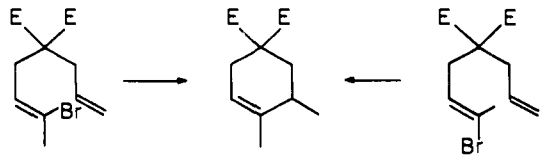
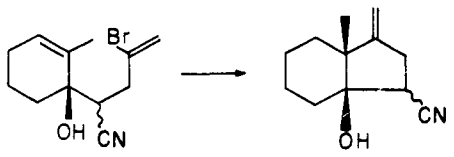


24 26 25

$10^7$ to $3 \times 10^9$ $s^{-1}$)[18] than the anticipated[7] rate of cyclization. From pure **24** or **25**,[19] the cyclic product **26**[20] was indeed obtained in the same yield (75%) in either case.

The general procedure for the vinyl radical cyclization is given in detail below: A solution of 200 mg of bromide **11** in 34 mL of dry benzene containing 2 mg of azobis(isobutyronitrile) and 1.1 equiv of tributylstannane was irradiated with a GE 275-W sunlamp, with aluminum foil to prevent scattering of the light. Heat from the sunlamp was used to keep the solution at reflux for 0.5–1 h (vinyl iodides) or 3–4 h (vinyl bromides). The residue after removal of benzene was stirred rapidly for 1 h with 5 mL of diethyl ether and 5 mL of saturated aqueous potassium fluoride solution. Filtration, extraction with ether, drying (sodium sulfate), and concentration, followed by purification by flash chromatography[21] (5% ethyl acetate in 30–60 °C petroleum ether), gave a mixture (3:1) of **12** and **13** in 87% yield, in addition to ~13% recovered starting material.

We conclude with an example that emphasizes the unique features that make vinyl radical cyclization so promising: Cyclization under the standard conditions of the (bromobutenyl)-cyclohexenol **27**[22] gave, in 70% yield, the methyleneindanol **28**.[23]



27 28

This illustrates that (1) a new carbon–carbon bond is formed in good yield even though, in this particular case, it produces a quaternary center and (2) the double bond in the newly formed ring is at a predefined position, ready for further elaboration.[24]

Studies of the cyclization process with substituents other than alkyl on the radical center and of other means of generating the required vinyl radicals are in progress.

**Acknowledgment.** We thank the National Institutes of Health and the National Science Foundation for their support of this work.

**Registry No. 9**, 81230-93-5; **10**, 42741-51-5; **11**, 81230-94-6; **12**, 81230-95-7; **13**, 81230-96-8; (*E*)-**14**, 81230-97-9; **15**, 81230-98-0; **16**, 81230-99-1; **17**, 81231-00-7; (*Z*)-**19**, 81231-01-8; **20**, 81231-02-9; **21**, 81231-03-0; (*Z*)-**22**, 81231-04-1; *cis*-**23**, 81231-05-2; (*Z*)-**24**, 81231-06-3; (*E*)-**25**, 81231-07-4; **26**, 81231-08-5; **27**, 81231-09-6; **28**, 81231-10-9; *trans*-**23**, 81231-11-0.

(18) Fessenden, R. W.; Schuler, R. H. *J. Chem. Phys.* **1963**, *39*, 2147. See: Kampmeier, J. A.; Fantazier, R. M. *J. Am. Chem. Soc.* **1966**, *88*, 1959.

(19) These were made by alkylation with (*Z*)- or with (*E*)-1,3-dibromo-2-butene, themselves synthesized from pure (*E*)- or pure (*Z*)-3-bromo-2-butenoic acid: Le Noble, W. J. *J. Am. Chem. Soc.* **1961**, *83*, 3897.

(20) $^1$H NMR: 5.33 (1 H, m), 3.7 (6 H, s), 1.6 (3 H, bs), 1.0 (3 H, d, $J$ = 6.8 Hz).

(21) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(22) Prepared by addition of the anion of 4-bromo-4-pentenenitrile (LDA–THF, −78 °C) to 2-methyl-2-cyclohexenone. The bromonitrile was made by starting with 3-bromo-3-buten-1-ol.

