$\begin{tikzcd}
d_4 \arrow[r, "2k_d"] \arrow[d, "2k_l"'] & d\text{-}d_3 \arrow[r, "k_d"] \arrow[d, "2k_l"'] & d\text{-}d_2 \arrow[d, "2k_l"'] \\
l\text{-}d_3 \arrow[r, "2k_d"] \arrow[d, "k_l"'] & i\text{-}d_2 \arrow[r, "k_d"] \arrow[d, "k_l"'] & d\text{-}d_1 \arrow[d, shift right, "k_l"'] \\
l\text{-}d_2 \arrow[r, "2k_d"] & l\text{-}d_1 \arrow[r, shift left, "k_d"] & d_0 \arrow[l, shift left] \arrow[u, shift right]
\end{tikzcd}$$

the presence of **2** at various pHs. The line in Figure 3 is based on the $k_d$ and $k_l$ values obtained in the run at pH 8.03. (By definition, $k_l$ is the larger of the two rate constants in Scheme IV.)

The ratio $k_l/k_d$ measures the degree of stereoselectivity. Values near 70 are obtained around pH 7. The estimates of $k_p$ may be uncertain by 50%, but the values of $k_4$ are 30-1800 times as large. It is therefore clear that very little of the reaction and hence very little of the dominant $k_l$ process is a simple base-catalyzed process. Hence, most of the stereoselectivity, at least, arises from the bifunctionally catalyzed reaction proceeding via internal imine formation. The $k_4$ values in Table III are much larger than would be reasonable for imine formation by unprotonated or diprotonated **2**.[23] Imination must therefore arise very largely from monoprotonated **2**, where internal acid catalysis of dehydration of the intermediate carbinolamine makes possible a relatively rapid reaction, as we have seen in the case of acetone. The presence of three equivalent deuterium atoms in the imine derived from acetone-$d_6$ and **2** make it possible to calculate a value of $k_{im}$ and $r$ in each kinetic run (if $q$ is significantly less than 1.0), as shown in Table I. The imine from cyclopentanone-$d_4$ and **2** does not have equivalent deuterium atoms and hence $k_{im}$ and $r$ cannot be calculated directly. If $k_6$ in eq 3 is replaced by $k_4$ to make the equation appropriate for cyclopentanone exchange, and $k_{im}$ is replaced by $k_{ah}[2H^+]$, the result may be rearranged to give

$$k_{ah}r/(1 + r) = (k_4 - k_p)/[2H^+] \tag{9}$$

The values of $k_{ah}r/(1 + r)$ shown in Table III decrease with decreasing pH. In terms of reaction schemes analogous to I and II and eq 6, it is seen that $k_{ah}$, $k_i$, $k_{dh}$, and $k_k$ are constants and that the decreases in $k_{ah}r/(1 + r)$ arise from decreases in $k_x$, the rate constant for removal of deuterons from the $-NDMe_2^+$ group of the intermediate enamine.

Since the fraction $r/(1 + r)$ must be less than 1.0, the values of $k_{ah}r/(1 + r)$ in Table III are minima for $k_{ah}$. The fact that the resulting $k_{ah}$ (>1.6 $M^{-1}$ $s^{-1}$) is larger for **2** than for any other amine studied[23] is plausible since the same thing was observed for acetone.

The relatively greater rate of exchange of two of the deuterium atoms of cyclopentanone-$d_4$ in the presence of $2H^+$ causes a fairly large fraction of the ketone to be present as the $d_2$ species at certain times during the reaction (cf. Figure 3). Stereoselectivity should make this material optically active. Cyclopentanone was isolated after 1700 s from a run at pH 8.42 using 1.0 M ketone and 0.0048 M total **2**. The optical rotatory dispersion curve of this material, which contained 1.2% $d_4$, 12.8% $d_3$, 84.6% $d_2$, 0.9% $d_1$, and 0.5% $d_0$, is curve 1 in Figure 4. Although the specific rotations in the visible region are small, there is a positive Cotton effect that gives large rotations in the ultraviolet region. Assuming that the $d_1$ and $d_3$ have specific rotations half that of $d_2$, a specific rotation of −250 °C may be calculated for $d_2$ at the 277-nm negative maximum. The absolute value of this rotation would be larger if the compounds were optically pure.

