Photochemical Experiments. The irradiations were carried out in a Rayonet RPR-208 photoreactor, equipped with eight RUL 3500 lamps and Pyrex vessels and a Rayonet RPR-204 photoreactor, equipped with four RUL 2537 lamps and quartz vessels.

Isolation of the Photoproducts. The excess of the sensitizer 4-benzoylbiphenyl was removed by crystallization from *n*-hexane. Then the residual oil was separated by high-pressure LC with a 20 cm × 4.6 cm column packed with 10-μm Nucleosil. The eluent was 0.20% CH_3CN in hexane at a flow rate of 4.2 mL/min, yielding three bands: band A, retention time 5.0 min, 34 mg of ODPM isomers **14** and **15**; band B, retention time 5.5 min, 15 mg of 4-benzoylbiphenyl; band C, retention time 7.0 min, 52 mg of DPM isomer **13**.

Fraction A: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.4-7.0 (m, 4 H, Ar), 6.03 (dd, J = 9, 17 Hz, 1 H, olefinic H of **14**), 5.67 (dd, J = 10, 16 Hz, 1 H, olefinic H of **15**), 5.30-5.05 (m, 4 H, methylene H's of **14** and **15**), 2.8-2.5 (m, 2 H), 2.4-2.2 (m, 4 H), 2.17 (s, 3 H, acetyl H's of **15**), 1.90 (s, 3 H, acetyl H's of **14**), 1.85-1.60 (m, 2 H), 1.38 (s, 1 H, cyclopropyl H of **14**), 1.08 (s, 1 H, cyclopropyl H of **15**); IR (liquid capillary) 3060 (w), 3050 (w), 2980 (m), 2940 (m), 2870 (m), 1705 (s), 1630 (w), 1490 (m), 1450 (m) 1355 (m), 765 (m), 750 (m), 740 (m) cm^{-1}. (N.b.: Fraction A contained about equal amounts of **14** and **15**.)

Fraction C: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.35-6.95 (m, 4 H, Ar), 6.04 (dd, J = 11, 16 Hz, 1 H, olefinic), 5.21 (dd, J = 1.5, 11 Hz, 1 H, olefinic), 5.18 (dd, J = 1.5, 17 Hz, 1 H, olefinic), 2.73-2.57 (m, 1 H), 2.40-2.15 (m, 2 H), 2.00-1.80 (m, 1 H), 1.90 (s, 3 H, acetyl), 1.35 (s, 3 H, methyl), 1.26 (s, 1 H, cyclopropyl); IR (liquid capillary) 3060 (w), 3020 (w), 2930 (m), 2880 (w), 1700 (s), 1630 (w), 1490 (m), 1450 (w), 1355 (m), 770 (m), 750 (m), 740 (m) cm^{-1}.

Pyrolysis of the DPM and ODPM isomers. The isomers **16** and **17** were isolated by preparative GLC by using a copper column, 5 m × 0.25 in. with Chromosorb W-AW (60-80 mesh) coated with 15% DC-550 at 260 °C. The carrier gas employed was helium at a flow rate of 60 mL/min. Upon pyrolysis of **13**, a new compound, viz. the isomer **16**, was obtained: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.15-7.00 (m, 3 H, Ar), 7.00-6.90 (m, 1 H, Ar), 6.05 (s, 1 H, H_Z olefinic), 5.38 (q, J = 7 Hz, 1 H, olefinic), 5.28 (s, 1 H, H_E olefinic), 5.18 (s, 1 H, aliphatic), 2.98-2.85 (m, 1 H), 2.83-2.70 (m, 1 H), 2.60-2.40 (m, 1 H), 2.32 (s, 3 H, acetyl), 2.25-2.13 (m, 1 H), 1.73 (dd, J = 2, 7 Hz, 3 H, methyl); IR (liquid capillary) 3100 (w), 3060 (m), 3020 (m), 2940 (m), 2920 (s), 2850 (m), 1680 (s), 1620 (m), 1490 (m), 1450 (m), 1360 (m), 1235 (m), 1115 (m), 1100 (m), 940 (m), 700 (w), 675 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{18}O$: C, 83.96; H, 8.05. Found: C, 83.60; H, 8.02. High-resolution mass spectrum (70 eV): calcd for $C_{14}H_{16}O$, m/z 226.1355; found, m/z 226.1355.

Upon pyrolysis of the mixture of **14** and **15**, complete conversion into one new isomer, viz., **17**, was observed: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.5-7.1 (m, 4 H, Ar), 5.95 (dd, J = 9, 16 Hz, 1 H, olefinic), 5.18 (dd, J = 1, 9 Hz, 1 H, olefinic), 5.17 (s, 1 H, aliphatic), 5.09 (dd, J = 1, 16 Hz, 1 H, olefinic), 2.75-2.60 (m, 2 H), 1.95-1.75 (m, 2 H), 1.77 (s, 3 H, acetyl), 1.56 (s, 3 H, methyl); IR (liquid capillary) 3080 (m), 3060 (m), 3020 (m), 2920 (s), 2880 (m), 2850 (m), 1705 (s), 1660 (m), 1490 (m), 1450 (s), 1430 (s), 1385 (s), 1210 (m), 1160 (m), 985 (s), 940 (s), 910 (s), 700 (w), 650 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{18}O$: C, 83.96; H, 8.05. Found: C, 83.70; H, 8.03. High-resolution mass spectrum (70 eV): calcd for $C_{14}H_{16}O$, m/z 226.1355; found, m/z 226.1356.

Eu(fod)$_3$ Complexation. For the Eu(fod)$_3$ experiments a solution Eu(fod)$_3$, purchased from Aldrich Chemical Co. (Gold Label 99%), in deuterated chloroform was used (50 mg/mL). This solution was added (in portions) to a solution of 1 mg/0.3 mL of isomer in $CDCl_3$.