(23) $^1$H NMR: 5.87 (2 H, m), 3.35 (1 H, dd, $J$ = 11, 4 Hz), 0.96 (3 H, s). IR (thin film) 3490 (s), 3100 (w), 2960 (s), 2885 (s), 2240 (m), 1660 (m), 1450 (s), 1380 (m), 1060 (m), 900 (m), 885 (m) cm$^{-1}$. Mass spectrum, (C.I., isobutane) 192 (m + 1), 154 (m − H 20). One of the cyano epimers crystallized: mp 94–94.5 °C; Anal. C, 75.35; H, 8.96; N, 7.32.

(24) The cis ring junction is simply the result of the required geometry of approach of the vinyl radical to the ring double bond.

# Metal Effect on Aldol-Type Stereoselection. Erythro-Selective Condensations with Aldehydes via α-Mercurio Ketones

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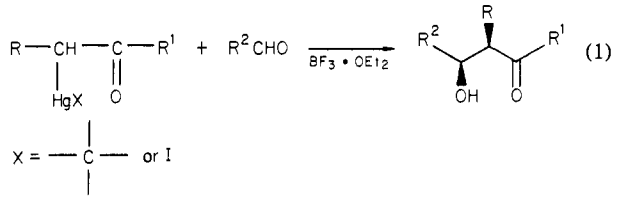
*Received December 2, 1981*

Development of crossed aldol and related reactions as a basic synthetic strategy to acyclic stereoselection has seen rapid growth in recent years. With the intention of predicting and explaining the stereoselection, both cyclic[1-5] and acyclic[6-8] mechanisms have been proposed. The cyclic mechanism has been proposed for metal enolates in which the metal can chelate the two oxygen atoms, i.e., for M = Li,[1] Mg,[2] Zn,[2] B,[3] Al,[4] and Ti.[5] With the cyclic mechanism, kinetic aldol product stereochemistry depends upon the enolate geometry. Trans enolates afford threo aldols predominantly, and cis enolates give erythro derivatives preferentially. An acyclic mechanism has been proposed for both TAS enolates[6] and the $BF_3$-mediated addition of crotyltins to aldehydes.[7] In these reactions, kinetic erythro-selective condensations are observed irrespective of the geometry of the starting enolates or the crotyl unit. For TAS enolates, erythro selectivity is ascribed to the absence of a cationic species to make the metal-linked six-membered transition state. For the crotyltin reactions, erythro selectivity is attributed to the coordination of $BF_3$ to the oxygen atom of aldehydes, which then prevents the coordination of the Sn atom. We now wish to report yet a third possibility of producing erythro selectivity based on the fact that α-mercurio ketones react with aldehydes in the presence of $BF_3$·$OEt_2$ to give kinetic erythro aldols, either predominantly or exclusively (eq 1). This result



(1)

provides not only a synthetically useful method but also a new conceptual model for the metal effect on aldol stereochemistry.

We recently reported that triphenyltin enolates generated in situ undergo a rapid aldol condensation with aldehydes to give erythro aldols predominantly regardless of the geometry of the starting enolates.[9] Furthermore, Evans[10] and we[11] independently observed similar erythro-selective condensations via zirconium enolates. As to the origin of this erythro stereoselection, Evans speculated that steric factors originated from the sterically demanding cyclopentadienyl ligands and that their interactions with the enolate substituents determined the structure of the pericyclic

(1) For example: Dubois, J. E.; Fellmann, P. *Tetrahedron Lett.* **1975**, 1225. Kleschick, W. A.; Buse, C. T.; Heatcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247. Meyers, A. I.; Reider, P. J. *Ibid.* **1979**, 101, 2501.

(2) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

(3) For example: Fenzl, W.; Köster, R.; Zimmerman, H.-J. *Liebigs Ann. Chem.* **1975**, 2201. Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. Masamune, S.; Van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, 1665. Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120.

(4) Jeffery, E. A.; Meisters, A.; Mole, T. *J. Organomet. Chem.* **1974**, *74*, 373. Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705.

(5) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, 96, 7503. Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, 4029.

(6) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106.

(7) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107.

(8) Mulzer, J.; Brüntrup, G.; Finke, J.; Zippel, M. *J. Am. Chem. Soc.* **1979**, *101*, 7723. For the addition of the carboxylic acid dianions to aldehydes, the metal chelation is of no importance, and the threo stereoselection is explained by merely the HOMO–LUMO interactions.

(9) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1981**, 162.

(10) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, 3975.

(11) Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1980**, 4607.

