Asymmetric Induction in an Enammonium-Iminium Rearrangement. Mechanistic Insight via NMR, Deuterium Labeling, and Reaction Rate Studies. Application to the Stereoselective Synthesis of Pyrroloisoquinoline Antidepressants[1]

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Abstract: Reductive deoxygenation of **5a**, **5b**, **7a**, or **7b** with borane-THF in trifluoroacetic acid yielded a product mixture (**6a**/**6b** or **4a**/**4b**) highly biased (90-95%) in favor of the trans diastereomer (**6b** or **4b**). The mechanism of this process was probed by NMR spectroscopy and the use of deuterium-labeled reagents and substrates. Thus, we eliminated several possible mechanisms and determined that the reaction proceeds via (1) dehydration of the substrate to an enammonium salt (**11a**/**11b** or **17a**/**17b**) comprised mainly of the cis-fused diastereomer (**11b** or **17b**), (2) prototropic rearrangement to an iminium salt (**12a**/**12b** or **18a**/**18b**) highly enriched in the (6,10b)-trans isomer (**12b** or **18b**), and (3) hydride transfer to the iminium carbon at the 5-position. In further support, a mixture of iminium species **12a** and **12b** (35:65) was isolated and characterized as a perchlorate salt. Also, the stereochemistry of the enammonium salts was proven by studies with methiodides **22a** and **22b**, the latter of which was characterized by single-crystal X-ray analysis. Three critical factors appear to govern the stereochemical outcome of the reductive deoxygenation: (1) the much greater thermodynamic stability of the cis-fused enammonium salt, (2) a highly stereocontrolled (at least 99% for the major cis-fused diastereomer), suprafacial proton transfer from N4 to C6, and (3) reduction of the iminium salts before they equilibrate. Protonation of enamine **14** with CF_3CO_2D occurred directly on N4 and the resultant enammonium salts (**11a**/**11b**), present in an 8:92 ratio, rearranged in the usual manner. In the enammonium-iminium rearrangement, we observed a considerable degree of intramolecular proton transfer, while some exchange with the medium was occurring. The reaction rates for rearrangement of enammonium salts from various acid-addition salts of **7a**/**7b** in CF_3CO_2D were measured and found to increase by a factor of 75 in going from $HClO_4$ to CF_3CO_2H (pK_a ranging from -10 to 0). The body of evidence suggests that the enammonium-iminium rearrangement takes place largely within a tight solvent cage, in which the proton or deuteron on nitrogen is conducted suprafacially from N4 to C6. This internal control is responsible for the >98% stereoselectivity of the rearrangement. The synthesis of **4b** (McN-5652-Z) from 4-(methylthio)benzaldehyde and *N*-vinylpyrrolidin-2-one and an enantiospecific synthesis of (6*S*,10b*R*)-(+)-**4b** (McN-5652-X) are described in detail. A single-crystal X-ray analysis of **5a**·HBr showed the trans-fused ring geometry and a hydrogen-bond bridge involving the bromide atom, H_O, and H_{N4} (O-H···Br···H-N). On dissolution in $CDCl_3$, **5a**·HBr rapidly converted to a mixture of cis- and trans-fused species.

Ambident conjugated systems involving a three-atom framework, X=Y—Z:, can be protonated on two different terminal atoms to generate X=Y—Z—H or H—X—Y=Z.[4] The kinetic product mixture from this reaction can subsequently tautomerize by intramolecular or intermolecular proton transfer to achieve a thermodynamic product mixture.[5] Both of these processes have attracted considerable interest because of their fundamental importance to synthetic and mechanistic organic chemistry, as well as to structural theory.[4,5]

The enamine functional group, C=C—N:, represents a classical ambident system that has found wide application in synthetic organic chemistry.[6] Protonation of the commonly used tertiary enamines, C=C—NR_2, in solution phase occurs preferentially at the nitrogen site, in almost all cases, to yield enammonium salts, C=C—NR_2H^+, which are intrinsically unstable species that readily rearrange to the corresponding iminium salts, H—C—C=NR_2^+.[7] This enammonium-iminium rearrangement can, of course, play an integral role in the hydrolysis of enamines, depending on reaction conditions.[7b,d] More interestingly, however, it can form the basis for effective asymmetric induction at a pro-stereogenic β-carbon under the influence of a stereogenic center elsewhere in the molecule, or of an external chiral agent. For example, protonolysis and deuteriolysis experiments on tertiary enamines of cycloalkanones have furnished hydrolysis products with varying levels of diastereoselectivity, some with impressive magnitude.[7d] Enantioselective reactions have also been reported for the protonation/hydrolysis of enamines containing a chiral amine moiety, or of prochiral enamines by the agency of a chiral acid.[7d] To explain significant asymmetric induction, some researchers have implicated an enammonium-iminium rearrangement without dissociation to any free enamine, while others have invoked kinetic protonation of a liberated enamine;[7d] in any case, initial protonation of nitrogen has been accepted as the norm. Although this mechanistic issue has been addressed by the identification of enammonium[8a,9a,b] and iminium[8,9a,b,e] species, even

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(2) R. W. Johnson Pharmaceutical Research Institute.
(3) Janssen Research Foundation.
(4) Liler, M. *Adv. Phys. Org. Chem.* **1975**, *11*, 267.
(5) Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89.
(6) Gadamasetti, G.; Kuehne, M. E. In *Enamines*, 2nd ed.; Cook, A. G., Ed.; Marcel Dekker: New York, 1988; Chapter 9, p 531.
(7) (a) Cook, A. G. In *Enamines*, 2nd ed.; Cook, A. G., Ed.; Marcel Dekker: New York, 1988; Chapter 1, p 1. (b) Stamhuis, E. J.; Cook, A. G. In *Enamines*, 2nd ed.; Cook, A. G., Ed.; Marcel Dekker: New York, 1988; Chapter 3, p 165. (c) Paukstelis, J. V.; Cook, A. G. In *Enamines*, 2nd ed.; Cook, A. G., Ed.; Marcel Dekker: New York, 1988; Chapter 6, p 275. (d) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975. (e) For reactions of other electrophiles, see: Alt, G. H.; Cook, A. G. In *Enamines*, 2nd ed.; Cook, A. G., Ed.; Marcel Dekker: New York, 1988; Chapter 4, p 181.
(8) (a) Barthelemy, M.; Bessière, Y. *Tetrahedron* **1976**, *32*, 1665. (b) Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5956. (c) Heinstein, P.; Stoeckigt, J.; Zenk, M. H. *Tetrahedron Lett.* **1980**, *21*, 141.

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Table I. Reductive Deoxygenation of Amino Alcohol Substrates

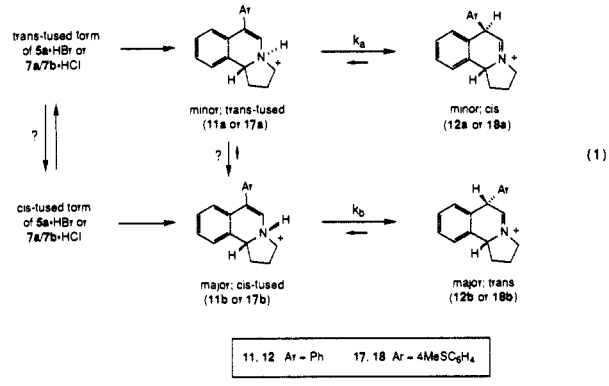
substrate $\xrightarrow{CF_3CO_2H}$ $\xrightarrow[0-5\ °C]{\text{reagent}}$ products

substrate	reagent	products/ratio	remarks
5a·HBr	BH_3·THF	**6a**:**6b**/10:90	90% yield
5a·HBr	$NaBH_4$	**6a**:**6b**/13:87	ca. 90% yield
5a·HBr	$NaBH_3CN$	**6a**:**6b**/55:45	ca. 90% yield
5a·HBr	Et_3SiH		little **6a**/**6b** formed after 24 h[a]
5a·HBr	H_2/Pt[b]	**6a**:**6b**/40:60	several contaminants in product
5b·HBr	BH_3·THF	**6a**:**6b**/7:93	97% yield
7a/**7b**·HCl[c]	BH_3·THF	**4a**:**4b**/6:94	90% yield
7a	BH_3·THF	**4a**:**4b**/5:95	90% yield
7b	BH_3·THF	**4a**:**4b**/5:95	90% yield

[a] Product was mainly enamine **14**, presumably from basification of **11a**/**11b**. [b] Reaction was performed at 23 °C. [c] Ratio of **7a**:**7b** was 75:25.

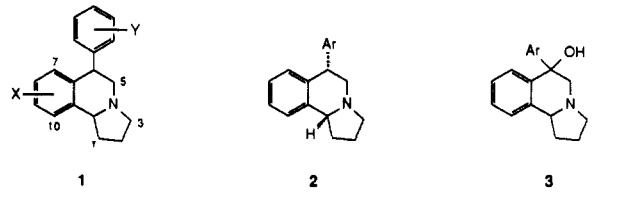
within a stereochemical context,[8,9c-e] as well as by mechanistic studies,[8a,9] some lingering questions still exist.[7d]

We encountered a highly stereoselective enammonium–iminium rearrangement (eq 1) in a program for the synthesis of pyrroloisoquinolines of formula **1**.[10-12] The biological activity of this series of potential antidepressant drugs, powerful inhibitors of the neuronal uptake of biogenic amines, resides largely in the trans diastereomers (viz. **2**), and almost exclusively in a single enantiomeric set.[11] Consequently, we required a stereoselective route



(1)

to the trans isomer that would also be amenable to producing the desired enantiomer. A solution was discovered in the stereoselective deoxygenation of 6-hydroxy derivatives **3** with borane–THF in trifluoroacetic acid.[10] In our early mechanistic work on this process,[10] we identified the intermediates in this transformation, deduced the likely route for their formation, and proposed the origin of the stereoselectivity. Full details of our research, which has focused on the critical enammonium–iminium rearrangement step, are presented herein. Additionally, we have now investigated (1) the question of intramolecular vs intermolecular proton transfer in this rearrangement by deuterium-labeling experiments, (2) the effect of anion on the rate of rearrangement, and (3) direct enamine protonation. These results afford an intriguing insight not only into our rearrangement system and its extraordinary stereocontrol but also into enammonium–iminium rearrangements in general. Finally, we describe the overall synthetic sequence for diastereoselective synthesis of **4b** (McN-5652-Z) and an enantiospecific synthesis of (6*S*,10b*R*)-(+)-**4b** (McN-5652-X).[13]



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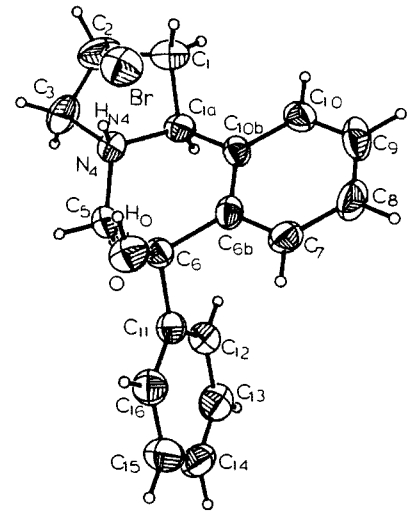


Figure 1. Perspective drawing of the molecular structure of **5a**·HBr from a single-crystal X-ray analysis. Nonhydrogen atoms are represented by thermal ellipsoids of 50% probability, whereas the hydrogen atoms are just represented by small spheres.

Results and Discussion

The Deoxygenation Reaction. In seeking a stereoselective synthesis of *trans*-pyrrolo[2,1-*a*]isoquinolines **2**, we came to examine the acid-promoted hydride reduction of 6-hydroxy derivative **5a**·HBr, the stereochemistry of which was established unequivocally by X-ray analysis (Figure 1).[14] The results for various deoxygenation procedures[15] are displayed in Table I. Reaction of **5a**·HBr with borane–THF in trifluoroacetic acid at 0–5 °C afforded a mixture of **6a** and **6b** in good yield, with a desirable isomer ratio of 10:90. Deoxygenation of the diastereomeric salt, **5b**·HBr, also gave a good yield of **6a** and **6b** in a 6:94 ratio, which demonstrates the stereoconvergence of this process. Analogously, reduction of amino alcohols **7a**/**7b**, as individual free bases or as a 75:25 mixture of HCl salts,[16] produced **4a** and **4b** in approximately a 5:95 ratio (Table I). The stereoconvergence indicates

(9) (a) Matsushita, H.; Tsujino, Y.; Noguchi, M.; Yoshikawa, S. *Chem. Lett.* **1976**, 1087. (b) Idem. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1513. (c) *Ibid.* **1976**, *49*, 3629. (d) Matsushita, H.; Tsujino, Y.; Noguchi, M.; Saburi, M.; Yoshikawa, S. *Ibid.* **1978**, *51*, 201. (e) *Ibid.* **1978**, *51*, 862.

(10) Preliminary communication: Maryanoff, B. E.; McComsey, D. F.; Mutter, M. S.; Sorgi, K. L.; Maryanoff, C. A. *Tetrahedron Lett.* **1988**, *29*, 5073.

(11) (a) Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. *J. Med. Chem.* **1987**, *30*, 1433. (b) Maryanoff, B. E.; Shank, R. P.; Gardocki, J. F. *Drugs Future* **1986**, *11*, 18. (c) Shank, R. P.; Gardocki, J. F.; Schneider, C. R.; Vaught, J. L.; Setler, P. E.; Maryanoff, B. E.; McComsey, D. F. *J. Pharmacol. Exp. Ther.* **1987**, *242*, 74.

(12) (a) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062. (b) Maryanoff, B. E.; McComsey, D. F.; Almond, H. R., Jr.; Mutter, M. S.; Bemis, G. W.; Whittle, R. R.; Olofson, R. A. *Ibid.* **1986**, *51*, 1341. (c) Maryanoff, B. E.; McComsey, D. F. *J. Heterocycl. Chem.* **1985**, *22*, 911. (d) *Tetrahedron Lett.* **1979**, 3797.

(13) These are powerful potentiators of serotonin; for detailed biological properties, see: Shank, R. P.; Vaught, J. L.; Pelley, K. A.; Setler, P. E.; McComsey, D. F.; Maryanoff, B. E. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1032.

(14) (a) Details for the single-crystal X-ray analysis are reported in the Experimental Section and microfilm supplement.[14b] (b) See paragraph at the end of this paper regarding supplementary material.

(15) For reductive deoxygenation methods, see: (a) Borane complexes in trifluoroacetic acid: Maryanoff, B. E.; McComsey, D. F. *J. Org. Chem.* **1978**, *43*, 2733. McComsey, D. F.; Reitz, A. B.; Maryanoff, C. A.; Maryanoff, B. E. *Synth. Commun.* **1986**, *16*, 1535. (b) Sodium cyanoborohydride in trifluoroacetic acid: Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proced. Intl.* **1985**, *17*, 317. (c) Triethylsilane with boron trifluoride or trifluoroacetic acid: Doyle, M. P.; West, C. T.; Donnelly, S. J.; McOsher, C. C. *J. Organomet. Chem.* **1976**, *117*, 129. West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *38*, 2675. Olah, G. A.; Arvanaghi, M.; Ohannecian, L. *Synthesis* **1987**, 770. Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Ibid.* **1974**, 633. Adlington, M. G.; Orfanopoulos, M.; Fry, J. L. *Tetrahedron Lett.* **1976**, 2955.