Attempted Trapping of the DPM Intermediate with MeOH.[36] A solution of **1** (10 mg/mL) was irradiated at λ 350 nm in methanol with 4-benzoylbiphenyl as triplet sensitizer (10 mg/mL). After 35 min **1** had disappeared and the irradiation mixture was treated in the same way as described under isolation of the photoproducts. The ^{1}H NMR spectrum consisted of the same absorptions of **13-15** in the same ratio as observed for the irradiation of **1** in benzene.

Acknowledgment. This work was carried out under the auspices of the Netherlands Foundation for Chemical Research (S.O.N.) with financial support from the Netherlands Organization for Advancement of Pure Research (Z.W.O.).

Registry No. (±)-**1**, 85553-98-6; (±)-(*E*)-**2**, 85553-99-7; (±)-(*Z*)-**2**, 85554-00-3; (±)-**3**, 85554-01-4; **4**, 41791-31-5; (±)-**5**, 85554-02-5; **6**, 20451-53-0; **7**, 85554-03-6; (±)-**8**, 85554-04-7; (±)-**9**, 85554-05-8; **11**, 825-25-2; **12**, 85554-06-9; (±)-**13**, 85611-56-9; (±)-**14**, 85611-57-0; (±)-**15**, 85611-58-1; (±)-(*Z*)-**16**, 85554-07-0; (±)-(*Z*)-**17**, 85554-08-1; (*E*)-**35**, 34541-74-7; (±)-(*E*)-**36**, 85554-09-2; (*E*)-**37**, 85554-10-5; (±)-(*E*)-**38**, 85554-11-6; (±)-(*E*)-**39**, 85554-12-7.

(36) D. J. Patel and D. I. Schuster, *J. Am. Chem. Soc.*, **90**, 5137 (1968).

Four-at-Once Dedeuteration of Cyclopentanone-2,2,5,5-d_4[1]

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Contribution from the Department of Chemistry, The Ohio State University, Columbus Ohio 43210. *Received December 20, 1982*

Abstract: In aqueous solutions containing 3-(dimethylamino)propylamine (**1**) or 2,2-dimethyl-3-(dimethylamino)propylamine (**2**), cyclopentanone-2,2,5,5-d_4 undergoes dedeuteration largely by forming iminium ions. In the iminium ions deuterium is exchanged with the solvent via internal basic catalysis by the dimethylamino group from the catalyst. At most pH's studied the most common result of iminium-ion formation was exchange of all four deuterium atoms from the ketone. This contrasts with earlier studies of acetone-d_6 and certain diamines, in which the most common result of iminium-ion formation was exchange of all three deuterium atoms on one side of the ketone. Apparently, in the present case, but not in the earlier cases, the intermediate iminium ion undergoes cis-trans isomerization more rapidly than it is hydrolyzed back to ketone. It is proposed that this isomerization can take place via reaction of the iminium ion with a second molecule of diamine catalyst to give a *gem*-diamine or *gem*-diamine derivative that can revert to either geometric isomer of the iminium ion. Rapid transimination via *gem*-diamine formation apparently also takes place in the presence of other primary amines. The dedeuteration of cyclopentanone-d_4 catalyzed by 0.005 M **1** was studied in the presence of added 2-(dimethylamino)ethylamine (**3**), an amine that forms iminium ions rapidly but is a poor catalyst for deuterium exchange. At about pH 8, 0.05 M **3** increases the rate of formation of the iminium ions derived from cyclopentanone and **1** by about 16-fold; simultaneously, the ratio of the rate of dedeuteration to the rate of hydrolysis of these iminium ions decreases by about 16-fold. Other possible mechanisms for cis-trans isomerization of the intermediate iminium ions are discussed as are reasons why such isomerization is faster than iminium-ion hydrolysis in some cases but not in others.

Three types of α-hydrogen exchange have been observed for ketones. (1) Many achiral monofunctional bases and acids give one-at-a-time exchange nonstereoselectively.[2-5] (2) Certain primary-tertiary diamines give exchange by the mechanism shown

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Scheme I

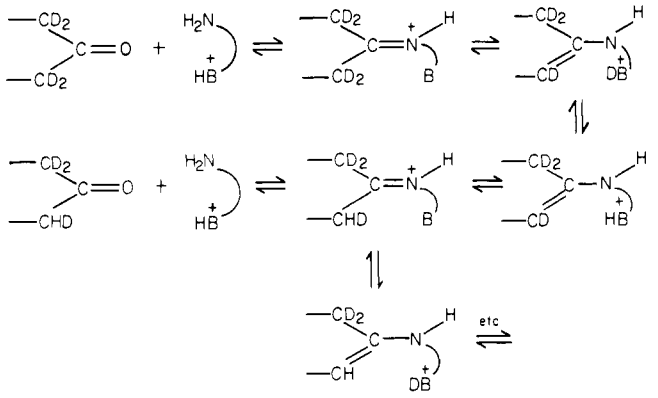


Table I. Dedeuteration of Cyclopentanone-*2,2,5,5-d_4* in the Presence of 3-(Dimethylamino)propylamine (**1**)[a]

pH	$10^3 \cdot [1]_t$,[b] M	I[c]	$10^5 \cdot k_4$, s^{-1}	$10^5 \cdot k_p$, s^{-1}	$10^5 k_{im}$, s^{-1} l.s.[d]	$10^5 k_{im}$, s^{-1} calcd[e]	r	% std dev[f]
7.995	1.00	0.30	0.93	0.14	0.913	0.77	8	0.6
8.006	5.0	0.30	4.50	0.45	4.5	3.9	10	1.3
8.010	20.7	0.030	25.1	3.2	24	22	12	0.5
8.047	20.7	0.030	24.3	3.3	24	22	10	2.2
8.115	10.0	0.30	10.3	1.4	9.7	8.9	11	0.7
8.329	21.5	0.027	35.6	4.5	34	29	11	1.3
9.010	19.7	0.020	43.2	6.6	40	35	10	0.7
9.499	21.5	0.016	56.2	10.9	51	42	8	0.9
9.941	19.9	0.011	61.0	16.3	52	43	5.5	1.1

[a] In aqueous solution at 35 °C. [b] Total concentration in all states of protonation. [c] Ionic strength. [d] From least-squares fit of the data to Scheme III. [e] From rate constants for imine formation by 1 and $1H^+$ (ref 9). [f] Of the calculated from the observed values of d_4, d_3, d_2, d_1, and d_0 in the least-squares treatment that gave k_{im} (l.s.) and r.