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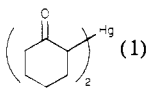
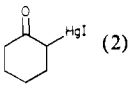
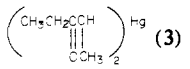
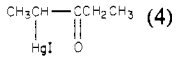
Table I. Erythro-Selective Condensations via α-Mercurio Ketones[a]

| entry | α-mercurio ketone | aldehyde | solvent | time[b] | erythro, % | threo, % | total, %[c] |
|---|---|---|---|---|---|---|---|
| 1[d] |  (1) | PhCHO | THF | 2 h, rt[e] | ~80 | ~20 | trace |
| 2 | **1** | PhCHO | THF | 2 h, rt | 80 | 20 | 85 |
| 3 |  (2) | PhCHO | THF | 7 h, rt | 90 | 10 | 60 |
| 4 | **2** | PhCHO | $CH_2Cl_2$ | 2 min, 0 °C | >98 | trace | 35 |
| 5 |  (3) | PhCHO | THF | 10 min, rt | 74 | 26 | 82 |
| 6 | **3** | PhCHO | THF | 13 h, rt | 74 | 26 | 85 |
| 7 | **3** | PhCHO | $CH_2Cl_2$ | 1 min, 0 °C | 96 | 4 | 56 |
| 8 | **3** | PhCHO | $CH_2Cl_2$ | 2 h, 0 °C | 89 | 11 | 87 |
| 9 | **3** | $CH_3(CH_2)_3CHO$ | THF | 2 h, rt | 72 | 28 | 75 |
| 10 | **3** | $CH_3(CH_2)_3CHO$ | $CH_2Cl_2$ | 2 min, 0 °C | 73 | 27 | 70 |
| 11 |  (4) | PhCHO | THF | 2 h, rt | 90 | 10 | 40 |

[a] All reactions were carried out on a 1-mmol scale as described in ref 20. The erythro/threo ratios of entries 1–8 and 11 were determined by $^1H$ NMR spectra of the reaction mixture by using the $J_{threo} > J_{erythro}$ relationship, and those of entries 9 and 10 by GLPC analyses using CW-6000 as a column. [b] The reaction time and temperature. [c] GLPC yield based on the aldehyde. The aldehyde was recovered when the reaction was not completed. [d] The reaction was without $BF_3 \cdot OEt_2$. [e] Room temperature.

transition state,[12] i.e., pseudoboat or pseudochair structures. Seebach suggested that erythro selectivity was due to the very bulky groups of zirconium and tin enolates.[13] We, however, explained erythro selectivity by an acyclic transition state, assuming that the reaction proceeded through an enolate form rather than the α-metallo ketone form.[9] It had been reported that certain tributyltin enolates existed only in the α-tributylstannyl ketone form.[14] $^1H$ NMR examination revealed that acetophenone was converted into α-(tributylstannyl)- and α-(triphenylstannyl)-acetophenone in $C_6D_6$ at room temperature,[15] while phenyl ethyl ketone gave the corresponding tributyltin and triphenyltin enolates under similar conditions.[16] The corresponding zirconium derivatives of acetophenone and phenyl ether ketone existed in the enolate form.[17] Although these results seemed to weigh strongly on the side of the enolate form as the real intermediate of erythro-selective condensations, it appeared desirable to examine the stereoselection of the aldol-type condensation, if possible, in a structurally rigid α-metallo ketone.

Consequently, the reaction of α-mercurioketones[18] with aldehydes was examined.[19] To our surprise, erythro-selective condensations were realized under kinetic control. The results are summarized in Table I.[20] The presence of $BF_3 \cdot OEt_2$ caused a marked acceleration of the reaction. As is evident from entry 1, $BF_3 \cdot OEt_2$ acts as the activating agent of the carbonyl groups and does not exert an influence upon stereoselection.[21] The reaction proceeds with higher speed and greater erythro selectivity in $CH_2Cl_2$ than in THF. Isomerization from erythro to threo isomer is slow in THF (entries 5 and 6), while that in $CH_2Cl_2$ is rapid (entries 7 and 8). For example, the ratio of erythro/threo in entry 4 changed to 25/75 after 5 h at 0 °C.[20]