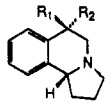
(16) The stereochemical assignment for **7a** and **7b** was predicated on a comparison of their ^1H and ^{13}C NMR spectral data with those for **5a** and **5b**.

Table II. H/D Isotope-Exchange Experiments with **5a**

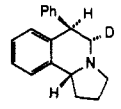
5a substrate $\xrightarrow[2.\ BH_3\text{·THF},\ 0\ °C]{1.\ CF_3CO_2H(D)}$ **6b**-*6d* + **6a** + **6b**

substrate	acid	relative amount of products: **6b**–*6d*	**6a**	**6b**
5a·HBr	CF_3CO_2D	30	10	60
5a	CF_3CO_2D	80	15	5
5a·DCl	CF_3CO_2H	25	10	65

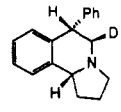
that the reaction proceeds through a common intermediate, and at the outset, we naturally surmised dissociation of the protonated hydroxyl to a diarylcarbocation followed by direct hydride addition to C6.[15,17]



4a R_1 = 4MeSC$_6$H$_4$; R_2 = H
4b R_1 = H; R_2 = 4MeSC$_6$H$_4$
5a R_1 = Ph; R_2 = OH
5b R_1 = OH; R_2 = Ph
6a R_1 = Ph; R_2 = H
6b R_1 = H; R_2 = Ph
7a R_1 = 4MeSC$_6$H$_4$; R_2 = OH
7b R_1 = OH; R_2 = 4MeSC$_6$H$_4$

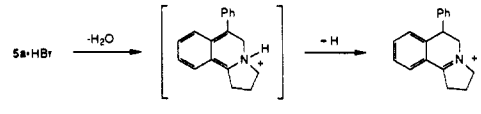


8a



8b

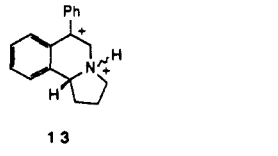
Appropriate experiments were performed to test for this and alternative mechanisms.[10] Treatment of **5a**·HBr with BD_3·THF in trifluoroacetic acid at 5 °C resulted in a high yield of C5 monodeuterated products, **8a** and **8b**, in a 9:91 ratio. In these compounds, the deuterium was introduced predominantly (>90%) anti to the phenyl substituent on C6. Since there was no incorporation of deuterium into the C6 position, the obvious direct substitution mechanism is not operative. Also, this labeling result excludes a mechanism involving dehydration with a loss of H10b to give an *o*-quinone dimethide intermediate, **9**, en route to iminium salt **10** (eq 2),[18] which would capture deuterium at C10b.



9 **10** (2)

The failure to observe **10**[11a] in later NMR experiments and the obtainment of complete retention of configuration at C10b in reductive deoxygenation of a mixture of (6*R*,10b*R*)-**7a** and (6*S*,10b*R*)-**7b** (98% ee) also ruled out this type of pathway (details appear below).

At this juncture, we envisioned two other mechanistic possibilities. The first was dehydration of **5a**·HBr by an E1 elimination to yield enammonium salts **11a**/**11b**, in which the proton on nitrogen is already fixed in a particular stereochemistry. This could rearrange to iminium salts **12a**/**12b** (eq 1), which would then receive hydride or deuteride at C5. Secondly, dissociation of the protonated OH in **5a**·HBr could lead to a transient carbocation with predetermined nitrogen stereochemistry (**13**), which could undergo a 1,2-hydride shift (from C5 to C6) to give iminium salts **12a**/**12b**. Another aspect of **13** is an aziridinium species arising from N-deprotonation of **13** and formation of a bond between N4 and C6 (eq 3). However, we have not detected any



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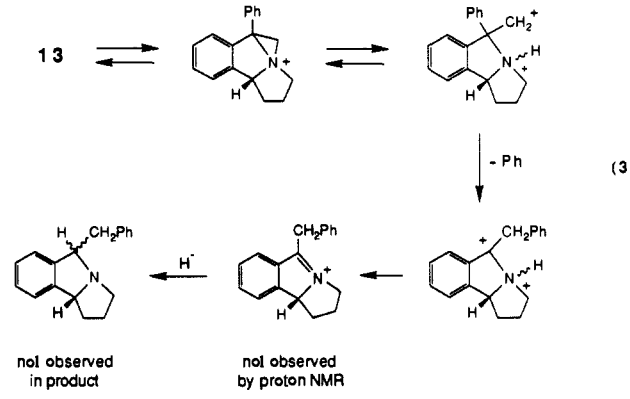
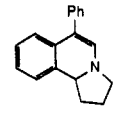


not observed in product — not observed by proton NMR (3)

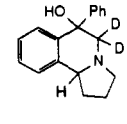
products from alternative cleavage of such an aziridinium species (eq 3), by isolation or proton NMR (vide infra). Thus, we view an aziridinium intermediate as being chemically equivalent to **13** under the strongly solvolytic conditions in trifluoroacetic acid.

To differentiate between the two remaining mechanistic options, at least preliminarily, we probed the origin of the proton on C6 in products **6a** and **6b** by reducing **5a**·HBr and **5a** (free base) with borane–THF in CF_3CO_2D and **5a**·DCl with borane-THF in CF_3CO_2H (Table II). In the experiment with **5a**·HBr, only a minor amount of the 6-deuterated product was obtained, indicating the possibility of a 1,2-hydride shift, or a considerable intramolecular component to the proton migration from nitrogen to C6 in an enammonium–iminium rearrangement. Since exchange of the N–H with deuterium in the acid medium may very well compete with this N4–C6 proton transfer, the ca. 67% (for **6b**: 60/90 × 100%) of intramolecularity represents a lower limit. Free base **5a** gave the 6-deuterated product almost exclusively (ca. 95%), and the small amount of **6b** present could be attributed to the proton from the eliminated OH group. Given the failure of a proton on C5 to find its way to C6 in this experiment, the enammonium–iminium mechanism is strongly supported. With **5a**·DCl, the 6-deuterated compound was present to a significant degree (ca. 28%), again reflecting some intramolecular proton migration in an enammonium–iminium mechanism. The diminished level of intramolecular transfer with **5a**·DCl is a reasonable consequence of a primary isotope effect, whereupon intermolecular proton exchange is more competitive. Considering the abundant extramolecular pool of acid available for protonation or deuteration, and the potential for exchange of N–H or N–D with its counterpart in the medium prior to the transfer step, an intramolecular component of 65%, or even 30%, is mechanistically significant. This issue will be discussed further in the next subsection.

We were able to prepare and isolate enamine **14** as a light yellow oil by combining **5a**·HBr with polyphosphoric acid and then basifying the mixture. This exceedingly air-sensitive substance (instantly turned purple and decomposed on exposure to air) was dissolved in trifluoroacetic acid at 0 °C and reduced with borane–THF (0 °C) to give a 12:88 mixture of **6a**:**6b**. Surprisingly, this high level of stereoselectivity closely approximates that obtained from direct deoxygenation of **5a**·HBr. Such a result would be consistent with stereoselective protonation of **14** to generate



14



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a mixture of **11a** and **11b**, substantially enriched in the latter, and stereospecific rearrangement to a mixture of **12a** and **12b**, enriched in the latter (see next subsection); reduction would then yield the

(17) (a) Smonou, I.; Orfanopoulos, M. *Tetrahedron Lett.* **1988**, *29*, 5793. (b) Fry, J. L.; Adlington, M. G. *J. Am. Chem. Soc.* **1978**, *100*, 7641.

(18) The iodide salt of **10**, prepared independently,[11a] was reduced with sodium borohydride in methanol, hydrogen and platinum oxide, or borane–THF in trifluoroacetic acid with poor stereoselectivity (**6a**:**6b** = ca. 1:1).

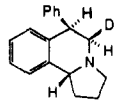
observed products. When this reaction was performed at 23 °C, a **6a**:**6b** ratio of only 26:74 was realized. By contrast, the reductive deoxygenation of **5a**·HBr at 23 °C proceeded with acceptably high stereoselectivity (**6a**:**6b** = 9:91). Some erosion of stereocontrol did occur in the reductive deoxygenation of the **7a**/**7b** mixture around 25–30 °C with reactions that were scaled up to 10–50 g. A possible cause of this sensitivity in the larger reactions may be epimerization of the intermediate iminium ions due to poor heat dissipation in the reduction step.[7d,8a,b]

The Enammonium–Iminium Rearrangement. To elucidate the mechanism further, we sought to identify intermediates and monitor them during the reaction course. Thus, the fate of **5a** and **5a**·HBr in CF_3CO_2H or CF_3CO_2D was studied by NMR spectroscopy. The 360-MHz ^1H NMR spectrum of **5a** in CF_3CO_2H at 0 °C revealed a mixture of two major and two minor substances. The predominant species were enammonium salt **11b**, especially characterized by resonances at 6.1 ppm for H5 and 5.1 ppm for H10b, and iminium salt **12b**, characterized by these signals: δ(H5) 8.9, δ(H7) 6.9, δ(H6) 5.1, and δ(H10b) 5.1 (**11b**:**12b** = ca. 25:75). The minor signals were attributed to the corresponding isomers **11a** and **12a**. The enammonium salt signals disappeared entirely after 2 h at 10 °C, and the signals for **12b** and **12a** (δ(H5) 9.0 and δ(H7) 7.1, respectively) persisted. The **12a**:**12b** ratio of 7:93 (integration of H5) nicely reflected the high stereoselectivity observed in a standard reduction experiment. In fact, addition of borane–THF at this stage furnished **6a** and **6b** in a 9:91 ratio. With **5a** in CF_3CO_2D at 0 °C, there was an identical bias for enammonium salt **11b**. At the outset, however, this solution contained ca. 50% unreacted **5a**·CF_3CO_2D, ca. 50% enammonium salt **11b**, and just a trace of **12b**. Over 2 h at 10 °C, **5a**·CF_3CO_2D and **11b** disappeared to the benefit of iminium salts **12a** and **12b** (highly labeled at C6 with deuterium), present in a 5:95 ratio.

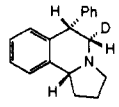
When we dissolved **5a**·HBr in CF_3CO_2D, a very clean NMR spectrum for enammonium salt **11b** was obtained; there was only a very small amount of **11a**, assigned on the basis of two minor signals: δ(H10b) 4.7 and δ(H5) 6.6.[19a] Integration of the H5 resonances determined a 5:95 ratio for **11a**:**11b**. Over 2 h at 20 °C, the signals for **11a** and **11b** slowly vanished, by about 25%, while the signals for **12a** and **12b** (5:95) grew by that amount. In this early phase of the rearrangement, the ratios for **11a**:**11b** and **12a**:**12b** were precisely the same. A comparison of the integrated area for the envelope at δ 5.1 (H10b of **11b**; H6 and H10b of **12**) with that for the doublet at 6.9 (H7 of **12**) established a 75:25 H/D ratio at C6 in **12**, which indicates a high degree of intramolecular 1,3-proton migration, as mentioned in the previous subsection. After 16 h at 20 °C, the H/D ratio at C6 of **12b** was 37:63. The low level of proton incorporation at C6 is presumably due to H–D exchange with the medium at the iminium salt stage,[19b] as **12a** and **12b** have been exposed to epimerization conditions for a prolonged period of time (vide infra).[7d,8a,b]

Support for the overall mechanistic picture emerged from a dehydration–rearrangement experiment with labeled salt **15**·HBr in CF_3CO_2D. The initial ^1H NMR spectrum at 0 °C exhibited signals for some unreacted starting material (ca. 10%) and **11a**/**11b** monodeuterated at C5 (measured by the signals for H10b because of the C5 deuteration). One should note that the signal ascribed to H5 in **11a** was absent from the spectrum, as expected. After 30 min at 0 °C, there was little rearrangement; however, rearrangement did occur slowly at 10 °C, to the extent of ca. 25% after 2 h (estimated by integration of H7 in **11b** and H1/H2 in **12b**). After ca. 16 h at 20 °C, the composition and deuterium content were evaluated by 55.3-MHz ^2H NMR. At this point, enammonium salt **11b** accounted for only 10% of the material (D on C5 at 6.1 ppm) and the H/D ratio at C6 of **12b** was ca. 20:80 (D on C5 at 8.9 ppm and D on C6 at 5.2 ppm).

The study with **15**·HBr in CF_3CO_2D militates against the 1,2-hydride shift mechanism, which we also demoted in the previous subsection. The formation of **16a** and **16b** without



16a

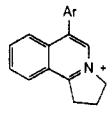


16b

deuterium at C6 (<5%), in the reductive deoxygenation of **15**·HBr in CF_3CO_2H corroborates this conclusion. However, in such experiments with the 5,5-dideutero compound, the actual 1,2-deuteride shift is unfairly impeded by the primary isotope effect. Thus, we examined the reaction of **5a**-OD·DBr in CF_3CO_2D, wherein a 1,2-hydride shift would cause a proton to be found at C6 in the final products. Since this did not happen, a hydride-shift mechanism can be disregarded. Also, there was no evidence from NMR studies for the presence of iminium ion **10**, an aziridinium species derived from **13**, or an iminium ion from possible reorganization of an intermediate aziridinium salt (see eq 3).

A 360-MHz ^1H NMR experiment on the 75:25 mixture of **7a**/**7b** in CF_3CO_2D at ca. −10 °C, showed formation of enammonium salts **17a** and **17b** (H5 at 6.63 and 6.17 ppm) and subsequent slow conversion to a 6:94 mixture of iminium salts **18a** and **18b** (vinyl singlets at δ 9.07 and 8.92). This ratio of iminium salts was confirmed by borane–THF reduction of an aliquot. At 25 °C, the formation of **18a** and **18b** (6:94) was much more rapid, but over 90 h the ratio had shifted to 33:67, presumably because of a proton-exchange-based equilibration;[7d,8a,b] at 60 °C, a 60:40 ratio of **18a** and **18b** was ultimately attained in just 2 h. Deuterium incorporation into **18a**/**18b** on contact with CF_3CO_2D supported the proton-exchange process.

Our attempts to isolate and characterize reaction intermediates in a conventional manner were hampered by the instability of the species involved. The enammonium salts readily rearranged to the iminium salts and the iminium salts not only epimerized but also oxidized to isoquinolinium salts (viz. **20** and **21**). Diverse



20 Ar = Ph

21 Ar = 4MeSC$_6$H$_4$

attempts to isolate a mixture of iminium salts **12a** and **12b**, hopefully very enriched in **12b**, afforded **20** and decomposition products, along with some stereoisomerized iminium salt. Similarly, attempts to isolate **18a** and **18b** always led to isoquinolinium salt **21**. In one instance, we fortuitously isolated a clean perchlorate salt of **12a**/**12b** (35:65), as a white solid contaminated by less than 2% of **20**; the outstanding quality of this substance is evident from its ^1H NMR spectrum (Figure 2). The 35:65 ratio of **12a** and **12b** was confirmed by rapid reduction to a correspondent 37:63 mixture of **6a** and **6b** with $NaBH_4$ in ethanol or borane–THF in CF_3CO_2H, thereby ruling out stereoisomerization of a mixture highly enriched in **12b** on its dissolution in $CDCl_3$ for the NMR measurement.