Table II. Dedeuteration of Cyclopentanone-*2,2,5,5-d_4* in the Presence of 2,2-Dimethyl-3-(dimethylamino)propylamine (**2**)[a]

pH	$10^3 \cdot [2]_t$,[b] M	I[c]	$10^5 \cdot k_4$, s^{-1}	$10^5 \cdot k_p$, s^{-1}	$10^5 k_{im}$, s^{-1} l.s.[d]	$10^5 k_{im}$, s^{-1} calcd[e]	r	% std dev[f]
6.860	10.3	0.021	9.04	0.21	9.8	6.8	10	1.2
7.403	27.7	0.056	35.1	0.9	37	28	12	1.8
8.772	98.3	0.197	159	7	156	137	21	1.4
9.431	27.7	0.056	53.7	5.5	54	39	11	2.9
9.861	10.3	0.021	23.3	6.4	20	14	19	1.7

[a] In aqueous solution at 35 °C. [b] Total concentration in all states of protonation. [c] Ionic strength. [d] From least-squares fit of the data to Scheme III. [e] From rate constant for imine formation by 2 and $2H^+$ (ref 9). [f] Of the calculated from the observed values of d_4, d_3, d_2, d_1, and d_0 in the least-squares treatment that gave k_{im} (l.s.) and r.

in Scheme I.[2,4] With a chiral catalyst and a prochiral CD_2 group, one-at-a-time exchange may occur stereoselectively.[2,5-7] (3) When the rate of internally catalyzed deuterium exchange of the intermediate iminium ion in Scheme I is enough faster than its rate

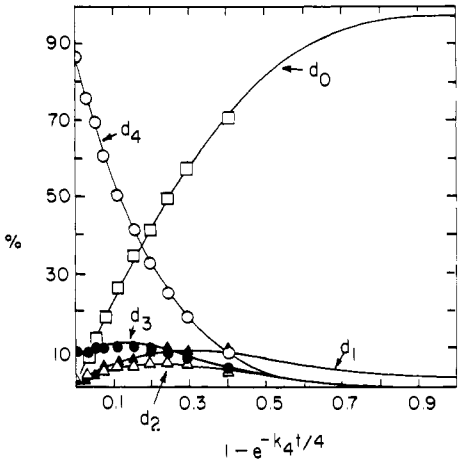


Figure 1. Kinetic plot for dedeuteration of cyclopentanone-d_4 in the presence of 0.0207 M 3-(dimethylamino)propylamine at pH 8.01: ○, d_4; ●, d_3; △, d_2; ▲, d_1; □, d_0.

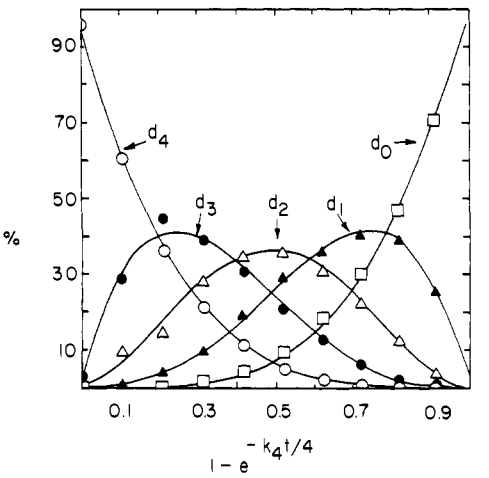
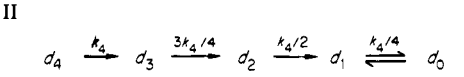


Figure 2. Kinetic plot for dedeuteration of cyclopentanone-d_4 in the presence of 0.30 M *N,N*-dimethyl-2-methoxyethylamine at pH 9.39.

Scheme II



of hydrolysis back to ketone, the most common result of iminium-ion formation may be exchange of all the deuterium atoms that are cis to the basic group B. With acetone-d_6, this all-on-one-side exchange has been observed with several catalysts,[2,4] most strikingly with 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine.[8]

We have now found a fourth type of behavior. The most common result of iminium-ion formation from cyclopentanone-*2,2,5,5-d_4* and 3-(dimethylamino)propylamine (**1**) or 2,2-dimethyl-3-(dimethylamino)propylamine (**2**) under certain conditions is exchange of all four deuterium atoms.

$Me_2N(CH_2)_3NH_2$ **1** $Me_2NCH_2CMe_2CH_2NH_2$ **2**

Results and Discussion

Tables I and II summarize some of the results obtained on the dedeuteration of cyclopentanone-*2,2,5,5-d_4* in the presence of **1** and **2**, respectively. The first-order rate constant for disappearance of cyclopentanone-d_4 is k_4. On the basis of a Brønsted plot for amines of the type RCH_2NMe_2,[6] which are known to be considerably better monofunctional catalysts than the corresponding primary amines (RCH_2NH_2), and of the known rate constant for hydroxide ions,[6] we have calculated a value of k_p, the estimated first-order rate constant for monofunctionally catalyzed dedeu-

(1) (a) Research supported in part by Grant GM 18593 from the National Institute of General Medical Sciences. Part 22 in the series Catalysis of α-Hydrogen Exchange. (b) For part 21 see: Hine, J.; Zeigler, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 7524–9. (c) Abstracted in part from the Ph.D. Dissertations of James P. Zeigler, 1978, and David E. Miles, 1982, The Ohio State University, Columbus, Ohio.

(2) Hine, J. *Acc. Chem. Res.* **1978**, *11*, 1–7.

(3) Hine, J.; Kaufmann, J. C.; Cholod, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 4590–5.

(4) Hine, J.; Cholod, M. S.; King, R. A. *J. Am. Chem. Soc.* **1974**, *96*, 835–45.