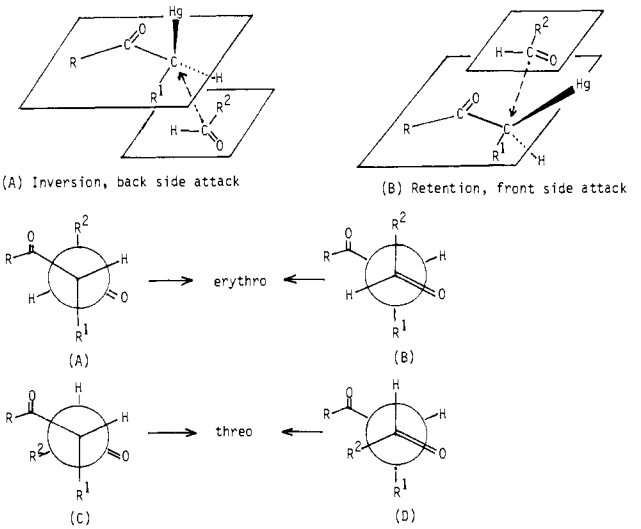



**Figure 1.** $S_E$-type displacement mechanism. Perspective views of C and D are not shown.

Erythro selectivity in these reactions can be accounted for by the steric effect arising from $S_E$-type displacement of the C–Hg bond by the carbonyl electrophile. As shown in Figure 1, the diastereomeric erythro transition state is the most stable among many possible conformations. At present, it is not possible to clarify the stereochemistry of the displacement of the C–Hg bond, i.e., it is a problem of either inversion or retention.

The easy preparation and stability of α-mercurio ketones, coupled with a moderate to very high level of erythro-selection, make this reaction potentially useful. Perhaps, however, the most important aspect of the present findings is to provide a new in-

(12) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(13) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, 64, 1413.
(14) Odic, Y.; Pereyre, M. *J. Organomet. Chem.* **1973**, *55*, 273.
(15) Acetophenone was treated with LDA in THF at 0 °C and then tributyl- or triphenyltin chloride was added. After 10 min, THF was removed under vacuum and $C_6D_6$ was added. Insoluble LiCl was separated by using a centrifuge. $PhC(O)CH_2SnBu_3$: δ (from $Me_4Si$) 2.82 (s) (the enolate protons were not detected); $PhC(O)CH_2SnPh_3$: δ 3.23 (s) (the enolate protons were not detected).
(16) $PhC(OSnBu_3)=CHCH_3$: δ 5.10 (1 H, q, $J$ = 7 Hz), 1.86 (3 H, d, $J$ = 7 Hz). $PhC(OSnPh_3)=CHCH_3$: δ 5.16 (1 H, q, $J$ = 7 Hz), 1.86 (3 H, d, $J$ = 7 Hz). The stereochemistry of these enolates is not determined, but presumably the enolate consists of a single isomer judging from the NMR spectra.
(17) $PhC(OZrCp_2Cl)=CH_2$: δ 4.12 (1 H) and 4.75 (1 H). The protons of the α-metallo ketone were not detected. $PhC(OZrCp_2Cl)=CHCH_3$: δ 5.02 (1 H, q, $J$ = 7 Hz), 1.75 (3 H, d, $J$ = 7 Hz).
(18) α-Mercurio ketones were prepared by House's method: House, H. O.; Auerbach, R. A.; Gall, M.; Peet, N. P. *J. Org. Chem.* **1973**, *38*, 514.
(19) For a review on organomercury compounds in organic synthesis, see: Larock, R. C. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 27.

(20) To a suspension of **1** (1 mmol) in dry THF (2 mL) were added benzaldehyde (1 mmol) and $BF_3 \cdot OEt_2$ (1 mmol). The suspension changed gradually to the clear solution, and the reaction was quenched with water. The reaction of diketomercurials proceeded more rapidly than that of the corresponding α-iodomercurio ketones. The reaction in $CH_2Cl_2$, where the α-mercurio ketones were dissolved, was very rapid. Retroaldolization was observed for a prolonged reaction. A referee suggested that the rapid erythro/threo isomerization in $CH_2Cl_2$ should be reexamined by taking a mixture formed in THF, removing the THF, replacing it with $CH_2Cl_2$, and then determining the rate of isomerization. Such an examination revealed that our conclusion was correct qualitatively. The erythro/threo nomenclature is based on Heathcock's convention.

terpretation of the metal effect on aldol-type stereoselection. Until now, it seems that the possibility through the $\alpha$-metallo ketone form has been neglected. There is the possibility that erythro selection of triphenyltin enolates proceeds through the $\alpha$-stannyl ketone form. Certain copper enolates, prepared from the conjugate addition of $Me_2CuLi$ to $\alpha,\beta$-unsaturated carbonyl compounds, undergo erythro-selective condensations.[22] This result can be explained by the intervention of $\alpha$-cuprio ketones, and such species are frequently suggested in many other reactions.[23] The most recent reports on erythro-selective condensations are also interesting in this respect.[24]

(21) If the transmetalation from Hg to B and subsequent formation of the boron enolate are involved, **1** and **2** should give the threo aldol due to their trans geometries.