In an attempt to isolate the chloride salt of enammonium salts **11a** and **11b**, ethereal HCl was added to an ethereal solution of **14** under argon. The resultant solid was treated with $CDCl_3$, but most of it did not dissolve (this material is **20**-chloride). A ^1H NMR spectrum of the solution at 0 °C revealed a 3:1 mixture of **20** and enammonium chloride, almost completely as the cis-fused form, **11b**. Since no formation of iminium salts was observed after 4 h at 0 °C, the NMR sample was warmed to 24 °C and monitored. After several hours, no iminium species were seen, while the isoquinolinium salt increased somewhat. Even after addition of CD_3OD, a "protic" solvent, just a slight amount of iminium salt formed on prolonged standing. In a subsequent experiment, a 25:75 mixture of **20** and enammonium chlorides

(19) (a) Maryanoff, B. E.; McComsey, D. F.; Inners, R. R.; Mutter, M. S.; Wooden, G. P.; Mayo, S. L.; Olofson, R. A. *J. Am. Chem. Soc.* **1989**, *111*, 2487. (b) We also observed H–D exchange at C5 arising from deuteron addition to C5 of the olefin unit in the enammonium salts. This process was slow, amounting to 5% at 2 h and ca. 30% at 16 h. In the rate studies, use of H5 integral areas required normalization for this exchange (see Experimental Section). Details on this issue will be addressed in a separate paper.

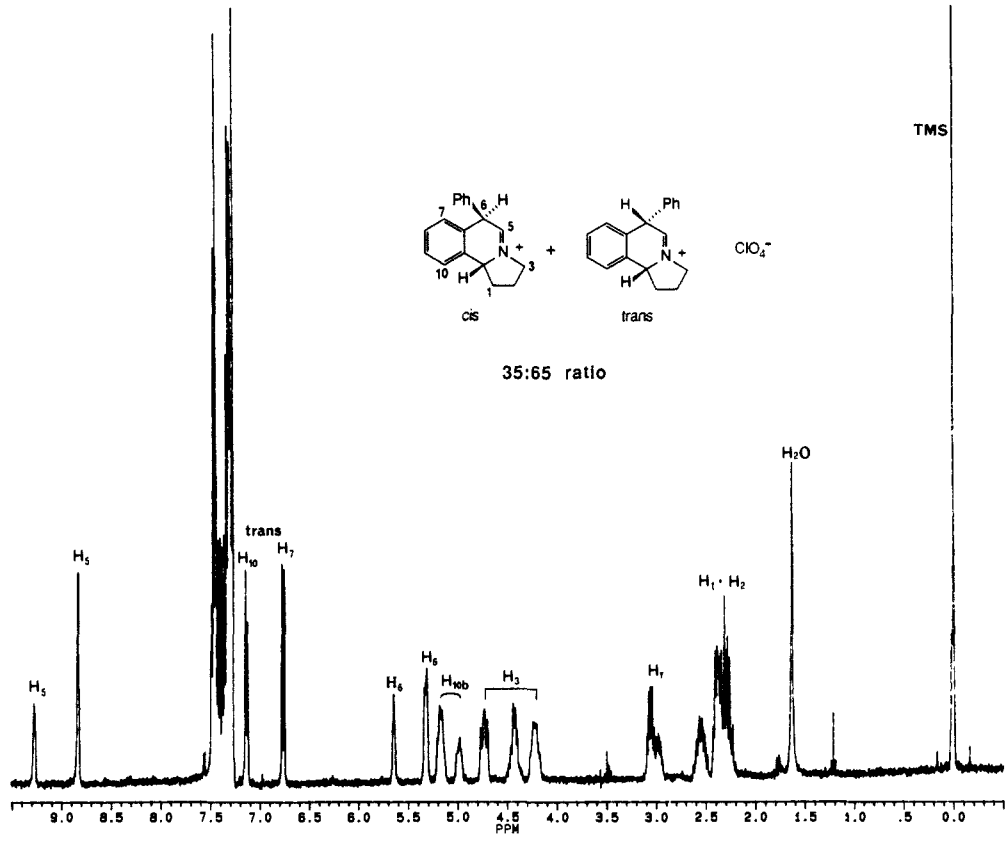


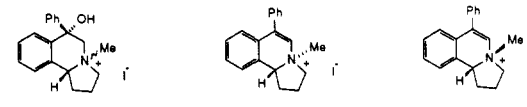
Figure 2. 360-MHz ^{1}H NMR spectrum of a 35:65 mixture of **12a** and **12b** perchlorate.

was prepared by treating **14** in $CDCl_3$ with 1 equiv of 1 N HCl. With respect to the enammonium salt isomers, the ^{1}H NMR spectrum showed a vast predominance of **11b**. Over 2.5 h, no rearrangement was detected; however, addition of some CF_3CO_2D (ca. 10 molar equiv) caused instantaneous conversion to 30:70 mixture of iminium salts **12a** and **12b** (mainly with D at C6). Evaporation of solvent and borane–THF reduction of the residual iminium salts gave a 40:60 ratio of **6a**:**6b** (D at C6). This erosion of stereocontrol may be related to insufficient CF_3CO_2D to construct a tight solvent cage required of the proposed conducted tour mechanism (to be discussed later). Nevertheless, the trifluoroacetic acid still exerted a dramatic rate-enhancing effect on the enammonium–iminium rearrangement. In this regard, dissolution of **14** in CF_3CO_2D at 0 °C furnished a ^{1}H NMR spectrum consisting mainly of **11a** and **11b** (with D on nitrogen) in an 8:92 ratio, along with ca. 10% of **12b** (with D on C6). At this temperature rearrangement occurred with a half-life of ca. 100 min to give an 8:92 mixture of **12a**:**12b** (D on C6). Thus, the carboxylic acid protonates, or deuterates, enamine **14** on the nitrogen atom first, then promotes the enammonium–iminium rearrangement to ultimately place H or D on the β-carbon. *These results highlight the importance of the carboxylic acid in facilitating rearrangement and in mediating stereoselectivity.*

With the MeS series, since enammonium perchlorate **17b** was fairly stable to rearrangement in trifluoroacetic acid (see the rate study, below), we tried to precipiate it as a solid with ether; however, the isolated solid was solely **21**-perchlorate. A similar difficulty was experienced in attempts to isolate the iminium salts, **18**.

We have not yet arrived at a satisfying explanation for the facile production of isoquinolinium salt on attempted isolation of enammonium or iminium species. Small amounts of hexahydropyrroloisoquinoline products were detected, but not enough to invoke disproportionation as a principal pathway. Perhaps, a trace amount of oxygen was responsible, in spite of the inert atmosphere employed.

Since the identification of **11b** as the major enammonium species was crucial to our mechanistic analysis, we sought to confirm our interpretation of the ^{1}H NMR spectral data. Valuable information was garnered via dehydration of methiodides **22a**/**22b** to enammonium salts **23a**/**23b**, which were perfectly stable to



rearrangement, as expected. Treatment of **5a** with MeI in acetonitrile afforded methiodide adducts as a 28:72 mixture of **22a** and **22b**. On dissolution in CF_3CO_2D, this mixture was rapidly dehydrated to a 30:70 mixture of enammonium salts **23a** and **23b** (^{1}H NMR), which did not change on prolonged standing or on treatment with borane–THF. The ^{1}H NMR spectral properties of these isomeric enammonium salts were remarkably consistent with those for **11a** and **11b** in CF_3CO_2D (see Experimental Section). Dissolution of the mixture of **22a** and **22b** in CF_3CO_2H, followed by evaporation of solvent, afforded an orange oil comprised of **23a** and **23b**, but no solid ever separated. Recrystallization of the mixture of **22a** and **22b** from ethanol fortunately rendered a stereoisomerically pure sample of hydroxy methiodide **22b** for independent study. A 400-MHz ^{1}H NMR spectrum of this sample in $CDCl_3$ indicated a cis A structure (δ(H5e) 4.66, δ(H3) 4.80, and δ(H10b) 5.53). An ^{1}H NMR spectrum of this material in CF_3CO_2D initially showed a mixture of starting material **22b** and dehydration product **23b**, but, after 1 h, only isomerically pure, cis-fused enammonium salt **23b** was present. An X-ray analysis was performed on needlelike crystals of **22b**, grown slowly from methanol/2-propanol. In the solid state, the molecule possesses a cis-fused (cis A[19a]) structure with the 6-phenyl and methyl substituents pseudoequatorial and H10b pseudoaxial,[20] which proves the cis-fused stereochemistry of **23b**. By logical extension, our structural assignments for **11a**/**11b** and **17a**/**17b**

(20) This X-ray analysis was performed in the laboratory of Dr. Masood Parvez at The Pennsylvania State University, University Park, PA 16802. The crystals were orthorhombic (space group *P*bca) with $Z = 8$; the R value was 0.07. Full details will be published separately.

Table III. Data for Rate Studies with Salts of **7a/7b** at 10 °C

salt	relative ratio 7a/7b	17a/17b	18a/18b	$k(min^{-1})$	$t_{1/2}$(min)	rel rate
7·CF_3CO_2H	>99:1	6:94	3:97	4.76×10^{-2}	14.6	75
7·HCl	96:4	6:94	5:95	4.38×10^{-3}	158	7
7·HBr	>99:1	6:94	7:93	1.72×10^{-3}	403	3
7·$HClO_4$	91:9	6:94	6:94	6.35×10^{-4}	1091	1

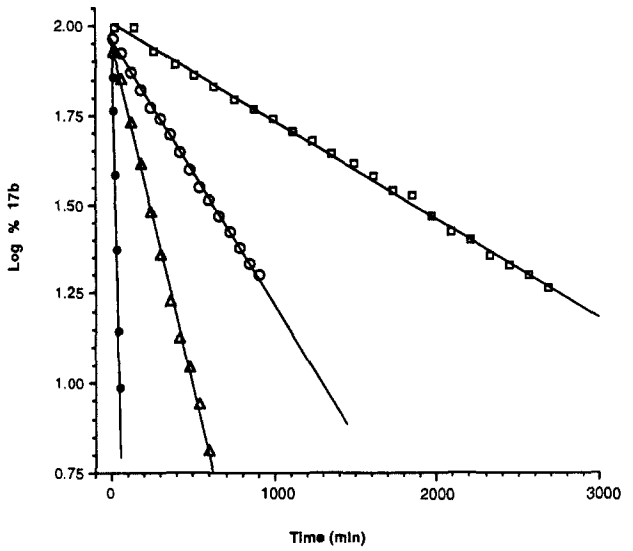


Figure 3. Plot of the rate data for rearrangement of **17a/17b** to **18a/18b** at 10 °C with substrates 7·CF_3CO_2H (●), 7·HCl (△), 7·HBr (○), and 7·$HClO_4$ (□).

are confirmed, as well. A comparison of the high-field ^1H NMR spectra for **22b** and **5a**·HBr in $CDCl_3$ indicated that one of the two species from dissolution of **5a**·HBr possesses a cis A structure (vide infra), albeit just the trans-fused structure is manifested in the solid state (Figure 1). This supports a mechanistic point relating to the facility of cis–trans isomerization at the ring fusion via N–H bond dissociation, which we will discuss later in more detail.

In the early phase of this project, we noticed that the rate of the enammonium–iminium rearrangement was dependent on whether the amino alcohol free base, HCl salt, or HBr salt was employed. For example, by ^1H NMR we observed rearrangement half-lives of ca. 150 min at 0 °C, 40 min at 20 °C, and 175 min at 20 °C with **5a**, **5a**·HCl, and **5a**·HBr in CF_3CO_2D, respectively. Previous reports have referred briefly to the effect of acid strength on the rate of rearrangement[8a] or to the effect of anion on the rate of iminium salt epimerization.[8b] We therefore decided to conduct a careful rate study involving four different forms of amino alcohol **7a/7b**. In our rate experiments, **7a/7b**·CF_3CO_2H, **7a/7b**·HCl, **7a/7b**·HBr, or **7a/7b**·$HClO_4$ (ca. 40 mg) was dissolved in CF_3CO_2D at 0–10 °C, and ^1H NMR spectra (at 10 °C) representing the transformation of **17a/17b** to **18a/18b** were recorded at appropriate intervals. Since the initial concentration of **17a** was relatively minor (**17a:17b** ≈ 5:95), we have only treated data for the disappearance of **17b** with time. Rate data are collected in Table III and a plot of log (percent of **17b**) vs time is depicted in Figure 3. The relative rates of these four rearrangements, involving the anions $CF_3CO_2^-$, Cl^-, Br^-, and ClO_4^-, are 75, 7, 3, and 1, respectively,[21] a trend which roughly parallels the pK_a values for the conjugate acids: CF_3CO_2H = 0.59, HCl = −7, HBr = −9, and $HClO_4$ = −10.[22] It should be noted, however, that this range of the rates is fairly narrow, i.e., confined

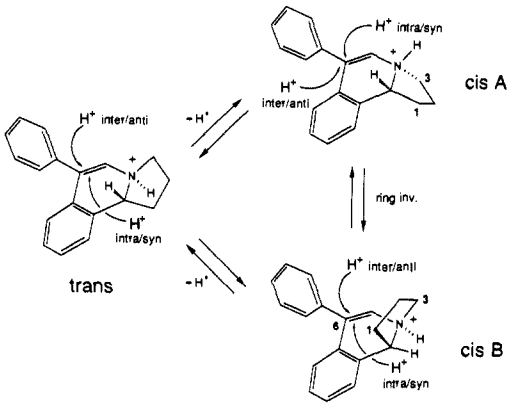


Figure 4. Views of **11a** (trans) and **11b** (cis A and cis B) depicting approximate conformations, derived from molecular modeling with SYBYL[25a] and the examination of Dreiding models, and favored modes of proton delivery to C_6 ("intra" = intramolecular; "inter" = intermolecular). The trans form is changed into the cis forms by N–H dissociation, accompanied by nitrogen inversion (cis A) or nitrogen and ring inversion (cis B). The cis A and cis B forms are interconverted by facile ring inversion. (Note: The cis B structure, as drawn, is enantiomeric to the others.)

within 2 orders of magnitude. We also examined the reaction of **7a/7b** in CF_3CO_2D, the rearrangement rate for which was identical (within experimental error) with the rearrangement rate found with **7a/7b**·CF_3CO_2H in CF_3CO_2D. The absence of a deuterium isotope effect may be ascribed to dispersal of the bound CF_3CO_2H into a sea of CF_3CO_2D, rather than to mechanistic consequences. However, as indicated below, rearrangement rates can be dependent on whether CF_3CO_2H or CF_3CO_2D is used for the reaction medium.

The decrease in rate with increasing acid strength, albeit modest, does agree with the observations of Barthelemy and Bessière[8a] and Evans et al.[8b] This suggests that the anion plays some role in the rearrangement process, the mechanism of which would entail either (1) dissociation of the enammonium salt to enamine followed by reprotonation at C6 to give iminium salt or (2) solvent-assisted transfer of the proton from N4 to C6 in a tight cage (a conducted tour mechanism[23]).[24] Our observation of intramolecular H/D transfer, described earlier, is a clear example of a cage phenomenon, and lends further credence to the latter mechanism.