The optically active ketone was racemized by adding a 3-dimethylaminopropionitrile buffer. From the ORD curves obtained at various times (Figure 4) a second-order rate constant of $6.75 \times 10^{-4}$ $M^{-1}$ $s^{-1}$ for racemization by the amine catalyst was obtained. Racemization of a chiral center occurs when either a deuterium or a protium atom is removed. From the rate constant $1.03 \times 10^{-4}$ $M^{-1}$ $s^{-1}$ *per deuterium* atom that may be calculated from Table II, this gives a rate constant of $5.72 \times 10^{-4}$ $M^{-1}$ $s^{-1}$ for removal of protium from a chiral center, and a primary deuterium kinetic isotope effect ($k^H/k^D$) of 5.6 (neglecting secondary isotope effects).

Figure 5 shows the transition state for deuteron transfer in the iminium ion formed from $2H^+$ and cyclopentanone-$d_4$. All of the hydrogen atoms except the deuterium being transferred have been deleted to give a clearer view of the framework of carbon and nitrogen atoms. The eight-membered ring that

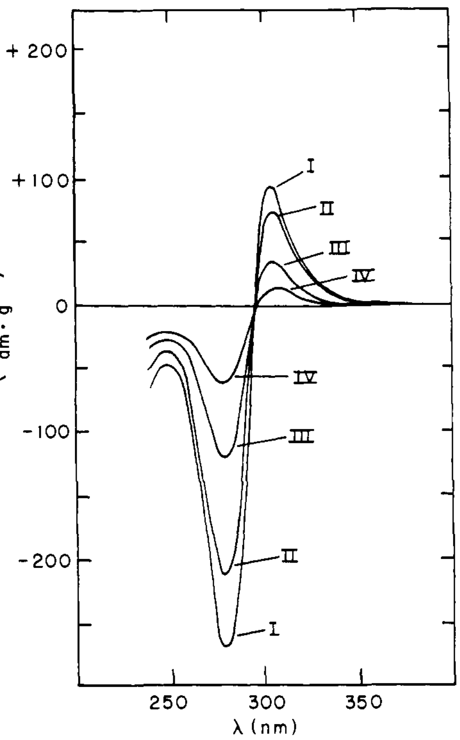
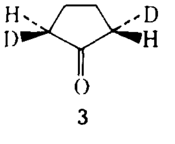


**Figure 4.** Optical rotatory dispersion curves for partially deuterated cyclopentanone. Curve I is for material isolated after partial dedeuteration of cyclopentanone-*2,2,5,5*-$d_4$ by $2H^+$. Curves II, III, and IV are for the same material after further exchange in the presence of a 3-dimethylaminopropionitrile buffer.

exists only *while* the deuteron is being transferred ("the transition-state ring") can be regarded as a seven-membered ring for some purposes because of the necessity for the C–D–N hydrogen bond to be fairly linear. This ring is too large to be coplanar but too small to contain a trans double (or 1½) bond without excessive strain. Four of the ring atoms (the iminium nitrogen atom and the three carbon atoms between the two nitrogens) are forced by the bicyclo[2.2.1] ring system to be almost coplanar. The other four transition-state ring atoms must, for steric reasons, lie on the other side of this plane from the $CH_2CH_2$ bridge of the bicyclo[2.2.1] ring system (a fact that becomes more obvious when the missing hydrogen atoms are added to the model in Figure 5). Because of these restrictions only the *pro S* deuterium atom shown can be transferred internally via a low-strain transition state. In the transition state shown, by introducing much smaller amounts of strain at other positions, a hydrogen bond that is bent by no more than ~10° results.

The stereochemistry of partly exchanged ketone is not controlled by what deuterium is removed, but by where protium is put when the exchanged enamine is transformed to exchanged iminium ion. However, by the principle of microscopic reversibility, the favored transition state for forming exchanged iminium ion must be just like the one in Figure 5, but with a proton instead of a deuteron being transferred. Therefore the cyclopentanone-$d_2$ produced in the exchange must be largely the 2*S*,5*S* species **3**. Because a protium is more



**3**

polarizable than a deuterium substituent,[24] the octant rule[24,25] in its simplest form predicts that **3** will have a negative Cotton effect. This disagrees with the experimental fact (Figure 4),