(22) Heng, K. K.; Smith, A. J. *Tetrahedron* **1979**, *35*, 425. Heng, K. K.; Simpson, J.; Smith, R. A. *J. Org. Chem.* **1981**, *46*, 2932. See also: House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443. Posner, G. H.; Lenz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934.

(23) Berlan, J.; Battioni, J. P.; Koosha, K. *J. Organomet. Chem.* **1978**, 152, 359 and references cited therein.

(24) Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, 4691. Shieh, H. M.; Prestwich, G. D. *J. Org. Chem.* **1981**, *46*, 4319.

(25) **Note Added in Proof**: After the submission of this paper, two conflicting papers on tin enolates appeared: threo selective reactions of isolated $R_3Sn$ enolates (Shenvi, S; Stille, J. K. *Tetrahedron Lett.* **1982**, 627) and erythro selective condensations of divalent tin enolates (Mukaiyama, T.; Stevens, R. W.; Iwasawa, N. *Chem. Lett.* **1982**, 353).

## Nitrogen to Nitrogen Proton Transfer. Significance of Large Negative Entropies of Activation

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*Received October 31, 1981*

In studying the kinetics of proton exchange of *N,N*-dimethylcyclohexylamine hydrochloride, catalyzed by bases such as pyridine (eq 1, R = cHx), Menger, Singh, and Bayer[1] have

$$RNHMe_2^+ + Py \xrightarrow{k_2} RNMe_2 + PyH^+ \quad (1)$$

observed that $\Delta S^\ddagger$ in chloroform as solvent is large and negative, ca. −30 eu. They also found a Hammett $\rho$ value of −6.4 and a Brønsted $\beta$ value of 1.1 (for variations of the catalyzing base) and normal reactivity for 2,6-di-*tert*-butylpyridine, without any steric retardation. These latter results suggested that the transition state resembles products, so that the charge contents of reactant and transition state would not differ appreciably. The large negative $\Delta S^\ddagger$ was then interpreted in terms of ion-pair dissociation. We now wish to show that eq 1 is not the correct mechanism for the proton exchange. Instead, we propose that the mechanism is a chain reaction, with eq 1 as initiation step and with a propagation step whose transition state is consistent with a large negative $\Delta S^\ddagger$.

The mechanism of any exchange reaction must be symmetrical.[2] To take eq 1 as the rate-limiting step implies that its reverse must also be the rate-limiting step, since the transition states are identical. We therefore should adapt eq 1 by explicitly writing it as reversible (eq 2). Of course, the $PyH^+$ must return a

$$RNHMe_2^+ + Py \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} RNMe_2 + PyH^+ \quad (2)$$

*different* proton to the amine, in order to qualify as exchange. However, we are then led to consider whether $PyH^+$ is the only acid that can return a proton.

Might $RNHMe_2^+$ also serve (eq 3)? Each occurrence of either

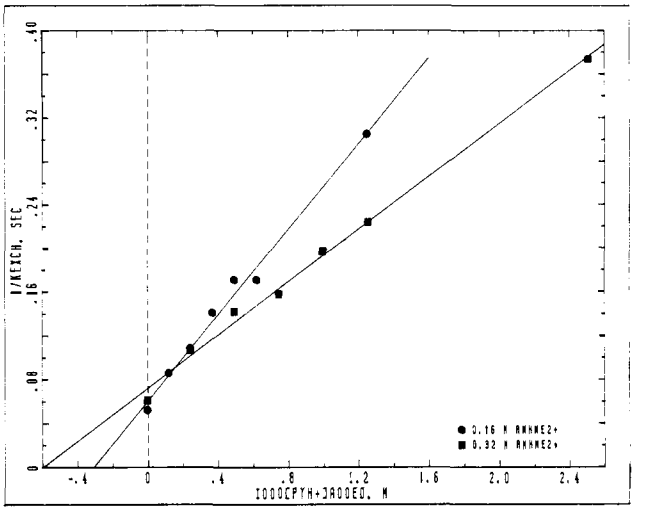


**Figure 1.** Kinetics of proton exchange of *N,N*-dimethylcyclohexylamine hydrochloride (0.16 and 0.32 M) in chloroform at 34 °C, catalyzed by $2.47 \times 10^{-3}$ M added Py and inhibited by added $PyH^+$.