Another point of curiosity is the long time that is required to finish the enammonium–iminium rearrangement when starting with acid-addition salts of the amino alcohol. One might wonder: How can reductive deoxygenation reactions go to completion in less than 1 h at 0–5 °C when the necessary rearrangement is so sluggish? In the first place, we did note that the enammonium-iminium rearrangement with **5a**·HBr as educt is much faster in CF_3CO_2H; the rearrangement had a half-life of 3–4 min at 20 °C, making it about 50 times faster than the same rearrangement in CF_3CO_2D. (However, as mentioned above, there was no difference in rate between CF_3CO_2H and CF_3CO_2D with free base **7a/7b** as educt.) Even so, reduction of **5a**·HBr in CF_3CO_2D was effectuated prematurely, too; the mixture of **6a/6b** was completely formed in less than 1 h at 0–5 °C. Apparently, there must be some kind of catalysis taking place in the reductive deoxygenation process. We tested $(CF_3CO_2)_3B$ as a possible catalyst in a rate study with **5a**·HBr in CF_3CO_2D, but the additive had no effect on the rate of enammonium–iminium rearrangement. Perhaps, a borane reagent with a B–H bond left intact is acting as a catalyst. The source of this catalysis phenomenon is currently unresolved.

Given this information, we can now construct a plausible rationale for the high stereoselectivity of the reductive deoxygenation.

(21) A rate study with **7a/7b**·HPF_6 in CF_3CO_2D was confounded by solvolysis of the PF_6^- counterion; one to three fluoro substituents were replaced by a trifluoroacetate moiety.

(22) (a) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Chapman and Hall: London, 1971. (b) Kortum, G.; Vogel, W.; Andrussow, K. *Dissociation Constants of Organic Acids in Aqueous Solutions*; Butterworths: London, 1961.

(23) (a) Broadhurst, M. D.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 581. Almy, J.; Hoffman, D. H.; Chu, K. C.; Cram, D. J. *Ibid.* **1973**, *95*, 1185. Almy, J.; Cram, D. J. *Ibid.* **1969**, *91*, 4459. (b) Also, see: March, J. *Advanced Organic Chemistry*; 3rd ed.; Wiley: New York, 1985; pp 518–519, 525.

(24) A thermal, concerted 1,3 proton shift is highly unlikely because of orbital symmetry considerations, whereas a stepwise process is perfectly reasonable.[5,7d]

Acid-induced dehydration of **5a/5b** or **7a/7b** produces enammonium salts **11a/11b** or **17a/17b**, respectively, which are highly enriched in the cis-fused isomer (i.e., ca. 95% of **11b** or **17b**). We believe that this cis form, comprised of rapidly interconverting "cis A" and "cis B" conformers (Figure 4), is thermodynamically much more stable than the trans form on the basis of results from a separate study of protonated pyrrolo[2,1-*a*]isoquinolines.[19a,25] In the hexahydropyrroloisoquinoline case, the cis A conformer (equatorial NH) turned out to be somewhat more stable than the cis B conformer (axial NH).[19a] However, with the removal of certain critical 1,3 syn-axial interactions in the tetrahydropyrroloisoquinoline system, it may be reasonable to project that the two cis conformers (Figure 4) have nearly the same stability.[25] Any of the three forms could theoretically give rise to the preferred iminium product either by intramolecular ("intra") or intermolecular ("inter") proton transfer to C6 (Figure 4). However, the results show as the major reaction **11b** → **12b** and as the minor reaction **11a** → **12a**.

It is important to recognize that the X-ray structure of substrate **5a**·HBr shows a trans ring fusion (Figure 1), which would presumably be disfavored in solution.[19a] Thus, when solid **5a**·HBr is dissolved in CF_3CO_2H or CF_3CO_2D, it will first possess this trans arrangement. Whether this form is converted directly to **11a** en route to **11b** or to the cis-fused form of **5a**·HBr en route to **11b** is not known (eq 1). Indeed, an ^1H NMR spectrum of **5a**·HBr in $CDCl_3$, immediately after dissolution, showed a nearly 55:45 mixture of two species, assigned as the cis A (δ(H10b) 5.76) and trans ring-fused isomers (δ(H10b) 5.24) of **5a**·HBr, the ratio of which did not change on standing for 3 days (cf. the ^1H NMR spectral data for **22b**). Although the interconversion of cis- and trans-fused species would be slower in a strongly acidic medium,[19a] the instant attainment of the cis–trans equilibrium in this case (possibly assisted by the presence of the 6-hydroxy substituent) makes fast isomerization in trifluoroacetic acid a reasonable possibility (eq 1). A rapid interconversion of **11a** and **11b** is also a reasonable possibility (eq 1). We do know that the ratio of **11a** and **11b** is tremendously biased toward **11b** at the earliest possible point of NMR inspection, even when unreacted **5a**·HBr is still present. This reflects the strong intrinsic preference for the cis-fused geometry. During the cis–trans equilibration of the substrate (**5a**·HBr), or the possible isomerization of enammonium salt (**11a** with **11b**), both of which involve dissociation to a weak base and a proton followed by recombination, a solvent-cage effect may be important, as signalled by the lack of rapid H/D exchange in the labeling experiments. The isotopic leakage observed could be due to escape from the solvent cage surrounding the tight ion pair. Despite facile interconversion of the trans- and cis-fused enammonium salts, probably fast relative to the rates of rearrangement (k_a and k_b in eq 1), the stereochemical outcome does not suffer. *Both* the trans- and cis-fused forms of the enammonium salts (**11a/11b**; **17a/17b**) rearrange with high stereospecificity: ca. 99% for the major cis-fused form and at least 80–85% for the minor trans-fused form (see Table III).[26] Because of the various equilibria, the rates of rearrangement, k_a and k_b, should be nearly the same, to guarantee the same **a**/**b** ratio for enammonium and iminium salts.

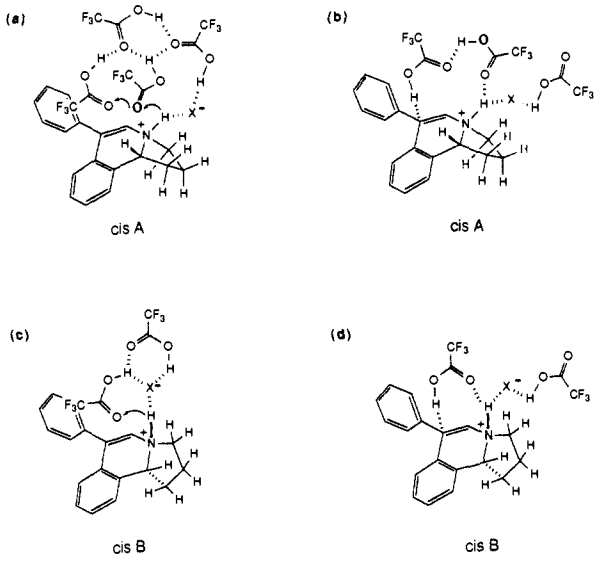
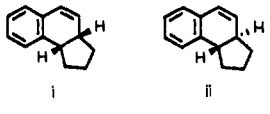


Figure 5. Conceptual representations of solvent-assisted, syn-stereospecific 1,3 proton transfer involving the cis-fused enammonium salt, **11b**, as cis A and cis B conformers. The tight solvent cage impedes exchange of the labile hydrogen with the medium. In panels (a) and (c), proton migration from N4 to C6 is mediated by the carbonyl group of trifluoroacetic acid; in panels (b) and (d), proton transfer is mediated by trifluoroacetic acid in a relay mechanism.

The enammonium–iminium rearrangement proceeds by protonation of the carbon–carbon double bond at C6 of the enammonium species (S_E2'-type mechanism) or of an incipient dissociated enamine species (S_E1'-type mechanism), with high diastereofacial selectivity syn to H10b. For the purpose of discussion, we will assume a nondissociative S_E2 process and, in the case of intermolecular protonation at C6, a preference for attack antiperiplanar to the N–H bond.[27] Several modes of reaction are then open for consideration (Figure 4). For the trans form (**11a**), "inter/anti" attack would yield major iminium salt **12b** (not observed), while the "intra/syn" reaction would yield minor iminium salt **12a** (*observed*). For the cis B form, inter/anti would give **12a** (not observed) and intra/syn would give **12b** (*observed*). With the cis A form the anti direction may be more tolerable for the "inter" reaction, yielding **12a** (not observed), although one might argue that intermolecular protonation could occur from the syn direction because the endo face of the double bond is more sterically hindered (by C3). The intra/syn mode for the cis A form would afford major iminium salt **12b** (*observed*). But, the equatorial disposition of the N–H in the cis A form may not offer as auspicious a geometry for transfer as the axial N–H in the cis B form (see Figure 5), suggesting that the cis B form is the main conduit to observed product. From this analysis, we must conclude that intra/syn proton transfer is of paramount importance, as it is unlikely that the high stereospecificity (around 99% syn for **11b** → **12b**) can be achieved through stereoelectronic effects (e.g., steric hindrance and antiperiplanar control) in an intermolecular protonation mechanism.

Given our data on the rearrangement, solvent-assisted, intramolecular syn proton transfer from N4 to C6 sounds rather appealing. This pathway may be effectuated by a suprafacial "conducted tour" mechanism involving trifluoroacetate in a tight ion pair.[23] Two possible conceptualizations of this process are

(25) (a) Empirical force field calculations on the related hydrocarbon isomers i and ii were conducted with SYBYL (Tripos Associates, Inc., St. Louis, MO, Version 5.1) and MM2.[25b] Thus, we determined three minimized structures with the following energies (kcal/mol): 7.8 for cis B, 8.3 for cis A, and 10.2 for trans.[19a] These results reinforce our proposal of a low energy cis form, both cis A and cis B, for **11b** (cf. results in ref 19a). (b) Allinger, N. L.; Yuh, Y. H. *QCPE* **1980**, *12*, 395.



i ii

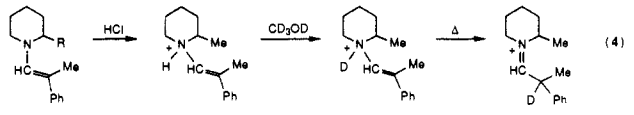
(26) Please note that the small quantity of the minor forms made it impossible to determine the degree of stereospecificity for their rearrangement. Although we feel that the minor enammonium species rearrange with >95% stereospecificity, the data are not accurate enough to establish this conclusion.

(27) Generally, anti addition of H^+ to a carbon–carbon double bond in an intermolecular S_E2' reaction is strongly favored over syn addition, on the basis of theoretical studies[27a] and experimental results with allylsilanes.[27b,c] However, syn protonation can occur to a significant degree in certain circumstances.[27c,d] See: (a) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435 and ref 1 and 2 cited therein. (b) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *Ibid.* **1982**, *104*, 4962. Hayashi, T.; Ito, H.; Kumada, M. *Tetrahedron Lett.* **1982**, *23*, 4605. Wickham, G.; Kitching, W. *J. Org. Chem.* **1983**, *48*, 612. (c) Fleming, I.; Terrett, N. K. *J. Organomet. Chem.* **1984**, *264*, 99. Idem. *Tetrahedron Lett.* **1983**, *24*, 4153. (d) Wetter, H.; Scherer, P. *Helv. Chim. Acta* **1983**, *66*, 118. Wickham, G.; Kitching, W. *Organometallics* **1983**, *2*, 541.

portrayed in Figure 5 for the cis A and cis B conformations of **11b**. Here, exchange with the medium would be restricted by the supramolecular structure of the solvent cage, held together by noncovalent bonds (e.g., ionic and hydrogen bonding). In Figure 5a,c the 1,3 proton migration is mediated by the carbonyl group of trifluoroacetic acid, X^- is intimate to the complex, and there would be limited H–D exchange. Thus, the results of the H–D exchange experiments could be readily explained. This process would probably be more likely, by virtue of geometry and structural simplicity, for the cis B conformer (Figure 5c). In Figure 5b,d the proton is delivered by a relay mechanism involving trifluoroacetic acid and X^- is complexed to some degree. For this depiction, the H–D labeling results are harder to rationalize; however, one could suppose exchange between N–H and O–D (or N–D and O–H) within the cage (with limited escape) prior to proton transfer. The resultant iminium salts, **12a/12b** or **18a/18b**, emerge highly enriched (ca. 95%) in trans isomer (**12b** or **18b**), and subsequent reduction is effected with the complete maintenance of stereochemical integrity.

Even though we suggest the predominance of solvent-assisted proton transfer, we cannot accurately gauge the extent of its participation and we cannot exclude some contribution of intermolecular proton delivery. In the final analysis, there are three critical points that govern the high stereocontrol in the reduction of **5a**, **5b**, **7a**, or **7b**: (1) a high intrinsic preference for the cis-fused enammonium salt, (2) essentially stereospecific proton transfer in the enammonium–iminium rearrangement, and (3) iminium salt reduction prior to epimerization.

From information in our introduction to this paper, it is clear that various researchers have probed into mechanistic aspects of enamine protonation and hydrolysis, enammonium–iminium rearrangements, and iminium ion epimerization.[7-9] One group, in particular, reported an interesting H/D labeling experiment (eq 4) related to the experiments that we have investigated here.[9a,b]

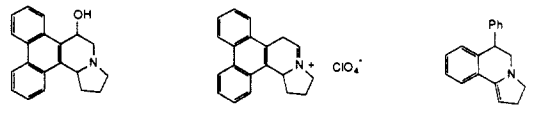


24 R = Me, R = H **25** **26** **27**

Treatment of a benzene solution of **24** with dry HCl deposited **25**, as an unstable crystalline solid. Dissolution of **25** in CD_3OD resulted in considerable H–D exchange to give **26**, which rearranged at 50 °C to **27**, an isolable substance. This example contrasts with ours in that the H–D exchange at nitrogen is facile in CD_3OD, so there is little retention of the proton in the final iminium salt. Although Matsushita et al.[9a,b] indicated a direct 1,3 transfer of deuterium, this is not possible as mentioned above;[24] however, their result is perfectly compatible with an intermolecular or a solvent-assisted intramolecular mechanism.[7d]

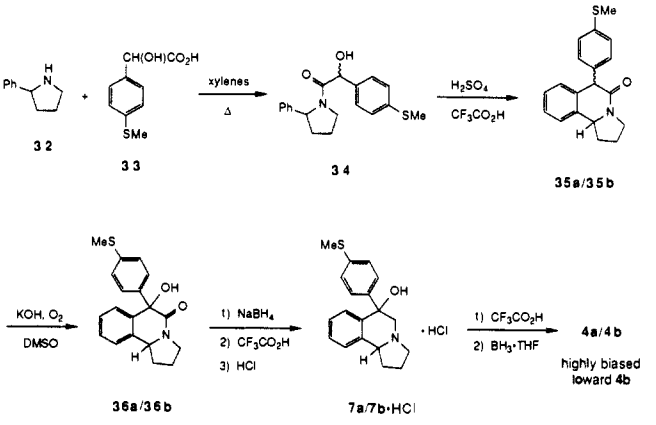
Another interesting paper from Matshushita et al. concerns asymmetric induction in the reaction of enamine **28** and (+)-10-camphorsulfonic acid (monohydrate) with subsequent hydrolysis to aldehyde.[9e] Although the enantiomeric excesses that they realized were quite small, thereby limiting the mechanistic significance, this asymmetric induction nevertheless points to a tight association of the anion in the enammonium–iminium rearrangement.