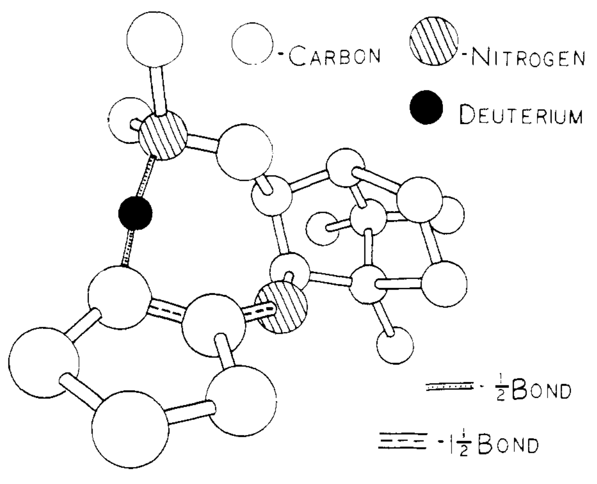


**Figure 5.** Transition state for internal deuteron transfer in the iminium ion derived from cyclopentanone-$d_4$ and $2H^+$. Only the carbon and nitrogen atoms and the deuterium being transferred are shown.

but a number of other cases are known in which the simple octant rule fails.[26]

## Experimental Section

**(1*R*,4*R*)-3-Dimethylaminomethyl-1,7,7-trimethyl-2-norbornanone Oxime.** The method of Minardi and Schenone[10] was used to prepare (1*R*,4*R*)-3-dimethylaminomethyl-1,7,7-trimethyl-2-norbornanone (**1**) hydrochloride: mp 207–208 °C (lit.[10] mp 207–209 °C dec); $[\alpha]_D$ + 5.20° (*c* 5.5, $C_2H_5OH$); $^1H$ NMR ($CDCl_3$) δ 0.92, 0.97, 1.06 (3s, $CH_3C$), 1.08–2.75 (m, ring H's), 3.0 (s, $CH_3N$), 3.0–3.25 (m, $CCH_2N$). Reaction of 20 g of **1**, 25 g of hydroxylamine hydrochloride, and 18.1 g of sodium acetate in 125 mL of water at room temperature for 8 days gave 16.3 g (70%) of the oxime: mp 154–158 °C; $[\alpha]_D$ +6.35° (*c* 5.6, $C_2H_5OH$); $^1H$ NMR ($CDCl_3$) δ 0.84, 0.92, 1.01 (3s, $CH_3C$), 1.08–2 (m, ring H's), 2.38 (s, $NCH_3$), 2.08–2.83 (m, $CCH_2N$); IR (KBr) 3070–3180 (OH), 1670 (C=N), and 944 $cm^{-1}$ (N—O); exact mass of the parent ion, calcd 224.1888, obsd 244.1891.

**(1*R*,2*S*,3*R*,4*R*)-3-Dimethylaminomethyl-1,7,7-trimethyl-2-norbornanamine (2).** To a stirred suspension of 10 g (0.26 mol) of lithium aluminum hydride in 500 mL of ether, 14.7 g (0.066 mol) of the oxime of **1** was added in small portions. After 48 h at reflux, 10 mL of water, then 10 mL of saturated sodium hydroxide, and 30 mL more of water were added. After filtration, evaporation of the ether gave 12.4 g (90%) of crude **2**, as a yellow liquid. Distillation gave a colorless liquid, bp 82° (~2 mm); whose GLC on a mannitol column showed two main components in an ~2:1 ratio. Repeated recrystallization of the hydrochloride salts from water–ethanol–ether–acetonitrile gave the pure salt of the more abundant component (longer retention time): mp 273–274 °C dec. Anal. Calcd for $C_{13}H_{26}N_2 \cdot 2HCl \cdot H_2O$: C, 51.82; H, 10.01; N, 9.16. Found: C: 51.52; H, 10.04; N, 9.30.

Treatment of the hydrochloride with base gave free **2**: 300-MHz $^1H$ NMR[27] (benzene-$d_6$) δ 3.06 (d of d, $J$ = 10.2, $J'$ = 1.8 Hz, 1, $CHNH_2$), 2.58 (d of d, $J$ = 11.8, $J'$ = 9.8 Hz, 1, $CH_aH_bNMe_2$), 2.21 (m, 1, $CHCH_2NMe_2$), 2.10 (s, 6, $N(CH_3)_2$), 2.02 (m, 1, endo H on C-5?), 1.91 (d of d, $J$ = 11.8, $J'$ = 5.8 Hz, $CH_aH_bNMe_2$), 1.52 (m, 1, H on C-4), 1.43 (m, 1, endo H on C-6?), 1.07–1.47 (m, ~1, exo H on C-5?), 1.14 (m, 1, exo H on C-6), 0.885, 0.887, and 0.78 (3s, 9, $CH_3C$); exact mass of parent ion, calcd 210.2096, found 210.2099.