$$RNHMe_2^+ + RNMe_2 \overset{k}{\rightleftharpoons} RNMe_2 + RNHMe_2^+ \quad (3)$$

eq 2 or eq 3 represents one proton exchange, but which is faster? Even though $RNHMe_2^+$ is a much weaker acid than $PyH^+$, rate constants for thermoneutral proton transfer involving nitrogen or oxygen are nearly as large as those for exergonic proton transfers.[3] Therefore the *rate* of protonation by the more abundant $RNHMe_2^+$ is likely to be even greater than the rate of protonation by $PyH^+$. Thus we expect eq 3 to be a faster reaction than eq 2. This suggests that the dominant mechanism of exchange is likely to be eq 3, utilizing $RNMe_2$ generated through eq 2. Moreover, the mechanism of eq 3 automatically satisfies the requirement for symmetry. However, this leads to eq 4, which

$$v = k_{exch}[RNHMe_2^+] = k[RNHMe_2^+][RNMe_2] \quad (4)$$

does not fit Menger's observed kinetics, which is first order in $RNHMe_2^+$ and first order in Py (eq 5). Even if eq 4 is trans-

$$v = k_{exch}[RNHMe_2^+] = k_2[RNHMe_2^+][Py] \quad (5)$$

formed by assuming that the steady-state $[RNMe_2]$ is governed by the equilibrium of eq 2, with equilibrium constant $K_e = k_2/k_{-2}$, the result (eq 6) still does not fit the observed kinetics, which is *not* second order in $RNHMe_2^+$.

$$v = k_{exch}[RNHMe_2^+] = kK_e\,[RNHMe_2^+]^2[Py]/[PyH^+] \quad (6)$$

It is the purpose of this paper to demonstrate that eq 6 nevertheless describes the kinetics of the exchange. Equation 6 may be reconciled with eq 5, observed by Menger, if $[RNHMe_2^+]/[PyH^+]$ was constant throughout all Menger's kinetic runs. This would hold if the *N,N*-dimethylcyclohexylamine hydrochloride had been contaminated by some excess HCl, which would be converted to $PyH^+$ under the conditions of the kinetic experiments. Indeed, the presence of excess HCl may be inferred from the stated requirement that the amine hydrochloride must be free of traces of unprotonated amine. Such contamination has been demonstrated[4] previously even for amine salts recrystallized twice.

Figure 1 shows our evidence[5] in favor of eq 6 over eq 5. It is quite clear that adding $PyH^+$ decreases $k_{exch}$, whereas eq 1 and 5 imply that $k_{exch}$ should be independent of $[PyH^+]$. The observed dependence on $[PyH^+]$ is sufficient to disprove eq 1 as the mechanism of exchange.

(1) Menger, F. M.; Singh, T. D.; Bayer, F. L. *J. Am. Chem. Soc.* **1976**, *98*, 5011.

(2) Perrin, C. L.; Schiraldi, D. A.; Arrhenius, G. M. L. *J. Am. Chem. Soc.* **1982**, *104*, 196.

(3) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

(4) Cocivera, M. *J. Am. Chem. Soc.* **1966**, *88*, 672.

(5) Amine hydrochlorides were prepared from the amine (redistilled *N,N*-dimethylcyclohexylamine or Spectroquality pyridine) and HCl in ether. Kinetics of proton exchange in reagent chloroform were followed on a Varian EM-390 NMR spectrometer at 34 °C. Rate constants, including a statistical factor of 2, were determined from the valley-to-peak intensity ratio of the *N*-methyl doublet,[6a] as calculation from the line-shape equation.[6b]

(6) (a) Grunwald, E.; Jumper, C. F.; Meiboom, S. *J. Am. Chem. Soc.* **1962**, *84*, 4664. (b) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228.

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