Our elimination route to enammonium salts, and entry into the enammonium–iminium rearrangement, is uncommon in that it relies on an elimination process, whereas direct protonation of enamines has generally been used.[7a,c,d] As far as we know, there is only one other paper in the literature that deals with this type of reaction sequence, reporting the production of iminium salt **30** from **29** with 70% $HClO_4$.[28a] The elimination route can be



29 **30** **31**

Scheme I



advantageous in that one can easily control the initial acid and be confident that protonation originates on nitrogen. It has been noted, in general, that mineral acids protonate enamines on nitrogen, whereas carboxylic acids protonate enamines on the β-carbon.[7a,c,d] In a discussion of the protonation of enamines with trifluoroacetic acid, Nilsson et al. ascribed this behavior to possible bifunctional catalysis by the carboxylic acid in the transformation of an initial N-protonated enammonium salt to an iminium salt.[28b] Our NMR and reaction rate studies nicely clarify this question. We were able to generate N-protonated and N-deuterated enammonium salts in, or with, trifluoroacetic acid and conveniently monitor their fate, despite the instability to rearrangement. Furthermore, we were able to visualize the direct N-protonation of enamine **14** with CF_3CO_2D by ^1H NMR. As a consequence, we suggest that enamines and carboxylic acids, under general circumstances, ought to furnish N-protonated enammonium salts, which subsequently convert to the corresponding iminium salts.

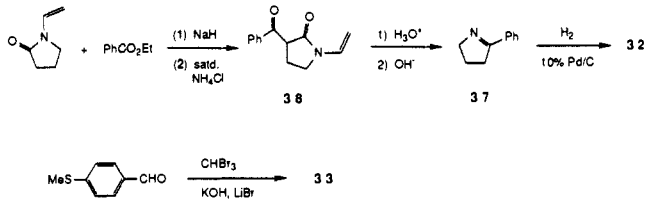
Synthesis of McN-5652-Z and McN-5652-X. We have been involved in the synthesis of pyrrolo[2,1-*a*]isoquinoline compounds because of their interesting biological properties.[10-12] Since the bioactivity is exhibited chiefly by the trans diastereomers, viz. **2**, we have sought a stereoselective avenue to this series. Unfortunately, most of the methods have afforded the cis diastereomers preferentially. One procedure was discovered for obtaining a 60% diastereomeric excess of the target trans stereoisomer. Treatment of the iodide form of **10** with NaOH generated enamine **31**, which was hydrogenated in ethanol over platinum in the presence of triethylamine to give a 20:80 mixture of **6a** and **6b**. However, this process could not be improved further because **6b** epimerized to **6a** under the reaction conditions and other hydrogenation protocols were less satisfactory.

The reductive deoxygenation of 6-hydroxy derivatives, discovered later, was highly promising. In early studies with **7a** and **7b**, variable results were obtained, but this problem was ironed out by control of the temperature and reaction conditions. Nevertheless, the successful optimization of the yield and stereoselectivity was closely linked to our extensive mechanistic investigation, reported above. To capitalize on this advance, we needed to develop a practical synthesis of **7a/7b**. Fortunately, the stereoconvergent nature of the reductive deoxygenation eliminated any need for a stereocontrolled synthesis of **7a** or **7b**; thus, we focused our attention on developing a short, efficient synthesis of racemic **7a/7b**, which would be amenable to an eventual enantiospecific synthesis. The highlights of this chemistry are outlined in Scheme I.

Our convergent synthesis of **7a/7b** began with thermal condensation of 2-phenylpyrrolidine (**32**) and 4-methylthiomandelic acid (**33**) to afford a 1:1 mixture of hydroxy amides **34** in near-quantitative yield. Reactant **32** was prepared in two steps from *N*-vinylpyrrolidin-2-one and ethyl benzoate, while reactant

(28) (a) Copado, C. R.; Grande, G. M. T.; Trigo, G. G.; Söllhuber, K. M. M. *J. Heterocycl. Chem.* **1986**, *23*, 601. (b) Nilsson, L.; Carlson, R.; Rappe, C. *Acta Chem. Scand. B* **1976** *30*, 271.

Scheme II



33 was prepared from 4-(methylthio)benzaldehyde and bromoform (Scheme II).[11a,29] 2-Phenyl-1-pyrroline (**37**) was obtained by a modification of the procedure of Brandage and Lindblom.[30] In their one-pot procedure, which entails sequential base-induced condensation of *N*-vinylpyrrolidinone and ethyl benzoate, acid-mediated hydrolysis/decarboxylation, and based-induced cyclization, intermediate keto lactam **38** was found to polymerize at a rate competitive with hydrolysis of the *N*-vinyl group. To avoid the polymer formation, we isolated **38** and conducted the hydrolysis/decarboxylation step under high-dilution conditions (see experimental description[14b]). This two-pot method furnished **37** in 85% isolated yield. Catalytic hydrogenation of **37** (40 psig, 10% Pd/C, ethanol) required careful monitoring to keep 4-phenylbutylamine, an over-reduction byproduct, to a minimum (ca. 5%). Hydroxy amides **34** were cyclodehydrated with concentrated sulfuric acid in a trifluoroacetic acid medium to afford a mixture of lactams, **35a/35b**, in a 5:1 ratio. Originally, we introduced the hydroxyl group by trapping the sodium enolates of **35a/35b** (prepared by using NaH in refluxing THF) with oxygen; the supposed hydroperoxide intermediates were reduced in situ to furnish **36a/36b**, as a 1:1 mixture.[11a] Ultimately, we developed a safer, more convenient hydroxylation procedure involving generation of the potassium enolates with solid KOH in warm dimethyl sulfoxide in the presence of oxygen; this gave a mixture of **36a** and **36b** enriched in the former. Reduction of the amide carbonyl in **36a/36b** with borane–THF resulted in some over-reduction to undesired **4a**. Hence, we employed sodium borohydride and CF_3CO_2H to selectively reduce the carbonyl group and complete the synthesis of **7a/7b**.[31] The mixture of **7a** and **7b** was isolated and purified as an HCl salt (**7a/7b** = 75:25) in an overall yield of 75% from **35a/35b**.

With a high-yielding synthesis of **7a/7b** firmly established, the final target molecule (**4b**) was obtained by using the highly stereoselective deoxygenation reaction with borane–THF in CF_3CO_2H. The aforementioned NMR studies helped to define the requirements for obtaining maximum selectivity in the deoxygenation step. The HCl salt of **7a/7b** was dissolved in CF_3CO_2H at −10 °C. One hour later, ^1H NMR analysis of the reaction mixture indicated the absence of **17a/17b**; thus, the borane–THF (1.5 molar equiv) was added dropwise. Following an extractive workup, **4a/4b** was isolated as the perchlorate salt in 92% yield, as an 8:92 mixture. Altogether, the synthesis of racemic **4b** was completed in seven steps from commercially available *N*-vinylpyrrolidin-2-one in an overall yield of 56%.

For an enantiospecific synthesis of (6*S*,10b*R*)-(+)-**4b** (McN-5652-X), 2-phenylpyrrolidine (**32**) was a suitable starting point because of the availability of the desired *R* enantiomer via classical resolution or enantioselective hydrogenation.[32] A sample of (*R*)-(+)-**32** (98% ee) from resolution of *R*-enriched material[32] with L-(+)-tartaric acid[12c] was employed in the above synthetic sequence to furnish (6*S*,10b*R*)-(+)-**4b**. However, the enantiomeric purity, as determined via 360-MHz ^1H NMR analysis of the Mosher's acid salt (1.5 molar equiv of (*R*)-(3)-α-methoxy-α-(trifluoromethyl)phenylacetic acid;[33] C_6D_6),[12c,34] was surprisingly only about 30%. This disappointing result prompted our reevaluation of the synthetic route.

We considered three reactions as possible points for racemization: the base-induced hydroxylation (**35** → **36**), the CF_3CO_2H-mediated borohydride reduction of **36a/36b**, and the stereoselective deoxygenation of **7a/7b**. Since racemization would involve the preset stereogenic center, we performed these reactions with either deuterated reactants or reagents. The facts already in hand (vide supra) indicated that the deoxygenation reaction was not problematic. To test for racemization of **36a/36b** during the sodium borohydride reduction, racemic **36a/36b** (95:5) was reduced with sodium borodeuteride and CF_3CO_2D and the product was isolated as an HCl salt. High-field ^1H NMR analysis of the resultant C5 dideuterio-**7a/7b** (>95:5, 85%) revealed no deuterium incorporation at C10b, thereby excluding racemization in this step. We then examined possible racemization at C10b of **35a/35b** before and after hydroxylation. Racemic **35a/35b** (ca. 80:20) was exposed to KOD (2 molar equiv) in DMSO-d_6 at 65 °C for 2.5 h. ^1H NMR analysis of the crude reaction mixture revealed ca. 44% deuterium incorporation at C10b of recovered **35a/35b** (ca. 92:8), thereby identifying a source of racemization. The product of hydroxylation was also tested indirectly for racemization by subjecting **36a/36b** to similar conditions. Again, ^1H NMR analysis showed ca. 48% deuteration at C10b of recovered **36a/36b** (90:10). These experiments clearly demonstrate that the erosion of enantiomeric purity originated in the base-mediated hydroxylation of **35a/35b**. Fortunately, this problem was easily solved by using just 1.0 molar equiv of NaOH and oxygen-sparged DMSO. With this new procedure, we completed the enantiospecific synthesis of (6*S*,10b*R*)-(+)-**4b**, obtaining >95% ee product (by NMR assay) from 98% ee (*R*)-(+)-**32**.

Conclusion

The reductive deoxygenation of **5a/5b** and **7a/7b** with borane–THF and trifluoroacetic acid to give **6a/6b** and **4a/4b**, respectively, is stereoconvergent and highly stereoselective for the trans isomer (generally 88–94% in favor of **6b** or **4b**). One key aspect of this process is a strong thermodynamic preference for the cis-fused enammonium salt, **11b** or **17b**, while another is the impressively high stereospecificity (ca. 99%) of the enammonium–iminium rearrangement.[36] In fact, both the major (cis-fused) and minor (trans-fused) enammonium diastereomers are similarly constrained to rearrange with suprafacial proton delivery to the β carbon (i.e., C6). Moreover, proton transfer was found to compete effectively with intermolecular exchange reactions. To rationalize the remarkable stereospecificity of the rearrangement, and the attendant intramolecular component, we have invoked a conducted tour mechanism involving a tight solvent cage. Such a solvated ion-pair aggregate, a complex solution structure that is held together by noncovalent bonding in a "supramolecule", can be quite reasonable for an ionic solute in a carboxylic acid medium.[35] Indeed, solvated intimate ion pairs have served a valid purpose in the description of solvolysis and nucleophilic substitution reactions at sp^3 carbon.[37a] Such species have also been important for explaining the chemistry of carbanion protonation.[23,37b] Recently, the relevance of aggregate species in the chemical behavior of lithium enolates has been aptly appreciated, whereupon Seebach noted that they "may influence the result of seemingly simple

(29) Reeve, W.; Compere, E. I., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 2755. Compere, E. L., Jr. *J. Org. Chem.* **1968**, *33*, 2565. Also, see: Compere, E. L., Jr.; Shockravi, A. *Ibid.* **1978**, *43*, 2702.

(30) Brandage, S.; Linblom, L. *Acta Chem. Scand. B* **1976**, *30*, 93. Also, see: Jacob, P., III *J. Org. Chem.* **1982**, *47*, 4165.

(31) Umino, N.; Iwakuma, T.; Itoh, N. *Tetrahedron Lett.* **1976**, 763.

(32) Becker, R.; Brunner, H.; Mahboobi, S.; Wiegrebe, W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 995.

(33) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(34) Villani, F. J., Jr.; Costanzo, M. J.; Inners, R. R.; Mutter, M. S.; McClure, D. E. *J. Org. Chem.* **1986**, *51*, 3715.

(35) (a) Etter, M. C. *Isr. J. Chem.* **1985**, *25*, 312. (b) Hojo, M.; Imai, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1963.

(36) Note **Added in Proof**: Reductive deoxygenation (BH_3·THF, CF_3CO_2H) of the 7-hydroxybenzo[*a*]quinolizine homologues of **5a**·HBr or **5b**·HBr gave a 32:68 mixture of *cis*- and *trans*-1,3,4,6,7,11b-hexahydro-7-phenyl-2*H*-benzo[*a*]quinolizines (related to **6a** and **6b**). The low stereoselectivity here is consistent with the much greater preference for trans-fused forms of protonated hexahydrobenzo[*a*]quinolizines,[19a] confirming the argument for high stereoselectivity proposed in this paper. Details of work on the benzo[*a*]quinolizine series will be published in due course.

(37) (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A; Structure and Mechanisms*; 2nd ed.; Plenum Press: New York, 1984; pp 204–6, 244–7, 283–4. (b) *Ibid.*, pp 379–380.

standard reactions of organic synthesis".[38] The enammonium–iminium rearrangement addressed in this paper extends the scope of such phenomena.

Experimental Section

General Methods. Melting points are corrected. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz), Bruker AM-360WB (360 MHz), or a Bruker AM-400 (400 MHz) instrument in $CDCl_3$ with Me_4Si as an internal standard, unless indicated otherwise (s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets). NMR proton assignments and coupling constants for **5a**·HBr were derived with the aid of 2D COSY and homonuclear decoupling experiments. ^{2}H NMR spectra were obtained at 55.3 MHz on the Bruker AM-360WB. ^{13}C NMR spectra were obtained at 90.6 MHz on the Bruker AM-360WB or 100.6 MHz on the Bruker AM-400 in $CDCl_3$, unless noted otherwise. Carbon multiplicities were determined by the DEPT technique. Chemical-ionization (methane) mass spectral data were recorded on a Finnigan 3300 spectrometer; electron-impact (70 eV) and fast-atom bombardment data were obtained on a VG Micromass 7035 instrument. TLC analyses were performed on Whatman 250-μ silica gel plates with visualization by UV fluorescence and iodine staining; GLC analyses were performed on a Hewlett Packard 5890 gas chromatograph using a Chrompack CP SIL 5 CB (25 m × 0.25 mm) column. The X-ray analysis of **5a**·HBr was performed by Crystalytics Company, Lincoln, NB. Trifluoroacetic acid (99%), trifluoroacetic acid-*d* (99% D), and 1 M BH_3·THF were purchased from Aldrich Chemical Co. and used as received.

^{1}H NMR Analysis of 5a·HBr.[11a] A ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5a**·HBr was taken immediately after dissolution of the solid. It showed a mixture of two forms in a ratio of ca. 55:45 (cis:trans), and there was little change with time. Data: δ 2.0–3.0 (m, 4 H), 3.37 (d, J = 11.5 Hz, H_5), 3.51 (d, J = 14.2 Hz, H_5), 3.74 (d, J = 13.7 Hz, H_5), 3.85–4.40 (m, 3 H), 5.24 (m, 0.45 H, H_{10b}), 5.76 (m, 0.55 H, H_{10b}), 6.96 (d, J = 7.7 Hz, H_7), 7.15–7.50 (m, aromatic), 12.10 (br s, NH), 12.23 (br s, NH). When the ^{1}H NMR spectrum was recorded with $CDCl_3$ and Me_2SO-d_6 as the solvent, we again noted a mixture of cis- and trans-fused forms, this time in a 74:26 ratio: δ 3.48 (d, J = 13.8 Hz, H_5 major), 3.69 (dd, J = 4.4, 13.8 Hz, H_5 major), 3.96 (d, J = 12.6 Hz, H_5 minor), 4.15 (m, H_3 major), 4.72 (m, 0.26 H, H_{10b}), 5.15 (m, 0.74 H, H_{10b}), 5.95 (s, 0.26 H, OH), 6.15 (s, 0.74 H, OH).