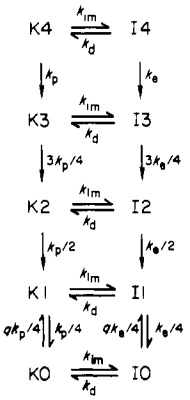
(5) Hine, J.; Li, W.-S. *J. Am. Chem. Soc.* **1975**, *97*, 3550–1.

(6) Hine, J.; Li, W.-S.; Zeigler, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 4403–9.

(7) Hine, J.; Zeigler, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 7524–9.

(8) Hine, J.; Li, W.-S. *J. Am. Chem. Soc.* **1976**, *98*, 3287–94.

Scheme III



teration, as described previously.[4,6] The observed rates of disappearance of d_4 are faster than would be expected if the catalysts were acting monofunctionally, by 3- to 10-fold in the case of **1** and 3- to 40-fold in the case of **2**. We therefore conclude that both catalysts are acting largely by the bifunctional mechanism shown in Scheme I.

Additional evidence that these reactions are not cases of simple base catalysis is the fact that the deuterium atoms are not exchanged one at a time. In every run where **1** or **2** was the only catalyst present, when the d_4 concentration dropped enough that d_4 was not the most abundant species, d_0 became the most abundant. There was no time when d_3, d_2, or d_1 was most abundant. This behavior, which is illustrated in Figure 1, contrasts with one-at-a-time exchange, where d_4, d_3, d_2, d_1, and d_0 are successively the most abundant species. One-at-a-time exchange is illustrated in Figure 2, where the lines are based on Scheme II. The type of exchange shown in Figure 1 also contrasts with all-on-one-side exchange, in which first the fully deuterated, then the half-deuterated, and finally the undeuterated species is most abundant. This type of exchange has not yet been observed with cyclopentanone-d_4 but has been with acetone-d_6.[2,8]

Data on dedeuteration of cyclopentanone-d_4 in the presence of **1** and **2** were fit to Scheme III, in which K4 represents the d_4 ketone, I3 represents the d_3 iminium ion, etc. Since the rate constant for cis–trans isomerization of the intermediate iminium ion is assumed to be large compared to k_d and k_e, it is not necessary to distinguish between the different d_2 species (both deuterium atoms on the same side or one on each side) or between the d_3 iminium ion in which the basic group B from the catalyst is cis to the CD_2 group and the one in which it is cis to the CHD group.

Reversibility is allowed for by the q-containing rate constants, where q is the equilibrium ratio of K1 to K0 (about 0.028 under the conditions used). For each of the runs in Tables I and II, a least-squares treatment gave a value of k_{im} and a value of r, which is the ratio k_e/k_d. These values are related to k_4, the first-order rate constant for disappearance of the d_4 ketone, as shown in eq 1. The results and the standard deviations of the calculated from

$$k_4 = \frac{k_{im} r}{r + 1} + k_p \qquad (1)$$

the observed values of d_4, d_3, d_2, d_1, and d_0 are shown in Tables I and II.

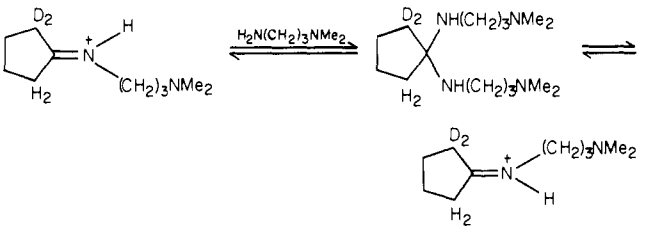
Also shown in Table I and II are values of k_{im} that were calculated from rate constants for imination of cyclopentanone by the unprotonated and monoprotonated forms of **1** and **2**, which were obtained by capturing the intermediate iminium ions with hydroxylamine.[9] There are several reasons why the two sets of k_{im} values would not be expected to agree perfectly. The present experiments deal with about 0.2 M cyclopentanone-d_4 and the hydroxylamine-capturing experiments with about 0.02 M cyclopentanone of natural isotopic content. The secondary deuterium kinetic isotope effect in imination of acetone and acetone-d_6 is positive, with an average h^D/k^H of 1.2.[10] The different concentrations of ketone, amines, and salts could have small medium effects. In addition, there are experimental errors in arriving at k_{im} values by either method, but probably larger ones by the present dedeuteration method, which is less direct.

Table III. Dedeuteration of Cyclopentanone-d_4 in the Presence of Some Methoxy Amines and 2-(Dimethylamino)ethylamine[a]

Am	$[Am]_t$,[b] M	pH	$10^5 \cdot k_4$, s^{-1}	$10^5 \cdot k_p$, s^{-1}	$10^5 \cdot k_{im}$,[c] s^{-1}	r[d]
$MeOCH_2CH_2NMe_2$	0.121	9.260	25			
$MeOCH_2CH_2NMe_2$	0.30	9.390	70			
$MeO(CH_2)_3NH_2$	0.15	9.302	25	24	90	0.01
$MeOCH_2CH_2NMe_2$	0.15	9.289	96	59	88	0.7
$MeO(CH_2)_3NH_2$	0.15					
$MeOCH_2CH_2NH_2$	0.15	7.981	3.5	3.4	7.8	0.01
$Me_2NCH_2CH_2NH_2$	0.020	7.961	1.6	0.8	560	0.001

[a] In aqueous solution at 35 °C and ionic strength 0.30. [b] Total concentration in all states of protonation. [c] Calculated from the rate constants for imine formation determined by hydroxylamine-capturing experiments (ref 9). [d] Calculated from eq 2.

Scheme IV



The raw data for the runs in Tables I and II were also fit to a reaction scheme in which no cis–trans isomerization of the intermediate iminium ions was assumed to occur, as described in more detail in the Appendix. The standard deviations of the calculated from the observed values of d_4, d_3, d_2, d_1, and d_0 averaged more than 10%—far larger than the values based on Scheme III, which are shown in Tables I and II.