The thermodynamic $pK_a$ values for $2H^+$ and $2H_2^{2+}$ at 35 °C were found to be 9.84 and 6.59, respectively, by potentiometric titration, as described previously.[12]

**Dedeuteration Kinetics.** The method of following the dedeuteration of acetone-$d_6$ by stopping the reaction with acid, extracting with chloroform, and making mass spectral measurements has been described in detail.[18] In the runs on cyclopentanone-*2,2,5,5*-$d_4$ 0.075 mL of ketone was injected into 4 mL of of catalyst solution in a serum-stoppered 5-mL ampoule at 35 °C. The reaction mixtures were quenched with hydrochloric or perchloric acid and extracted with 0.5 mL of ethyl bromide (or benzene in a few cases). The extracts were analyzed by use of a Du Pont Model 21-490 mass spectrometer with correction being made for natural abundance $^{18}O$ and $^{13}C$, and for

Table IV. Rate Constants and Kinetic Isotope Effects in Cyclopentanone-*2,2,5,5*-$d_4$ Exchange[a]

| catalyst | 100[cat]$_t$,[b] M | pH | $10^5 k_4$,[c] s$^{-1}$ | $z$[c] |
|---|---|---|---|---|
| BuNMe$_2$ | 9.1[d] | 9.24 | 25.6 ± 0.6 | 0.99 ± 0.01 |
| | 19.8 | 9.94 | 170 ± 12 | 1.05 ± 0.03 |
| | 23.0 | 9.92 | 202 ± 12 | 1.07 ± 0.02 |
| (EtO)$_2$CHCH$_2$NMe$_2$ | 9.56[e] | 8.35 | 4.77 ± 0.12 | 1.04 ± 0.01 |
| | 9.89[f] | 8.24 | 3.88 ± 0.12 | 1.06 ± 0.02 |
| MeOCH$_2$CH$_2$NMe$_2$ | 9.55[e] | 8.93 | 18.8 ± 2.5 | 0.99 ± 0.05 |
| | 9.75[f] | 8.92 | 16.2 ± 0.6 | 1.07 ± 0.01 |
| | 12.1[f] | 9.26 | 25.2 ± 0.9 | 1.05 ± 0.02 |
| NCCH$_2$CH$_2$NMe$_2$ | 9.68[g] | 7.53 | 3.16 ± 0.05 | 1.09 ± 0.01 |
| | 9.68[f] | 7.63 | 3.27 ± 0.06 | 1.05 ± 0.01 |
| NaOH | 0.40 | — | 84.8 ± 2.4 | 1.04 ± 0.01 |
| | 0.50 | — | 104 ± 4 | 1.05 ± 0.01 |
| HCl | 19.7 | — | 0.655 ± 0.011 | 1.02 ± 0.01 |

[a] In water at 35 °C. [b] Total catalyst concentration (regardless of the state of protonation of the amine catalyst). Unless otherwise stated the ionic strength was equal to the total catalyst concentration. [c] The ± figures are estimated standard deviations. [d] Ionic strength 0.073. [e] Ionic strength 0.040. [f] Ionic strength 0.049. [g] Ionic strength 0.02.

$m - 1$ formation, which was assumed to be independent of the isotopic content of the ketone and amounted to only ~2.85% under the conditions used (15 eV). Ordinarily, ten points at 0, 10, 20, . . . 90% reaction were taken for each run.

**Optically Active Cyclopentanone-*2,5*-$d_2$.** In one run 3 mL of cyclopentanone-$d_4$ (1.0 M) in 34.0 mL of aqueous 0.00481 M total **2** at pH 8.42 was kept at 35 °C for 1700 s and quenched with 1.75 mL of 1.0 M hydrochloric acid. The ketone was extracted with two 10-mL portions of ethyl bromide. Evaporation of the solvent and vacuum distillation gave 1.93 mL of ketone that was >99.5% pure by GLC. The ORD curve for this material is shown as curve 1 in Figure 4. The kinetics of racemization were studied at 35 °C by mixing equal volumes of 0.23 M ketone and 0.898 M total 3-dimethylaminopropionitrile that was 55.7% protonated with hydrochloric acid. At various times 5-mL samples were quenched with 1.25 mL of 1.0 M hydrochloric acid. The resulting ORD curves are shown in Figure 4.