Reductive Deoxygenation of 5a·HBr. General Procedure. Amino alcohol salt **5a**·HBr (45 mg, 0.13 mmol) was dissolved in trifluoroacetic acid (2 mL) under argon at room temperature. The solution was cooled to 5 °C in an ice bath, the hydride reducing agent (excess) was added, and the reaction was stirred at 5 °C usually for 15–30 min. The reaction was quenched by addition of water (5 drops) and stirred at room temperature for ca. 30 min. The solution was basified with 1 N NaOH and extracted with methylene chloride. The organic layer was washed once with water and once with brine, dried (K_2CO_3), and concentrated to give a mixture of **6a** and **6b**.

Example 1. A 1 M solution of borane in THF (0.50 mL, 0.50 mmol) gave **6a** and **6b** (30 mg, 90%) in a 10:90 ratio (GLC), which was verified by ^{1}H NMR (90 MHz): δ 1.7–3.1 (m, aliphatic), 3.55 (m, 1 H, H_{10b}), 4.20 (dd, 0.90 H, J = 5, 5 Hz, H_6), 4.40 (dd, 0.10 H, J = 6, 9 Hz, H_6), 6.8–7.3 (m, 9 H).

Example 2. Sodium borohydride (19 mg, 0.5 mmol, fragment of a pellet) gave **6a** and **6b** (27 mg, 84%) in a 13:87 ratio (GLC), which was verified by ^{1}H NMR (90 MHz).

Example 3. Sodium cyanoborohydride (60 mg, 1.0 mmol) gave **6a** and **6b** (30 mg, 90%) in a ratio of 55:45 (GLC and ^{1}H NMR).

Example 4. When a 1 M solution of triethylsilane in THF (0.50 mL, 0.50 mmol) was used as the hydride source, little reaction was noted by GLC even after 24 h at 5 °C. After workup, a dark green oil was isolated (20 mg, 56%), which was predominantly enamine **14** by ^{1}H NMR (90 MHz): δ 4.30 (dd, J = 6, 9 Hz, H_{10b}), 6.35 (s, H_5).

Reductive Deoxygenation of 5b·HBr. Following the general procedure, **5b**·HBr (10 mg, 0.029 mmol; generated from analytically pure fumarate salt[11a] via the free base in 2-propanol with the requisite quantity of 48% HBr, mp 197–198 °C) in trifluoroacetic acid (0.50 mL) was reduced with 1 M BH_3·THF (0.10 mL, 0.10 mmol); workup gave a mixture of **6a** and **6b** (7.0 mg, 97%) in a 7:93 ratio (GLC, ^{1}H NMR).

Reductive Deoxygenation of 5a·HBr with BD_3·THF. Amino alcohol salt **5a**·HBr (45 mg, 0.13 mmol) was dissolved in trifluoroacetic acid (2 mL) at room temperature under argon and stirred for 40 min. The reaction was cooled to 5 °C and a 0.85 M solution of BD_3·THF (1.0 mL, 0.85 mmol) was added dropwise. After 3 h, the reaction was worked up following the general procedure to afford a yellow oil (32 mg, 98%). Cl-MS (CH_4) analysis gave a MH^+ of 251, and GLC showed a 9:91 mixture of **8a** and **8b**. ^{1}H NMR of **8b** (360 MHz): δ 3.61 (dd, J = 7.4, 9.0 Hz, H_{10b}), 4.19 (d, J = 5.8 Hz, H_6), 6.90 (d, J = 7.4 Hz, H_7), 7.0–7.3 (m, aromatic). ^{1}H NMR of **8a**: δ 4.40 (d, J = 11 Hz, H_6), 6.85 (d, J = 12 Hz, H_7). ^{1}H NMR of **8b**·HCl (360 MHz, $CDCl_3$): δ 3.13 (dd, J = 11.0, 11.0, H_{5ax}), 4.76 (d, J = 11.8 Hz, H_{6ax}), 4.90 (m, H_{10b}), 6.79 (d, J = 7.6 Hz, H_7); the H_{5ax} and D_{5eq} confirms deuterium entry anti to the phenyl ring.

Reductive Deoxygenation of 5a or 5a·HBr in Trifluoroacetic Acid-*d*. Amino alcohol salt **5a**·HBr (50 mg, 0.14 mmol) was dissolved in CF_3CO_2D (2 mL) at 23 °C under argon and cooled to 5 °C. A 1 M solution of BH_3·THF (0.50 mL, 0.50 mmol) was added. After 30 min, the reaction was worked up to give partially deuterated **6a** and **6b** (40 mg, 100%) in a ratio of 9:91 (GLC); ^{1}H NMR (90 MHz) showed about 65% proton incorporation at position 6 of both isomers (signals at δ 4.0–4.4; rest of spectrum: δ 1.7–3.1 (m, 8 H, aliphatic), 3.50 (m, H_{10b}), 4.20 (dd, J = 5, 5 Hz), 6.8–7.4 (m, 9 H, aromatic)).

Likewise, **5a** (50 mg, 0.19 mmol) was reacted to give a mixture of amines **6a** and **6b** (40 mg, 85%) in a 16:84 ratio (GLC). ^{1}H NMR (90 MHz, $CDCl_3$) showed about 10–15% of proton incorporation at position 6 (δ 4.10–4.40), possibly because of the hydrogen from the OH of the substrate released as HDO. The remainder of the ^{1}H NMR spectrum was essentially identical with that from above reaction except for the sharp doublets at δ 3.00 and 2.80 (J = 11.5 Hz, 2 H_5).

^{1}H NMR Study of 5a·HBr in Trifluoroacetic Acid-*d*. Amino alcohol salt **5a**·HBr (49 mg, 0.14 mmol) was added to CF_3CO_2D (1 mL) at −5 °C in an NMR tube, which was then placed in the spectrometer (360 MHz) at 0 °C. The initial ^{1}H NMR spectrum showed only enammonium salts **11a** and **11b** in a 5:95 ratio: δ 2.28/2.45/2.63/2.75 (m, 4 H, H_1 and H_2), 3.62 (m, H_{3a}), 4.20 (m, H_{3e}), 4.73 (m, H_{10b} of **11a**), 5.24 (d, J = 14.7 Hz, H_{10b} of **11b**), 6.18 (s, 0.95 H, H_5 of **11b**), 6.58 (s, 0.05 H, H_5 of **11a**), 7.2–7.6 (m, 9 H). ^{13}C NMR (CF_3CO_2D, 164.0 ppm; 90 MHz; **11b** only): δ 23.55 (C_2), 31.95 (C_1), 59.40 (C_3), 66.51 (C_{10b}), 120.5 (C_5), 128.2, 129.3 (4° C), 130.2, 130.9 (2 C), 131.2 (2 C), 131.5 (C), 131.9, 132.0, 133.4, 135.9 (aromatic 4° C), 143.3 (aromatic 4° C). After the probe temperature was raised to 20 °C, slow rearrangement to iminium salts **12a** and **12b** was observed ($t_{1/2}$ = 175 min). Complete conversion required about 24 h and the final ratio of **12a** to **12b** was 9:91. ^{1}H NMR: δ 2.40–2.70 (m, 2 H_1 and H_{2a}), 3.23 (m, H_{2e}), 4.44 (m, H_{3a}), 4.70 (m, H_{3e}), 5.18 (m, 1.35 H, H_{10b} and H_6), 6.89 (d, J = 7.7 Hz, H_7 of **12b**), 7.30–7.60 (m, aromatic), 9.01 (s, 0.91 H, H_5 of **12b**), 9.22 (s, 0.09 H, H_5 of **12a**). ^{13}C NMR (CF_3CO_2D, 164.0 ppm; 90 MHz; **12b** only): δ 24.90 (C_2), 32.57 (C_1), 59.55 (C_6), 68.30 (C_3), 68.38 (C_{10b}), 126.8, 130.3, 130.8 (aromatic 4° C), 131.5, 131.8, 132.1 (2 C), 132.2, 132.4 (2 C), 132.6, 137.6 (aromatic 4° C), 178.0 (C_5). Reduction of this sample at 0 °C with 1 M BH_3·THF (1 mL) yielded **6a** and **6b** in a 10:90 ratio (GLC).

An identical experiment was set up at 20 °C, and after 1 h, 1 M tris(trifluoroacetoxy)borane in trifluoroacetic acid (5 drops) was added as a catalyst to observe any effects. After 4 h at 20 °C, the progress of the reaction was not changed by the added borane reagent ($t_{1/2}$ about 180 min), and **11** and **12** were formed in a 25:75 ratio.

^{1}H NMR Study of 5a in Trifluoroacetic Acid. Amino alcohol **5a** (44 mg, 0.16 mmol) was dissolved in CF_3CO_2H (1 mL) at −5 °C and the NMR tube was placed in the spectrometer (360 MHz) at 0 °C. The initial spectrum at 0 °C (30 min after mixing) showed that rapid rearrangement of **11** to **12** had already occurred; the ratio of **11** to **12** was ca. 25:75. After 1.5 h, only iminium salts **12a** and **12b** remained, present in a 7:93 ratio. Pertinent ^{1}H NMR signals: δ 4.87 (m, H_6 and H_{10b}), 6.64 (d, J = 7.6 Hz, H_7 of **12b**), 8.69 (s, 0.93 H, H_5 of **12b**), 8.83 (s, 0.07 H, H_5 of **12a**). Reaction of **5a** in CF_3CO_2D was slower (see rate studies), such that there was a 50:50 mixture of **11** and **12** after 1 h at 10 °C.

Preparation and Reductive Deoxygenation of 5a·DCl. Amino alcohol **5a** (30 mg, 0.11 mmol) in CD_3OD (0.50 mL, 99.5% D) was treated with 20% DCl in D_2O until the solution became acidic. The solution was evaporated with a stream of argon to give a solid, which was dissolved in CF_3CO_2H (2 mL) at 23 °C under argon. Following the general procedure, 1 M BH_3·THF (0.70 mL, 0.70 mmol) was added and the reaction was worked up to give partially deuterated **6a** and **6b** (30 mg) in a 13:87 ratio (GLC); ^{1}H NMR (90 MHz) showed mostly **6b** (ca. 90%) and about 70% of a proton at H_6 (δ 4.10–4.40).

^{1}H NMR Rate Studies with 5a. General Procedure. Amino alcohol **5a** or an acid-addition salt thereof (ca. 40 mg) was dissolved in CF_3CO_2D (1 mL) at an appropriate temperature and followed by ^{1}H NMR (360 MHz) with time. Data points were generally recorded at 10-min intervals. Integral values of specific protons in the enammonium salt at δ 3.70 (m, H_{3e}) or 6.25 (s, H_5) were compared to values of the iminium salt at δ 3.30 (m, H_{2e}), 7.00 (d, H_7), or 9.10 (s, H_5) to determine their ratio. For H_5 integral areas normalization to 100% was employed.[19b] The data

(38) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. Also, see: Polt, R.; Seebach, D. *J. Am. Chem. Soc.* **1989**, *111*, 2622.

were subjected to linear least-squares analysis (log % **11b** vs time) to obtain constants and the corresponding $t_{1/2}$ values ($r^2 > 0.99$ in all cases).

The HCl salt of **5a** was prepared from the free base in methylene chloride with ethereal HCl to give a white solid. This material was recrystallized from 2-propanol to afford a white powder, mp 227–228.5 °C. ^{1}H NMR (400 MHz, Me_2SO-d_6) showed an ca. 55:45 mixture of two forms: δ 1.80–2.90 (m, 4 H), 3.10–3.90 (m, 4 H), 4.78 (m, 0.58 H, H_{10b}), 4.91 (m, 0.42 H, H_{10b}), 6.58 (s, OH), 6.61 (s, OH), 6.92 (d, J = 7.5 Hz, H_7), 7.03 (d, J = 7.6 Hz, H_7), 7.20–7.45 (m, 8 H, aromatic), 11.05 (br s, 0.55 H, NH), 11.44 (br s, 0.45 H, NH). Anal. Calcd for $C_{18}H_{19}NO$·HCl: C, 71.63; H, 6.68; N, 4.64. Found: C, 71.54; H, 6.74; N, 4.62.

Generation and Isolation of Enamine 14. All operations here were conducted under an atmosphere of argon to minimize oxidation of this highly unstable intermediate. Amino alcohol salt **5a**·HBr (200 mg, 0.58 mmol) was combined with polyphosphoric acid (4.0 g) and the mixture was heated on a steam bath for 15 min. The reaction was cooled, diluted with water, basified with 3 N NaOH, and extracted with methylene chloride. The organic solution was washed with brine, dried (K_2CO_3), and concentrated to afford an air-sensitive, dark green oil, **14** (100 mg, 70%). ^{1}H NMR (90 MHz): δ 1.80–2.40 (m, 4 H, H_1 and H_2), 3.0–3.5 nm, 2 H, H_3), 4.36 (dd, 1 H, J = 6, 8 Hz, H_{10b}), 6.40 (s, 1 H, H_5), 6.9–7.45 (m, 9 H).

Reduction of 14. Enamine **14** (50 mg, 0.20 mmol) was dissolved in CF_3CO_2H (2 mL) at 5 °C, stirred 5 min, and treated with 1 M BH_3·THF (0.50 mL, 0.50 mmol). After 15 min, the reaction was worked up in the usual way to give amines **6a** and **6b** (40 mg, 80%) in a 12:88 ratio (GLC); ^{1}H NMR (90 MHz) verified this ratio: δ 4.10 (dd, 0.88 H, H_6 of **6b**) and 4.40 (dd, 0.12 H, H_6 of **6a**).

^{1}H NMR Study of 14 in Trifluoroacetic Acid-*d*. Enamine **14** (12 mg, 0.048 mmol) under argon at 5 °C was combined with CF_3CO_2D (1 mL) at 5 °C, transferred to an argon-purged NMR tube at 0 °C, and monitored by ^{1}H NMR (360 MHz) at 0 °C. At 5 min the spectrum showed **11** and **12** in a 5:2 ratio and the enammonium salts were highly biased to the cis conformation with a **11a** to **11b** ratio of 6:94 [δ 6.60 and 6.15 (pair of s, H_5)]. The enammonium salts disappeared with time (half-life for rearrangement of ca. 95 min) until only 1% remained after 20 h. Along with the trace of **11** were iminium salts **12a** and **12b**, present in a ratio of 3:97 [δ 8.95 and 9.10 (pair of s, H_5)].

^{1}H NMR Study of the Reaction of 14 with HCl. Enamine **14** (ca. 14 mg, 0.058 mmol) in $CDCl_3$ (1 mL) under argon was combined with 1 N HCl (0.058 mmol) and the mixture was shaken vigorously for 1 min at room temperature. The $CDCl_3$ layer was separated from the aqueous layer under argon. The ^{1}H NMR (360 MHz) showed a 1:3 mixture of isoquinolinium salt **20**[39] and enammonium salt **11b** (little if any **11a**). **20**: δ 2.78 (m, H_2), 4.08 (dd, J = 7.8, 7.8 Hz, H_1), 5.41 (dd, J = 7.7, 7.8 Hz, H_3), 7.0–7.5 (m, aromatic), 7.90 and 7.98 (dd, H_8 and H_9), 8.07 (d, J = 8.0 Hz, H_7), 8.28 (d, J = 8.2 Hz, H_{10}), 8.65 (s, H_5). **11b**: δ 1.99/2.18/2.43 (m, H_1 and H_2), 3.28 (m, H_{3a}), 3.46 (m, H_{3e}), 4.42 (dd, J = 5.9, 10 Hz, H_{10b}). 6.48 (s, H_5), 7.0–7.4 (m, aromatic). At room temperature, this ratio changed only slightly with time, with a few percent more **20** forming over 2.5 h. However, when CF_3CO_2D (0.50 mmol, ca. 40 μL) was added to the NMR tube, an immediate reaction took place (color change from dark green to light yellow) and the ^{1}H NMR spectrum showed **20** and iminium salts **12a** and **12b** in a 30:70 ratio (measured by the H_5 singlets at δ 8.93 and 9.20). (The loss of stereoselectivity may be due to the $CDCl_3$ solvent.) In a separate experiment, catalytic amounts of CF_3CO_2D (0.10 molar equiv and 0.50 molar equiv) were added to a $CDCl_3$ solution of **20** and **11b** at 0 °C; however, only rapid formation of the isoquinolinium salt **20** was recorded in this case.