It could be suggested that iminium ions derived from cyclopentanone-d_4 in general have such large rates of exchange relative to their rates of hydrolysis that they often exchange all four deuterium atoms via attack by external bases, which can occur at either α-carbon atom. It is already clear from the data in Table I that attack by external bases on intermediate iminium ions is not the principal path for exchange in the presence of **1**. In these reaction solutions the principal bases present are other molecules of **1**. The rate constant for exchange by the iminium ions (k_e) should increase with increasing **1** concentrations, just as k_p does. Since k_d should not be affected at constant pH, r should be roughly proportional to k_p at a given pH. Instead, it is seen that 20-fold changes in the concentration of **1** at pH 8.021 ± 0.026, which give 20-fold changes in k_p, do not give changes in r that are clearly beyond the experimental error. Additional evidence against this suggestion is given in Table III, which gives data on the dedeuteration of cyclopentanone-d_4 in the presence of 2-(dimethylamino)ethylamine and some methoxy amines. In all the runs using methoxy amines, the amine concentrations are much larger than in any of the runs in Table I. Nevertheless, the r values, which may be calculated from eq 2 (a rearranged form of eq 1), are all

$$r = (k_4 - k_p)/(k_{im} - k_4 + k_p) \qquad (2)$$

smaller than 1.0. That is, the iminium ions all hydrolyze faster than they exchange. Hence the large r values obtained with **1** and **2** arise from *internal* base catalysis. Thus, the all-at-once exchange of cyclopentanone-d_4 in the presence of **1** and **2** shows that the intermediate iminium ions undergo cis–trans isomerization more rapidly than they hydrolyze to ketone under our reaction conditions.

(9) Hine, J.; Zeigler, J. P.; Johnston, M. *J. Org. Chem.* **1979**, *44*, 3540–5.

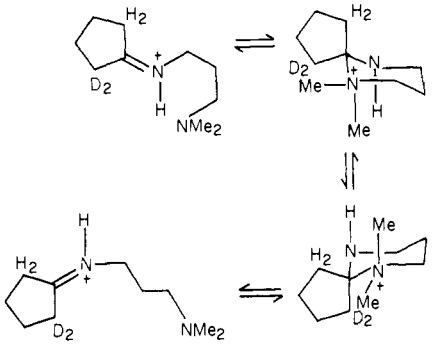
(10) Hine, J.; Li, W.-S. *J. Org. Chem.* **1975**, *40*, 2622–6.

Table IV. Dedeuteration of Cyclopentanone-d_4 in the Presence of 1 and 2-Methoxyethylamine[a]

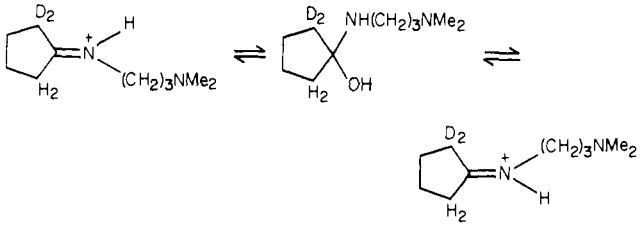
$[1]_t$,[b] M	$[MeO(CH_2)_2NH_2]_t$,[b] M	pH	10^5k_4, s^{-1}	10^5k_p, s^{-1}	10^5k_{im}, s^{-1} obsd[c]	10^5k_{im}, s^{-1} calcd[d]	r obsd[c]	r calcd[e]
0.005		8.006	4.5	0.45	4.5	3.9	10	10
0.005	0.005	8.071	4.7	0.71	4.6	4.7	10	9
0.005	0.005	8.030	5.3	0.66	5.4	4.5	9	9
0.005	0.075	7.980	8.9	2.2	7.4	7.7	7	5
	0.15	7.981	3.5	3.4		7.8	0.001[f]	

[a] In aqueous solution at 35 °C and ionic strength 0.30. [b] In all states of protonation. [c] From least-squares fit of the data to Scheme III. [d] From eq 3. [e] From eq 4. [f] From eq 2.

Scheme V



Scheme VI



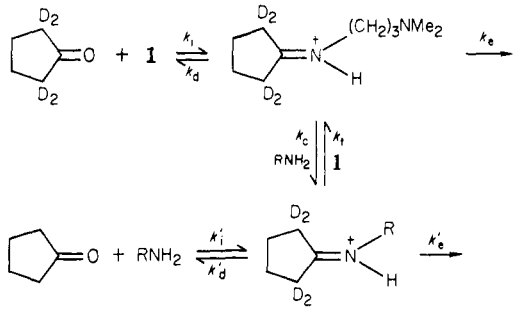
We have considered three possible mechanisms for this cis–trans isomerization: (1) the *gem*-diamine mechanism (Scheme IV), in which the iminium ion is attacked by a second molecule of diamine catalyst to give a *gem*-diamine (or *gem*-diamine derivative) that can decompose to either geometric isomer of the iminium ion; (2) the hexahydropyrimidinium-ion mechanism (Scheme V), in which the dimethylamino group of the iminium ion bonds to the iminium carbon atom to give a hexahydropyrimidinium ion that can undergo a chair–chair ring inversion and a pyramidal inversion at the secondary amino group to give a new conformation of the hexahydropyrimidinium ion, whose decomposition will lead to the other geometric isomer of the iminium ion; (3) the carbinolamine mechanism (Scheme VI), in which the iminium ion forms a carbinolamine in which rotation around a carbon–nitrogen single bond gives a new conformer whose loss of OH will give the other geometric isomer of the iminium ion.