## Appendix

**Kinetics of Monofunctionally Catalyzed Exchange.** In deriving the kinetic equation for Scheme III, the isotopes of hydrogen were assumed to distribute themselves randomly among the exchangeable positions at equilibrium. With the 0.206 M cyclopentanone used, containing ~92% $d_4$ and 8% $d_3$, at equilibrium there will be ~97% $d_0$, 3% $d_1$, 0.03% $d_2$, and less $d_3$ and $d_4$. Scheme III neglects the $d_2$, $d_3$, and $d_4$ present at equilibrium. Since $k_1 d_{1_{eq}}$ must equal $k_{-1} d_{0_{eq}}$, $k_{-1}$ may be set equal to $k_1 d_{1_{eq}}/d_{0_{eq}}$. The operator method[28] may be used to get eq 10-20 for Scheme III:

$$d_4 = d_{4_0} E_4 \tag{10}$$

$$d_3 = d_{3_0} E_3 + \frac{k_4 d_{4_0}}{k_4 - k_3}(E_3 - E_4) \tag{11}$$

$$\begin{aligned} d_2 = {} & \left[d_{2_0} + \frac{k_3 d_{3_0}}{k_3 - k_2} + \frac{k_3 k_4 d_{4_0}}{(k_3 - k_2)(k_4 - k_2)}\right] E_2 \\ & - \frac{k_3 d_3}{k_3 - k_2} - \frac{k_3 k_4 d_4}{(k_3 - k_2)(k_4 - k_3)} \end{aligned} \tag{12}$$

$$\begin{aligned} d_1 = {} & \left[d_{1_0} + \frac{k_1' d_{2_0}}{k_2 - k_1'} + \frac{k_2' k_3 d_{3_0}}{(k_2 - k_1')(k_3 - k_1')}\right. \\ & + \frac{k_2' k_3 k_4 d_{4_0}}{(k_2 - k_1')(k_3 - k_1')(k_4 - k_1')} - \frac{k_{-1} d_{3_0}}{(k_3 - k_1')} \\ & \left. - \frac{k_{-1} k_4}{(k_3 - k_1')(k_4 - k_1')} - \frac{k_{-1} d_{4_0}}{(k_4 - k_1')} - \frac{k_{-1}}{k_1'}\right] E_1 \\ & - \left[\frac{k_2' d_2}{(k_2 - k_1')} - \frac{k_2' k_3}{(k_2 - k_1')(k_3 - k_1')} - \frac{k_{-1}}{k_3 - k_1'}\right] d_3 \\ & + \left[\frac{k_{-1}}{(k_4 - k_1')} + \frac{k_{-1} k_4}{(k_3 - k_1')(k_4 - k_1')}\right. \\ & \left. - \frac{k_2' k_3 k_4}{(k_4 - k_3)(k_4 - k_2)(k_3 - k_2)}\right] d_4 - \frac{k_{-1}}{k_1'} \end{aligned} \tag{13}$$

$$d_0 = 1 - d_4 - d_3 - d_2 - d_1 \tag{14}$$

$$E_1 = \exp(-k_1 t) \tag{15}$$

$$E_2 = \exp(-k_2 t) \tag{16}$$

$$E_3 = \exp(-k_3 t) \tag{17}$$

$$E_4 = \exp(-k_4 t) \tag{18}$$

$$k_1' = k_1 - k_{-1} \tag{19}$$

$$k_2' = k_2 - k_{-1} \tag{20}$$

$d_{4_0}$, $d_{3_0}$, $d_{2_0}$, and $d_{1_0}$ are defined as the fractions of $d_4$, $d_3$, $d_2$, and $d_1$ initially.

Secondary deuterium kinetic isotope effects (Table IV) in the dedeuteration of cyclopentanone-$d_4$ may be discussed in terms of Scheme V, in which $d_{2a}$ has both deuterium atoms on the same $\alpha$ carbon atom, $a$ is the $\alpha$ deuterium isotope effect, and $g$ is the $\gamma$ deuterium isotope (which is assumed to be the same for cis as for trans $\gamma$ deuterium), both isotope effects being of the form $k^H/k^D$. The isotope effects are assumed to be independent of each other (i.e., multiplicative) and $a$ and $g$ are each assumed to be near 1.0. Since the rate constant for formation of $d_{2s}$ from $d_3$ is essentially twice that for $d_{2a}$ and the rate constants for disappearance of $d_{2a}$ and $d_{2s}$ are essentially identical, we assume that $d_{2s}$ is two times $d_{2a}$. These assumptions lead to