5,5-Dideuterio-1,2,3,5,6,10b-hexahydro-6-phenylpyrrolo[2,1-*a*]isoquinolin-6-ol Hydrobromide (15a). 1,2,3,5,6,10b-Hexahydro-5-oxo-6-phenylpyrrolo[2,1-*a*]isoquinolin-6-ol[11a] (an isomeric mixture; 2.0 g, 7.2 mmol) in dry THF (25 mL) was added slowly to 1 M BD_3·THF (30 mL, 30 mmol) at 5 °C under argon and the mixture was refluxed for 2 h. The solution was cooled with an ice bath, methanol (30 mL) was added slowly, and the reaction was refluxed for 20 min. After cooling, the solution was concentrated to a yellow oil, which was dissolved in 2-propanol (15 mL) and treated with 48% HBr (1.3 g, 7.7 mmol) to afford **15**·HBr (0.35 g), mp 201–203 °C. ^{1}H NMR (90 MHz) of this solid showed a 4:1 mixture of **15a** to **15b**: δ 1.70–2.50 (m, aliphatic, 5 H), 2.60–2.90 (m, 0.4 H, H_3 of **15b**), 3.0–3.35 (m, 1.6 H, H_3 of **15a** and H_{10b}), 3.70 (dd, J = 7.5, 7.5 Hz, H_{10b}, 0.20 H, **15b**), 6.8–7.5 (m, 9 H).

Reductive Deoxygenation of 15a·HBr. Amino alcohol salt **15a**·HBr (50 mg, 0.14 mmol) was added to CF_3CO_2H (2 mL), treated with 1 M BH_3·THF (0.50 mL, 0.50 mmol), and worked up following the general procedure to give **16a** and **16b** (30 mg, 83%) in a ratio of 16:84 (GLC). ^{1}H NMR (90 MHz) showed nearly a full proton for combined H_6: δ 1.6–3.0 (m, 7 H, aliphatic), 3.30–3.60 (m, 1 H, H_{10b}), 4.13 (d, J = 4.5 Hz, 0.75 H, H_6 of **16b**), 4.33 (d, J = 6 Hz, 0.15 H, H_6 of **16a**), 7.4–6.8 (m, 9 H).

^{2}H NMR Study of 15a·HBr in Trifluoroacetic Acid-*d*. Amino alcohol salt **15a**·HBr (44 mg, 0.13 mmol) was combined with CF_3CO_2D (1 mL) in an NMR tube at −5 °C and the sample was placed in the spectrometer (55.3 MHz for ^{2}H) at 0 °C. The initial ^{1}H NMR showed mostly enammonium salt. ^{2}H NMR: δ 6.60 (br s, D_5) and 9.50 (br s, ND). The temperature was raised to 10 °C, and after 2 h, about 20% of iminium salt was present (broad singlets at δ 5.30 (D_6) and 9.20 (D_5)). After 16 h at 20 °C, essentially no enammonium salt remained; there was an ca. 5:4 ratio of D_5 to D_6 at δ 9.30 (br s) and 5.50 (br s), indicative of some proton at H_6.

Attempted Isolation of 12b Salts. A. Iodide. Amino alcohol **5a**·HBr (50 mg, 0.14 mmol) was dissolved in trifluoroacetic acid (2 mL) and the solution was stirred for 1 h at room temperature under argon. ^{1}H NMR (90 MHz) showed only iminium salts **12**. The solvent was evaporated under a stream of argon to an give an oil which was redissolved in glacial acetic acid (6 mL). Addition of 47% hydriodic acid gave copper-colored crystals, which were found to be isoquinolinium salt **20** (periodide salt). CI-MS (CH_4): m/z 246 (MH^+). ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD): δ 2.89 (m, 2 H, H_2), 4.20 (t, J = 7.8 Hz, 2 H, H_1), 5.21 (t, J = 7.8 Hz, 2 H, H_3), 7.62 (s, 5 H, aromatic), 8.10 (m, 3 H, H_7/H_8/H_9), 8.39 (s, 1 H, H_5), 8.44 (d, J = 8.2 Hz, 1 H, H_{10}). Anal. ($C_{18}H_{16}N$·I_3) C, H, N, I.

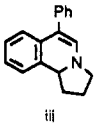
B. Perchlorate. In an identical manner, **12** was prepared and 70% perchloric acid (48 mg, 0.34 mmol) was added to the trifluoroacetic acid solution, followed by ether until the cloud point. The white solid that slowly crystallized was a mixture of **12a** and **12b** (43 mg, 81%). CI-MS (CH_4): m/z 248 (MH^+). ^{1}H NMR (see Figure 2) showed a 35:65 ratio of these salts. ^{1}H NMR (CF_3CO_2D, 400 MHz) showed chemical shifts nearly identical to those from our ^{1}H NMR studies: δ 3.20 (m, H_{1e}, **12b**), 5.10 (m, H_6 and H_{10b} of **12b**, H_{10b} of **12a**), 6.84 (d, J = 7.8 Hz, H_7 of **12b**), 8.87 (br s, H_5 of **12b**), 9.05 (br s, H_5 of **12a**). Reduction of this mixture (3 mg) in ethanol with excess sodium borohydride (10 mg) gave after workup (1 N HCl, followed by 3 N NaOH and extraction into methylene chloride) a mixture of amines **6a** and **6b** in a 37:63 ratio (GLC). Anal. ($C_{18}H_{18}N$·ClO_4) C, H, N.

1,2,3,5,6,10bα-Hexahydro-6β-hydroxy-4β- and 4α-methyl-6α-phenylpyrrolo[2,1-*a*]isoquinolinium Iodide (22a and 22b). Methyl iodide (0.30 g, 2.1 mmol) and **5a** (150 mg, 0.56 mmol) in acetonitrile (6 mL) were stirred (stoppered) at room temperature for 2 h. The solvent was evaporated to furnish a white solid (230 mg), a mixture of **22a** and **22b** in a 28:72 ratio by ^{1}H NMR (400 MHz): δ 2.0/2.57/2.87 (m, H_1 and H_2 of **22a** and **22b**), 7.10–7.50 (m, aromatic). **22a**: δ 3.05 (s, CH_3), 4.20 (m, H_{3a}), 4.47 (d, J = 13.5 Hz, H_{5a}), 4.70 (m, H_{3e}), 5.15 (d, J = 13.5 Hz, H_{5e}), 5.50 (dd, H_{10b}). **22b**: δ 3.27 (s, CH_3), 3.92 (m, H_{3a}), 4.31 (s, OH), 4.20 (d, J = 13.8 Hz, H_{5a}), 4.66 (d, J = 14.1 Hz, H_{5e}), 4.70 (m, H_{3e}), 5.37 (dd, J = 6.5, 7.3 Hz, H_{10b}). The mixture was recrystallized from ethanol to give white needles highly enriched in **22b** (100 mg). ^{1}H NMR (400 MHz): δ 2.29 (m, 1 H, H_1), 2.40 (m, 1 H, H_1), 2.59 (m, 1 H, H_2), 2.95 (m, 1 H, H_2), 3.40 (s, CH_3), 4.05 (m, 1 H, H_{3a}), 4.08 (d, J = 13.7 Hz, 1 H, H_{5a}), 4.63 (d, J = 13.7 Hz, 1 H, H_{5e}), 4.78 (m, 1 H, H_{3e}), 5.53 (dd, 1 H, H_{10b}, characteristic of a cis A conformation), 7.14 (d, 1 H, J = 7.6 Hz, H_7), 7.2–7.5 (m, 8 H, aromatic). Slow recrystallization of this material from methanol/2-propanol (1:2) gave long needles of **22b** suitable for X-ray analysis (mp 248–250 °C).[20] Anal. Calcd for $C_{19}H_{22}INO$: C, 56.03; H, 5.44; N, 3.44. Found: C, 56.06; H, 5.46; N, 3.40.

Reaction of 22a and 22b with Trifluoroacetic Acid-*d*. The mixture of **22a** and **22b** (27:73; 27 mg) was dissolved in CF_3CO_2D (1 mL) and examined by ^{1}H NMR (360 MHz). The spectrum showed immediate loss of water to give a mixture of enammonium salts **23a** and **23b** in a ratio of 30:70 with the following characteristic peaks: **23a** (minor) δ 2.94 (s, CH_3), 5.10 (dd, J = 8, 11 Hz, H_{10b}), 6.85 (s, H_5); **23b** (major) δ 3.35 (s, CH_3), 4.17 (dd, H_{3e}), 4.82 (dd, J = 8 Hz, H_{10b}), 6.12 (s, H_5).

Reaction of 22b with Trifluoroacetic Acid-*d*. Methiodide **22b** (2–3 mg) was dissolved in trifluoroacetic acid-*d* (1 mL) and placed in the ^{1}H NMR probe (360 MHz) at 20 °C. The initial spectrum showed about 25% of the starting methiodide, but after 1 h, the dehydration was complete and only **23b** was formed: δ 2.33 (m, 2 H, H_1), 2.54 (m, 1 H, H_2),

(39) Interestingly, treatment of **20** with aqueous NaOH provided dienamine iii [90-MHz ^{1}H NMR ($CDCl_3$) δ 2.70 (t, 2, H_3), 3.93 (apparent br t, 2, H_2), 6.38 (br s, 1 H_1), 6.9–7.5 (m, 10, s for H_5 at δ 7.12)], as an unstable oil.



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2.84 (m, 1 H, H_2), 3.35 (s, CH_3), 3.94 (m, 1 H, H_{3a}), 4.15 (m, 1 H, H_{3e}), 4.77 (dd, J = 9.5 Hz, 1 H, H_{10b}), 6.10 (s, H_5), 7.30–7.65 (m, aromatic).

***cis*- and *trans*-1,2,3,5,6,10b-Hexahydro-6-[(4-methylthio)phenyl]-pyrrolo[2,1-*a*]isoquinoline Hydrochloride (7a/7b·HCl).** Sodium borohydride powder (52.6 g, 1.38 mol) was added to a solution of crude **36a/36b**[14b] (100 g, 0.3 mol) in dry THF (0.5 L). The slurry was brought to reflux for 1 h and a solution of trifluoroacetic acid (157 g, 1.38 mol) in THF (350 mL) was added dropwise over 2.5 h. The mixture was refluxed for 4 h, cooled to room temperature, and slowly diluted with distilled water (500 mL). The two-phase solution was refluxed for 1 h, cooled to room temperature, made basic (pH 12) with 1 N NaOH, and extracted with methylene chloride (2 × 500 mL). The combined extracts were washed with water, dried ($MgSO_4$), and concentrated to yield **7a/7b**, as a dark red oil. Crystallization from 2-propanol (400 mL) containing concentrated HCl (25 mL) afforded 84.0 g (75% overall from **35a/35b**[14b]) of **7a/7b**·HCl, as a slight yellow solid, mp 226–228 °C. ^1H and ^{13}C NMR analysis of the free base revealed a 75:25 mixture of **7a/7b**. ^1H NMR (360 MHz): δ 1.56–2.00 (m, $2H_2/H_1$), 2.28–2.42 (m, H_1 and H_3), 2.46 and 2.47 (s, CH_3 of **7a/7b**), 2.65 and 3.02 (AB q, J_{AB} = 11.4 Hz, H_5 of **7b**), 2.72 and 3.24 (AB q, J_{AB} = 11.6 Hz, H_5 of **7a**), 2.78–2.89 (m, 2 H, **7b**), 3.07–3.37 (m, 2 H), 3.92–4.36 (s, 1 H, OH), 6.96–6.98 (m, 1 H), 7.09–7.14 (m, 2 H), 7.17–7.24 (m, 3 H). ^{13}C NMR (90 MHz): δ 15.85 (CH_3, **7a/7b**), 21.49 (CH_2, **7a**), 22.73 (CH_2, **7b**), 29.31 (CH_2, **7a**), 29.92 (CH_2, **7b**), 53.14 (CH_2, **7a**), 54.35 (CH_2, **7b**), 61.98 (CH_2, **7b**), 62.41 (CH, **7b**), 65.37 (CH, **7a**), 65.98 (CH_2, **7a**), 73.74 (COH, **7a**), 74.94 (COH, **7a**), 124.67 (CH, **7a**), 126.08 (CH, **7a**), 126.42 (CH, **7b**), 126.52 (CH, **7b**), 126.78 (CH, **7a**), 127.03 (CH, **7b**), 127.10 (CH, **7a/7b**), 127.31 (CH, **7b**), 127.37 (CH, **7a**), 128.53 (CH, **7b**), 129.31 (CH, **7a**), 136.52 (C_q, **7b**), 136.66 (C_q, **7a**), 137.79 (c_q, **7b**), 138.81 (C_q, **7a**), 139.80 (C_q, **7b**), 140.98 (C_q, **7a**), 141.99 (C_q, **7a**), 142.79 (C_q, **7b**); CI-MS (CH_4) m/z 340 (M^+ 29), 312 (MH^+), 294 ($MH^+ - 18$), 188. Anal. ($C_{19}H_{21}NOS$·HCl) C, H, Cl, N, S.

We prepared small samples of pure diastereomers **7a** and **7b** (noncrystalline) by reduction of each hydroxy lactam, **36a** and **36b**, with borane–THF (followed by workup with methanol).[11a]

Reductive Deoxygenation of 7a and 7b. Following the general procedure described for **5a**·HBr, **7a/7b**·HCl (75:25), **7a**, and **7b** were independently reduced with 1 M BH_3·THF; results are presented in Table I (GLC, ^1H NMR).

Preparation of 7a/7b·HBr. Free base **7a/7b** (ca. 1.8 g; enriched in **7a**) was dissolved in methylene chloride (50 mL) and 2-propanol (5 mL). Hydrobromic acid (47%) was added with stirring until the solution was acidic. Upon stirring and scratching of the flask walls, a precipitate of **7a/7b**·HBr was obtained (1.82 g), as a white solid: mp 185.0–186.5 °C; ^1H NMR analysis revealed a >99:1 ratio of **7a/7b**. Anal. ($C_{19}H_{21}NOS$·HBr) C, H, Br, N, S.

Preparation of 7a/7b·$HClO_4$. Free base **7a/7b** (ca. 0.9 g; enriched in **7a**) was dissolved in ethyl ether (50 mL) and 70% perchloric acid (ca. 0.5 mL) in 2-propanol (2 mL) was added with stirring. A precipitate formed immediately and then became an oil. The oil crystallized on stirring to afford **7a/7b**·$HClO_4$ (0.7 g) as a white solid: mp 169.5–171 °C; ^1H NMR analysis revealed a 91:9 ratio of **7a/7b**. Anal. ($C_{19}H_{21}NOS$·$HClO_4$) C, H, Cl, N, S.