If carbinolamine formation is the main path for cis–trans isomerization of the iminium ion, the carbinolamine must be transformed to the iminium ion faster than it decomposes to ketone and diamine. In such an event, carbinolamine formation (or some earlier step) would be the rate-controlling step in forming the iminium ion from ketone and diamine. It seems very unlikely that this is so in the reaction of cyclopentanone with **1**. For example, monoprotonated 2-(dimethylamino)ethylamine (**3**) transforms

$$Me_2NCH_2CH_2NH_2$$
3

cyclopentanone to iminium ions about 16 times as fast as monoprotonated **1** does.[9] This was explained in terms of increased efficiency of internal acid-catalyzed dehydration of the intermediate carbinolamine. It would certainly be unreasonable to suggest that $3H^+$ undergoes nucleophilic attack on cyclopentanone 16 times as fast as $1H^+$ does, considering that $1H^+$ is more than 40 times as basic as $3H^+$. It might be postulated that nucleophilic attack on the ketone to give a zwitterionic intermediate is reversible and capture of this intermediate by internal protonation by the $-NHMe_2^+$ group is rate controlling. However, if this were the case, then in the case of primary amines that have similar structures but lack the ability to capture the zwitterionic intermediate internally, external general acid and/or base catalyses should be observed,[11,12] but it is not.[9]

Scheme VII



Imines and iminium ions like those derived from cyclopentanone and **1** or **2** should undergo uncatalyzed geometric isomerization much too slowly[13,14] to compete with hydrolysis under our conditions.

If cis–trans isomerization of the iminium ion is occurring by the mechanism in Scheme IV, the molecules of 3-(dimethylamino)propylamine (**1**) in solution are rapidly adding to the iminium ion to give *gem*-diamine. If this is true, and some other primary amine is added to the solution, it too should transform the iminium ion rapidly to a *gem*-diamine, if it did not differ too much from **1** in basicity, steric accessibility of the amino group, or concentration. The *gem*-diamine formed in this way could lose **1** to give a new iminium ion, which could then hydrolyze to ketone. This would provide an added path for hydrolysis of the iminium ion and thus increase k_d in Scheme III. If k_e were not simultaneously increased too much, the value of r (the ratio k_e/k_d) would decrease. According to the principle of microscopic reversibility, a new path to the iminium ion derived from **1** will also be created (via attack of **1** on the iminium ion derived from the new amine to give the *gem*-diamine, which can decompose to give either iminium ion). Hence, the rate of exchange, as measured by k_4, should increase. To test the *gem*-diamine mechanism we studied the effect of added 2-methoxyethylamine on the dedeuteration of cyclopentanone-d_4 by **1** at pH 8.03 ± 0.05. The results are shown in Table IV. The value of k_4 in the presence of 0.005 M **1** is essentially doubled by the addition of 0.075 M 2-methoxyethylamine. Only 40% of this increase is accounted for by the increase in k_p. These results are interpreted in terms of Scheme VII, in which RNH_2 is 2-methoxyethylamine. We assume that k_c and k_i, the second-order rate constants for transimination, are so large that the sum $k_c[RNH_2] + k_d + k_e$ is well approximated

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Table V. Effect of 3 on Dedeuteration of Cyclopentanone-d_4 in the Presence of 1[a]

[1],[b] M	[3],[b] M	pH	$10^5 \cdot k_4$, s^{-1}	$10^5 \cdot k_p$, s^{-1}	$10^5 k_{im}$, s^{-1} obsd[c]	$10^5 k_{im}$, s^{-1} calcd[d]	r obsd[c]	r calcd[e]
0.005		8.006	4.6	0.46	4.5	4.5	10	10
0.005	0.005	7.872	11.4	0.55	14	12	3.3	3.7
0.005	0.020	8.059	25	1.2	39	35	1.6	1.3
0.005	0.050	7.760	31	1.6	78	80	0.56	0.56
	0.020	7.961	1.6	0.8				

[a] In water at 35 °C and ionic strength 0.30. [b] Total concentration in all states of protonation. [c] From least-squares fit to Scheme III. [d] From eq 6. [e] From eq 7.

as $k_c[RNH_2]$ and that $k_t[\mathbf{1}] + k_d' + k_e'$ is essentially equal to $k_t[\mathbf{1}]$. Thus the establishment of the transimination equilibrium is fast compared to competing processes. Reaction via Scheme VII is still consistent with Scheme III, of course, and an equation of the form of eq 1 still holds except that now k_{im}, the first-order rate constant for iminium-ion formation, is expressed as shown in eq 3, and r is expressed as shown in eq 4. (The k_e' term was neglected

$$k_{im} = k_i[\mathbf{1}]_t + k_i'[RNH_2]_t \quad (3)$$

$$r = \frac{(k_e/k_d)k_i[\mathbf{1}]_t}{k_i[\mathbf{1}]_t + k_i'[RNH_2]_t} \quad (4)$$

because estimates of k_e'/k_d' based on the r value for the run using only 2-methoxyethylamine and the various k_p values showed that such a term should never contribute more than 0.3% to r.) The concentrations with subscript t's are total concentrations in all states of protonation. The value of k_i, the "apparent" second-order rate constant for iminium-ion formation, can be calculated from eq 5, where k_a is the known[9] rate constant for imination by the

$$k_i = k_a f_0 + k_{ah} f_1 \quad (5)$$

unprotonated diamine, k_{ah} the value for monoprotonated diamine, f_0 the fraction of diamine that is unprotonated, and f_1 the fraction monoprotonated. A similar equation, in which k_{ah} is zero, gives k_i'. We have already described evidence that *very* little of the observed exchange arises from attack of external bases on the iminium ion; in the present treatment such exchange is neglected. Hence k_e/k_d is just equal to the value of r obtained at the same pH using **1** without added 2-methoxyethylamine. As the concentration of 2-methoxyethylamine is increased, the observed k_{im} values are seen to climb and the r values to fall, just as predicted by Scheme VII and eq 3 and 4. However, the magnitude of the changes in calculated k_{im} and r values is not enough larger than the experimental uncertainty in the observed values to provide a real quantitative test of the scheme.

In order to change k_{im} and r more drastically, we then carried out experiments using **3**, whose monoprotonated form iminates cyclopentanone more than 13 times as fast as either monoprotonated or unprotonated **1** or 2-methoxyethylamine.[9] No bifunctional catalysis was detected when acetone-d_6 was dedeuterated in the presence of **3** and $\mathbf{3H^+}$.[4] Comparison of the last entry in Table III with the third and fourth entries in Table I shows that **3** is only about $^1/_{15}$th as good a catalyst as **1** at pH 8.