$$k_3 = (a/4 + g/2)k_4 \tag{21}$$

$$k_2 = (ag/3 + g^2/6)k_4 \tag{22}$$

$$k_1 = ag^2 k_4/4 \tag{23}$$

We now replace $a$ by $1 + \alpha$ and $g$ by $1 + \gamma$ and, since $a$ and $g$ are near 1.0, $\alpha$ and $\gamma$ are each much smaller than 1.0. This substitution gives

$$k_3 = (3 + \alpha + 2\gamma)k_4/4 \tag{24}$$

$$k_2 = (3 + 2\alpha + 4\gamma + 2\alpha\gamma + \gamma^2)k_4/6 \tag{25}$$

$$k_1 = (1 + \alpha + 2\gamma + \gamma^2 + 2\alpha\gamma + \alpha\gamma^2)k_4/4 \tag{26}$$

Since $\alpha$ and $\gamma$ are much smaller than 1.0, the terms higher than first order in $\alpha$ and $\gamma$ are neglected to give

$$k_3 = 3zk_4/4 \tag{27}$$

$$k_2 = z^2 k_4/2 \tag{28}$$

$$k_1 = z^3 k_4/4 \tag{29}$$

**Scheme V**

$$\begin{tikzcd}
d_4 \arrow[r, "k_4"] & d_3 \arrow[r, "ak_4/4"] \arrow[d, "gk_4/2"'] & d_{2a} \arrow[d, "g^2k_4/2"'] & \\
 & d_{2s} \arrow[r, "agk_4/2"] & d_1 \arrow[r, "ag^2k_4/4"] & d_0
\end{tikzcd}$$

in which $z$ is equal to $1 + (\alpha + 2\gamma)/3$ or $(a + 2g)/3$. These equations are equivalent to eq 8.

**Kinetics of Stereoselective Catalysis.** If the initial concentrations of $d_0$, $d_1$, and $d_2$ are taken as 0 (although up to 2% $d_2$ was present initially, but essentially no $d_1$ or $d_0$) and reversibility is neglected, Scheme IV leads to

$$d_4 = d_{4_0}E_8 \tag{30}$$

$$d_3 = A_3E_7 - 4d_{4_0}E_8 \tag{31}$$

$$d_2 = A_2E_6 - 3A_3E_7 + 6d_{4_0}E_8 \tag{32}$$

$$d_1 = A_1E_5 - 2A_2E_6 + 3A_3E_7 - 4d_{4_0}E_8 \tag{33}$$

$$d_0 = 1 - d_1 - d_2 - d_3 - d_4 \tag{34}$$

in which $d_{4_0}$ is the initial fraction of $d_4$ and the $A$'s and $E$'s are defined in

$$A_1 = (d_{4_0} + 3)/2 \tag{35}$$

$$A_2 = (d_{4_0} + 1)/2 \tag{36}$$

$$A_3 = (3d_{4_0} + 1)/2 \tag{37}$$

$$E_5 = \exp(-k_dt) + \exp(-k_1t) \tag{38}$$

$$E_6 = \exp(-2k_dt) + 4\exp[-(k_d + k_1)t] + \exp(-2k_1t) \tag{39}$$

$$E_7 = \exp[-(2k_d + k_1)t] + \exp[-(k_d + 2k_1)t] \tag{40}$$

$$E_8 = \exp[-(2k_d + 2k_1)t] \tag{41}$$

To allow for reversibility, eq 33 was replaced by

$$d_1 = [A_1E_5 - 2A_2E_6 + 3A_3E_7 - 4d_{4_0}E_8 + (d_1/d_0)_{eq}(1 - d_4 - d_3 - d_2)]/[1 + (d_1/d_0)_{eq}] \tag{42}$$

**Statistical Treatment.** Rate constants, p$K_a$ values, etc., and their estimated standard deviations were calculated by nonlinear or linear least-squares treatments,[29] as appropriate. Observations were weighted so as to minimize the sum of the squares of $(k_{obsd} - k_{calcd})/k_{obsd}$ rather than $(k_{obsd} - k_{calcd})$. This is based on the assumption that the percent uncertainty is more nearly the same for the various $k$ values than is the absolute uncertainty.

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(21) Assuming that catalysis by the tertiary amino groups of **2** and **2H**$^+$ obeys the Brønsted plot in Figure 2, that the primary amino groups are one seventh as reactive as they would be if they were tertiary, and that the relative extents to which the primary and tertiary amino groups have become protonated in **2H**$^+$ may be calculated as described earlier[22] (which gives $f_t$ and $f_p$ values of 0.28 and 0.18, respectively, for **2**).
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