Preparation of 7a/7b·CF_3CO_2H. Free base **7a/7b** (ca. 0.6 g; enriched in **7a**) was dissolved in ethyl ether (20 mL) and a solution of trifluoroacetic acid in ethyl ether (50:50) was added with stirring until solution was acidic. A precipitate formed immediately and then turned to an oil. The oil crystallized on stirring to afford **7a/7b**·CF_3CO_2H (0.56 g) as a white solid: mp 124.5–126 °C; ^1H NMR analysis revealed a >99:1 ratio of **7a/7b**. Anal. ($C_{19}H_{21}NOS$·CF_3CO_2H) C, H, F, N, S.

Large-Scale Preparation of 4b·$HClO_4$.[13] Unrecrystallized **7a/7b**·HCl (100 g, 0.29 mol) was added portionwise to a stirring solution of trifluoroacetic acid (640 mL) at −10 °C. The reaction mixture immediately turned purple and this color slowly disappeared over 1 h. While maintaining −5 °C (±5 °C), 500 mL of 0.9 M BH_3·THF (0.45 mol) was added slowly over 1.5 h. The reaction was warmed slowly to room temperature (1.5 h), diluted with water (500 mL), stirred overnight, poured into CH_2Cl_2 (1 L), and washed with water (2 × 1 L) and then 3 N NaOH (2 × 1 L). The organic layer was dried (Na_2SO_4) and concentrated to yield a light brown residue, which was dissolved in 2-propanol (1 L), filtered through a pad of Celite, and treated with 70% perchloric acid (41 g, 0.29 mol) with stirring. After 1 h, the resultant slurry was cooled in an ice bath and filtered, and the filter cake was washed with cold 2-propanol to afford 104.5 g (92%) of **4a/4b** as an off-white solid: mp 199–201 °C. ^1H NMR and GLC analysis showed an 8:92 ratio of **4a/4b**.

Enantiospecific Synthesis of (6*S*,10b*R*)-(+)-4b.[13] The synthesis was carried out predominantly by using the procedures described for racemic material,[14b] but starting with enantiomerically enriched 2-phenylpyrrolidine *R*-(+)-**32** (98% ee).[12c,32] The following modification to the hydroxylation step[14b] was instituted to prevent racemization in the hydroxylation of **35a/35b** (see Results and Discussion). Crude **35a/35b** (4.1 g, 13.26 mmol) and 40% NaOH (1.28 g, 12.85 mmol) were added to a solution of DMSO (25 mL). With stirring, oxygen was passed through the solution at such a rate to allow the reaction to exotherm only to ca. 40 °C. After just 20 min, TLC indicated the absence of starting material. The sparging was stopped; the reaction was cooled to room temperature and poured into a 50:50 mixture of CH_2Cl_2 and water (50 mL). Sodium bisulfite (6 g) was added, and the mixture was stirred for 1 h. The layers were separated, and the aqueous layer was reextracted. The combined organic layer was washed with water (four times), dried ($MgSO_4$), and concentrated to give 4.22 g (98%) of hydroxy lactams **36a/36b**, as an orange foam. We subjected this material, without purification, to the sodium borohydride reduction and the reductive deoxygenation to obtain crude (6*S*,10b*R*)-(+)-**4b**. 360-MHz ^1H NMR analysis of the Mosher's acid salt (1.5 equiv of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, C_6D_6)[12c,34] revealed an enantiomeric purity of >95%.

Attempted Isolation of 18a/18b·Perchlorate. At room temperature under argon, **7a/7b**·HCl (ca. 1.0 g) was added to trifluoroacetic acid (5 mL) with stirring. After 10 min, a solution of 70% perchloric acid in 2-propanol (5 mL, 1:1) was added. The mixture was quickly poured into dry ethyl ether (100 mL) and a solid slowly formed. ^1H NMR analysis showed no iminium (**17**) or enammonium (**18**) species. Recrystallization of a small sample from hot 2-propanol/ethyl acetate afforded a white solid, which was identified as isoquinolinium salt **21**, mp 128–131 °C. ^1H NMR (400 MHz): δ 2.54 (s, 3 H), 2.69–2.73 (m, 2 H), 4.02 (t, 2 H, J = 7.81 Hz), 5.11 (t, 2 H, J = 7.70 Hz), 7.36–7.47 (m, 4 H), 7.59–7.98 (m, 1 H), 8.04–8.10 (m, 2 H), 8.32–8.34 (m, 1 H), 8.34 (s, 1 H). ^{13}C NMR (100 MHz): δ 14.92 (CH_3), 20.50 (CH_2), 31.85 (CH_2), 59.81 (CH_2), 124.85 (C_q), 126.05 (CH), 126.20 (CH), 128.45 (CH), 129.00 (C_q), 129.60 (CH), 129.75 (CH), 130.10 (CH), 130.85 (CH), 135.95 (CH), 136.15 (C_q), 137.55 (C_q), 141.00 (C_q), 160.25 (C_q). FAB-MS: m/z 292 (MH^+), 277, 217, 180, 131, 109, 91.

NMR Rate Studies with 7a/7b. General Procedure. NMR experiments were carried out on a Bruker AM-360 spectrometer equipped with a 9-mm proton probe. The ^1H NMR tube was charged with approximately 40 mg of the salt or free base and cooled to 0–10 °C in an ice bath. Cold (0–10 °C) deuterated trifluoroacetic acid (0.5–0.7 mL), containing Me_4Si as internal standard, was added to the tube, which was quickly placed in the precooled (10 °C) NMR probe. The ^1H NMR spectra were recorded and integrated at regular, specified time intervals. To determine the percentage of both the enammonium and iminium salts (**17** and **18**) throughout the course of the reaction, the vinyl proton signals (H5; singlets at 6.17 and 8.92 ppm, respectively) were integrated and normalized to 100%.[19b] The log of the normalized percentage of enammonium salt (**17b**) was plotted vs time (see Figure 3) and the rate constant (k) was determined by using the slope of the straight line determined by least-squares analysis (r^2 > 0.99 in all cases). The half-lives were calculated from the rate constants (see Table III). NMR analysis revealed the rapid dehydration of **7a/7b** to afford the major enammonium salt **17b**: ^1H NMR (CF_3CO_2D, 360 MHz) δ 2.18–2.37 (m, 1 H), 2.43–2.48 (m, 1 H), 2.51–2.61 (m, 1 H), 2.58 (s, 3 H, CH_3), 2.66–2.78 (m, 1 H), 3.68–3.74 (m, 1 H), 4.14–4.23 (m, 1 H), 5.19 (t, J = 7.60 Hz, 1 H, H_{10b}), 6.17 (s, 1 H, vinyl), 6.63 (s, 1 H, vinyl or **17a**), 7.27–7.56 (m, 8 H). The fleeting nature of the enammonium salt prevented the carbon multiplicities from being determined for **17b**. ^{13}C NMR (CF_3CO_2D, 90 MHz): δ 15.99, 23.62, 31.69, 59.26, 67.09, 120.13, 128.37, 128.72, 129.97, 131.36, 132.80, 133.71, 141.89, 143.15.

With time, **17b** rearranged cleanly to the major iminium salt **18b**: ^1H NMR (CF_3CO_2D, 360 MHz) δ 2.24–2.62 (m, 3 H), 2.57 (s, 3 H, CH_3), 3.20–3.85 (m, 1 H), 4.19–4.45 (m, 1 H), 5.14 (br s, 1 H, H_{10b}), 6.87 (d, J = 7.77 Hz, 1 H, H_7), 7.25–7.53 (m, 7 H), 8.92 (s, 1 H, H_5). ^{13}C NMR (CF_3CO_2D, 90 MHz): δ 16.54 (CH_3), 24.94 (CH_2), 32.71 (CH_2), 52.55 (CH, C_6-deuterated), 59.68 (CH_2), 68.42 (CH, C_{10b}), 127.00 (CH), 130.40 (CH), 130.50 (C_q), 131.91 (CH), 132.11 (C_q), 132.51 (CH), 132.65 (2 CH), 134.76 (C_q), 142.47 (C_q), 177.77 (CH, C_5). Also observed as a minor component was **18a** (ca. 6%). After 4 days at room temperature, ^1H and ^{13}C NMR analysis showed 36% of the cis isomer **18a**. ^1H NMR (CF_3CO_2D, 360 MHz): δ 2.47–2.67 (m, 3 H), 2.49 (s, 3 H, CH_3), 3.12–3.26 (m, 1 H), 4.34–4.49 (m, 1 H), 4.55–4.61 (m, 1 H), 5.08–5.21 (m, 1 H), 7.10 (d, 2 H, J = 8.4 Hz), 7.18–7.64 (m, 6 H), 9.07 (s, 1 H, H_5). ^{13}C NMR (CF_3CO_2D, 90 MHz): δ 16.66 (CH_3), 24.35 (CH_2), 33.18 (CH_2), 51.50 (CH, C_6-deuterated), 59.73 (CH_2), 67.60 (CH), 127.50 (CH), 130.28 (CH), 130.50 (C_q), 131.24 (CH), 132.16 (CH), 132.42 (C_q), 132.61 (2 CH), 132.97 (CH), 133.24 (C_q), 142.91 (C_q), 174.43 (CH).

Single-Crystal X-ray Analysis of *trans*-1,2,3,5,6,10b-Hexahydro-6-phenylpyrrolo[2,1-*a*]isoquinolin-6-ol (5a) Hydrobromide. Crystals of $C_{18}H_{20}BrNO$ (mw 346.27, colorless rectangular parallelpipeds from

methanol/2-propanol) are monoclinic (space group $P2_1$) with a = 10.013 (2) Å, b = 12.588 (3) Å, c = 12.981 (3) Å, α = 90.00°, β = 102.75 (1)°, γ = 90.00°, V = 1596 (1) Å^3, and d_{calcd} = 1.442 g cm^{-1} for Z = 4. The intensity data were collected from a single crystal (0.30 × 0.60 × 0.62 mm^3) on a computer-controlled Four-Circle Nicolet Autodiffractometer with the ω scan technique at 293 K to a scattering angle of 3.0° < 2θ < 50.7° by using Mo Kα radiation (λ = 0.71073 Å; graphite monochromator). Of a total of 2914 independent reflections collected, 1956 intensities greater than 3.0$\sigma(I)$ were used. The structure was solved by the heavy-atom Patterson method with standard Lorentz and polarization corrections applied to the data; the hydrogen atoms were located. Structure refinement was accomplished by full-matrix least-squares methods with an anomalous dispersion correction for the bromine atom (anisotropically for nonhydrogen atoms and isotropically for hydrogen atoms). Specifically, hydrogen atoms H_O and H_{N4} were located from a difference Fourier synthesis and refined as independent isotropic atoms. The remaining hydrogen atoms were included in the structure factor calculations as idealized atoms. The final discrepancy factors were $R_1 = \sum||F_o| - |F_c||/\sum|F_o| = 0.046$ and $R_2 = \{\sum w(|F_o| - F_c|)^2/\sum w|F_o|^2\}^{1/2} = 0.045$. Besides the obvious features depicted in Figure 1, the molecular structure also has hydrogen bonds from the bromine atom to O–H_O (2.70 Å) and to N4–H_{N4} (2.43 Å), such that an O–H···Br···H–N bridge exists across the beta face of the tricyclic system. Details for this atomic arrangement are given in the microfilm supplement.[14b]

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Supplementary Material Available: Detailed data for the X-ray analysis of **5a**·HBr, including tables of bond lengths, bond angles, thermal and positional parameters, and atom contacts; experimental procedures and data for **32**, **34**, **35a/b**, **36a/b**, and **37** (11 pages). Ordering information is given on any current masthead page.

Dynamics of Hydride Transfer between NAD$^+$ Analogues[1]

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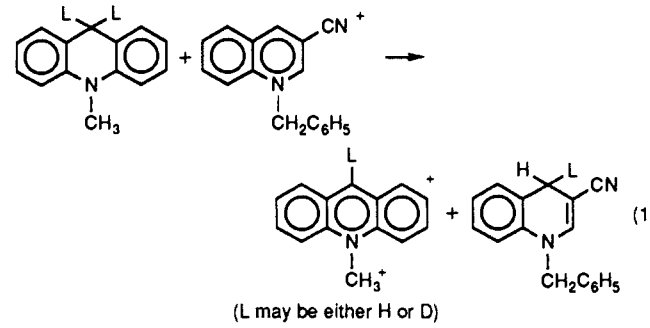
Abstract: Primary kinetic isotope effects (KIE) for hydride transfer between 10-methylacridan and 1-benzyl-3-cyanoquinolinium perchlorate have been measured in 15 different solvents. There is a reduction of the KIE from 5.2 to about 2.9 in the more viscous, nonhydroxylic solvents. Hydroxylic solvents give the larger KIE regardless of their viscosity. These results suggest a three-step process. In the first step, the heavy atoms and solvent are reorganized to a configuration intermediate between reactants and products, while the hydride retains its original attachment. In the second stage, the hydride is transferred, probably by tunneling. In the final step the products are stabilized by further solvent and heavy-atom reorganization. For nonhydroxylic solvents, translational and rotational diffusion governs the heavy-atom reorganization steps and, therefore, determines which step is rate-limiting. Only when the heavy-atom reorganizations are fast is the second step rate-limiting and the KIE maximized. The rate constant for the tunneling process is assumed to be solvent-independent. It is of the right order of magnitude to compete with solvent relaxation. Changes in rate constant, k, and equilibrium constant, K, are modest, but there is a linear correlation between ln k and ln K, with a slope of 0.87. This slope suggests that it is the third step, rather than the first, which shares rate-limiting character with the second. There is no visible trend toward a maximum isotope effect at K = 1.

The purpose of this paper is to suggest that hydride transfer between NAD$^+$ analogues, A_i^+ and A_j^+, involves the prior achievement of a solvent configuration intermediate between that of ^+A_i·HA_j and that of A_iH·A_j^+. This theory requires considerably reduced primary hydrogen isotope effects for slowly relaxing solvents, and this has now been observed for a number of viscous, nonhydroxylic liquids. All hydroxylic solvents appear to give about the same, maximal isotope effect. The equilibrium constant has also been measured, in each of the solvents. It is somewhat solvent-sensitive, and the rate constant is correlated with the equilibrium constant, but these variations, in themselves, do not seem to offer a reasonable explanation for the substantial changes in the isotope effect.

We have chosen to study the reaction shown in eq 1 because previous work[2] has shown that its rate and equilibrium constant can be measured with good precision by following the appearance of the 10-methylacridinium ion absorbance around 435 nm. At this wavelength none of the other reactants or products and none of our solvents has any measurable absorption. This reaction has an equilibrium constant, K, of 22.2 in a 4:1 mixture of 2-propanol and water.[2] In all the solvents of the present study K has been large enough to ensure that a reaction mixture initiated with only reactants present, and one reactant in large excess, would go to at least 90% of completion with no more than a few percent of back-reaction, which would redistribute the isotopes. At the same time K has been small enough to be measured directly, by starting with the products, without isotopic substitution, measuring the rate of the reverse reaction, and making K consistent with the rate constant for the reverse reaction.[3] The reactants and products have the same charge type and are structurally similar, so that



(1)

(L may be either H or D)

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(2) Kreevoy, M. M.; Lee, I.-S. H. *J. Am. Chem. Soc.* **1984**, *106*, 2550.

(3) Ostović, D.; Lee, I.-S. H.; Roberts, R. M. G.; Kreevoy, M. M. *J. Org. Chem.* **1985**, *50*, 4206.

0002-7863/90/1512-3579$02.50/0