Added **3** increases the rate of dedeuteration much more than added 2-methoxyethylamine does. As seen in Table V, at pH 8.01 ± 0.05, k_4 in the presence of 0.005 M **1** and 0.020 M **3** is four times as large as the sum of the k_4 values in the presence of the separate solutions of 0.005 M **1** and 0.020 M **3**. In addition, the added 0.020 M **3** has reduced r to less than one-sixth of its value in the absence of **3**. The addition of 0.05 M **3** at pH 7.76 reduces r to such a small value that we now see the characteristic pattern of one-at-a-time exchange; the most abundant species are successively d_4, d_3, d_2, d_1, and d_0. Although these changes are large, they are not as large as would be expected from eq 3 and 4. Apparently, the iminium ion derived from **3** is not transiminated faster than it is hydrolyzed. There is a good reason why the ratio $k_t[\mathbf{1}]/k_d'$ can be much larger when R is 2-methoxyethyl than when R is 2-(dimethylamino)ethyl. In the former case, k_i' may be

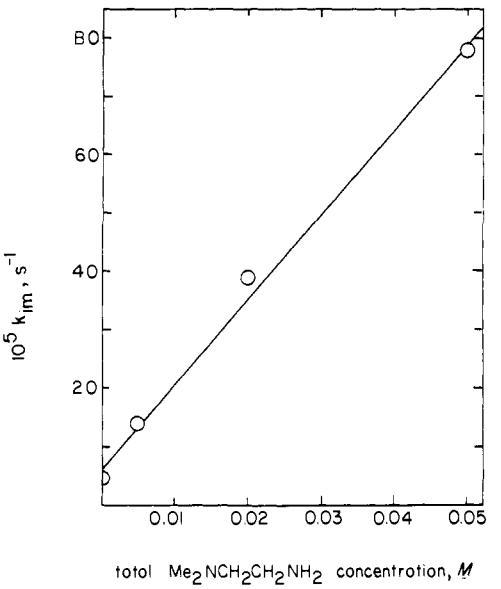


Figure 3. Plot of k_{im} vs. [3] for dedeuteration of cyclopentanone-d_4 in the presence of 0.005 M **1** at pH 7.88 ± 0.13; see eq 6 and 8.

calculated[9] to be 5.2×10^{-4} M^{-1} s^{-1} but in the latter case (**3** as RNH_2) k_i' is 0.27 M^{-1} s^{-1}—520 times as large. The difference in equilibrium constants (k_i'/k_d') should not be very large. Hence k_d' should be much larger when RNH_2 is **3** than when it is 2-methoxyethylamine.

We therefore treated the data in Table V using Scheme VII *without* assuming that transimination is fast compared to competing processes. Neglect of exchange via the k_e' path is an even better approximation with **3** than it was with 2-methoxyethylamine; larger rates of exchange are brought about by smaller amounts of RNH_2 in the case of **3** than in the case of 2-methoxyethylamine. These assumptions again lead to a rate equation of the form of eq 1, but now k_{im} and r are defined as shown in eq 6 and 7. With k_e/k_d being the value of r in the absence of

$$k_{im} = k_i[\mathbf{1}]\left(1 + \frac{(k_t/k_d')(k_i'/k_i)[\mathbf{3}]}{1 + (k_t/k_d')[\mathbf{1}]}\right) \quad (6)$$

$$r = \frac{(1 + (k_t/k_d')[\mathbf{1}])(k_e/k_d)}{1 + (k_t/k_d')([\mathbf{1}] + (k_i'/k_i)[\mathbf{3}])} \quad (7)$$

3 and k_i' and k_i being obtainable from eq 5, the only new term is the ratio k_t/k_d'.

According to eq 6, a plot of k_{im} against the concentration of **3** at constant [**1**] and constant pH should give a straight line whose intercept is $k_i[\mathbf{1}]$ and whose slope is given in eq 8. Such a plot

$$\text{slope}_{im} = \frac{k_i'(k_t/k_d')[\mathbf{1}]}{1 + (k_t/k_d')[\mathbf{1}]} \quad (8)$$

is shown in Figure 3 for the first four runs in Table V (pH 7.91 ± 0.15). The slope and values of k_i' and [**1**] gave a value of 11.1 M^{-1} for k_t/k_d'. Inverting eq 7 gives eq 9, according to which a

$$\frac{1}{r} = \frac{1}{k_e/k_d} + \frac{(k_t/k_d')(k_i'/k_i)[\mathbf{3}]}{(1 + (k_t/k_d')[\mathbf{1}])(k_e/k_d)} \quad (9)$$

plot of $1/r$ vs. [**3**] will also give a straight line. From the slope and intercept of this plot (Figure 4) a value of 11.6 M^{-1} is obtained for k_t/k_d'. The same value is obtained from a least-squares treatment of the k_{im} and r values for the first four runs in Table V. Values of k_{im} and r calculated from this value for k_t/k_d' are seen in the table to agree satisfactorily with those obtained from the d_4, d_3, d_2, d_1, and d_0 values by a least-squares fit to Scheme III. This supports Scheme VII for the effect of **3** on the dedeuteration reaction.

Multiplication of k_t/k_d' by [**1**] gives a value of 0.058 for $k_t[\mathbf{1}]/k_d'$, the ratio of the rate of transimination to the rate of

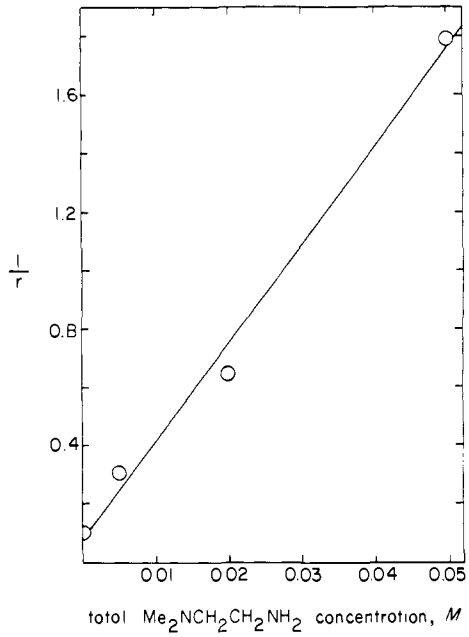
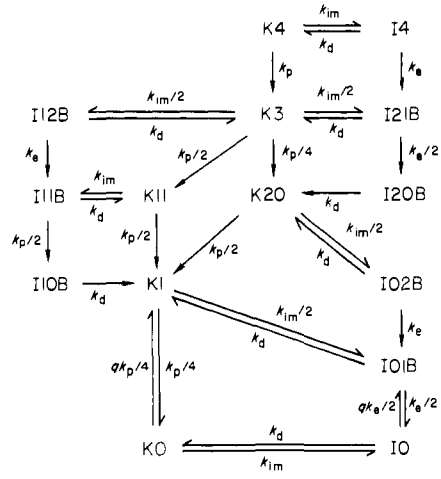


Figure 4. Plot of $1/r$ vs. [3] for dedeuteration of cyclopentanone-d_4 in the presence of 0.005 M **1** at pH 7.88 ± 0.13; see eq 9.

hydrolysis by the iminium ion derived from **3** under our average reaction conditions. Since k_i'/k_i, whose value is known, is equal to $k_d'k_c/(k_dk_t)$, division by k_t/k_d' gives a value of 373 M^{-1} for k_c/k_d. At the highest concentration of **3** used, multiplication by [3] gives 19 as the ratio of the rate of transimination by **3** to the rate of hydrolysis of the iminium ion derived from **1**. What does this tell about the rate of transimination by attack of **1**, which will take place even in the absence of added **3**? Attack by the primary amino groups in **1** and $\mathbf{1H^+}$ on the iminium ion derived from **1** to give *gem* diamine should be faster than attack by **3** and $\mathbf{3H^+}$, respectively, since the latter species are weaker bases.[15,16] However, because of the differences in basicities, a smaller fraction of the total **1** is present in the unprotonated and monoprotonated forms around pH 8, where our measurements were made. We have estimated the relative apparent second-order rate constants for attack by **1** and **3**, assuming that the relative rates of attack by the various primary amino groups are the same as their relative basicities, assuming that all the primary amino groups had the same reactivities, and making intermediate assumptions. The results ranged from estimating that the two species had about the same reactivity to estimating that **3** was three times as reactive as **1**. In drawing conclusions concerning cis–trans isomerization of the iminium ion via attack by **1**, it should be noted that k_c is a minimum value for those nucleophilic attacks by **3** that could result in cis–trans isomerization of the iminium ion derived from **1**. The reaction governed by k_c involves nucleophilic attack by a primary amino group from **3**, followed by loss of a proton from an NH_2^+ group in the immediate product to give the *gem*-diamine, followed by loss of **1** (not **3**) from the *gem*-diamine to give the iminium ion derived from cyclopentanone and **3**. Geometric ismerization of the iminium ion derived from **1** could take place via attack of a primary amino group from **3** without subsequent loss of a proton, via formation of *gem*-diamine that reverts to the original iminium ion, or via attack of a *tertiary* amino group from **3**. If none of these alternative paths are important, and if we define

Scheme VIII



k_g as the second-order rate constant for geometric isomerization of the iminium ion derived from **1** by attack of total **1**, then k_g should be of the same order of magnitude as k_c. In this event, $k_g[\mathbf{1}]/k_d$, the ratio of the rate of geometric isomerization by this path to the rate of hydrolysis of the iminium ion derived from **1**, will be only about 0.3 in the presence of 0.001 M total **1**, the smallest concentration of **1** at which we made measurements. If k_g is the only path for geometric isomerization, then a value of 0.3 is too small to explain why the dedeuteration in the presence of 0.001 M **1** follows the four-at-once path (Scheme III) so cleanly. We do not have good evidence to tell whether the extra geometric isomerization comes from attack by **1** (variants of the *gem*-diamine mechanism) or whether it comes from the hexahydropyrimidinium-ion mechanism (Scheme V).

After the four-at-once exchange of cyclopentanone-d_4 reported herein was first observed, it was discovered at acetone-d_6 undergoes six-at-once exchange in the presence of 3-*exo*-dimethylaminomethyl-2-*exo*-norbornanamine.[17]

Experimental Section

The cyclopentanone-*2,2,5,5-d_4*, amines, and amine hydrochlorides were obtained as described previously.[3,6,9] Dedeuteration of the ketone was followed by stopping the reaction with acid, extracting the aqueous solution with ethyl bromide, and making mass spectral measurements on the dried extract as described previously.[6]

Appendix

Dedeuteration of cyclopentanone-d_4 was also treated in terms of Scheme VIII. In this scheme K0, K1, K3, and K4 have the same definition they had in Scheme III, but it is necessary to specify the two components of K2, namely, K11 (cyclopentanone-*2,5-d_2*) and K20 (cyclopentanone-*2,2-d_2*). Similarly, I0 and I4 are the same as in Scheme III, but I21B is the iminium ion with one deuterium cis and two trans to the basic dimethylamino group from the catalyst, I02B has both deuteriums cis, and I20B has neither cis to the basic group, etc. Certain processes that occur but do not lead to exchange, such as transformation of K20 to I20B, are neglected.

Registry No. **1**, 109-55-7; **2**, 53369-71-4; **3**, 108-00-9; $MeOCH_2CH_2NMe_2$, 3030-44-2; $MeO(CH_2)_3NH_2$, 5332-73-0; cyclopentanone-*2,2,5,5-d_4*, 3997-89-5.

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(16) Hine, J.; Sachs, W. H. *J. Org. Chem.* **1974**, *39*, 1937–42.
(17) Tsay, H.-W. M.S. Thesis, The Ohio State University, 1982.