138052-90-1; **18**, 91550-06-0; **18**·HCl, 138052-91-2; **19**, 138052-92-3; **20**, 138052-93-4; **23**, 91550-07-1; **27**, 138052-94-5; **28** (isomer 1), 138052-95-6; **28** (isomer 2), 138052-96-7; **29**, 33857-76-0; **30**, 91550-08-2; **31a**, 138052-97-8; **31b**, 138052-98-9; **32**, 138128-10-6; **33**, 91550-09-3; **34**, 91550-10-6; **35** (isomer 1), 138052-99-0; **35** (isomer 2), 138128-11-7; **36**, 138053-00-6; **37**, 131636-15-2; **38**, 131636-16-3; **39**, 66050-98-4; **40**, 132151-88-3; **41**, 91550-12-8; **42**, 91604-59-0; **43**, 10385-30-5; **44**, 138053-01-7; **45**, 138053-02-8; **46**, 96154-47-1; **47**, 91550-14-0; **48**, 91550-13-9; **49**, 138053-03-9; **50**, 91550-15-1; **51**, 138053-04-0; **52**, 91550-16-2; **53**, 90246-35-8; **54**, 91550-17-3; $MeOCH{=}C{=}CH_2$, 13169-00-1; $PhCH_2CH(OMe)_2$, 101-48-4; $ClCO(CH_2)_3Et$, 142-61-0; L-proline, 147-85-3; *N*-(*tert*-butoxycarbonyl)-L-proline, 15761-39-4; 2-mercaptopyridine, 2637-34-5; (4*R*,5*S*)-4-methyl-5-phenyloxazolidinone, 77943-39-6.

Supplementary Material Available: Experimental procedures and characterization data for intermediates **19**, **20**, **28**, **31**, **32**, **35**, **36**, **37**, **38a**, **39**, **43**, **44**, **45a**, and **46**; procedures for forming **11** and **31a**; ^1H and/or ^{13}C NMR spectra for **8**, **9**, **11**, **13**, **15**, **16**, **19**, **20**, **23**, **27**, **32**, **33**, **35**, **36**, **38**, **41**, **42**, **43**, **45**, **46**, **47**, **48**, **49**, **50**, **51**, **52** and **54** (35 pages). Ordering information is given on any current masthead page.

Stereospecific Enammonium–Iminium Rearrangements in a Benzo[*a*]quinolizidine System

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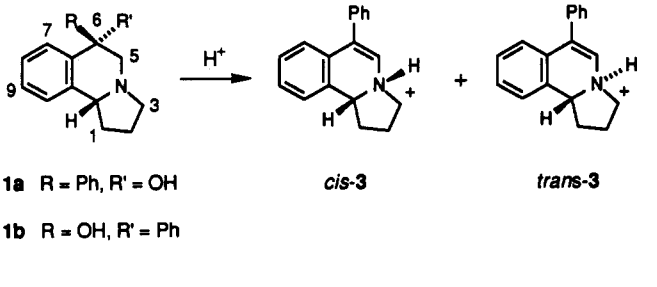
Reductive deoxygenation of amino alcohols **5a**·HBr or **5b**·HBr with borane–THF in trifluoroacetic acid produced a 68:32 mixture of amines **8a** and **8b**. This is a significant departure from the 8:92 ratio of amines **2a**:**2b** obtained in the reduction of amino alcohols **1a**·HBr or **1b**·HBr. The diminished trans selectivity with **5** arises from a reduced bias for a cis ring fusion in the N-protonated 6,6 system relative to the 5,6 system. By proton NMR, we observed dehydration of **5a**·HBr in CF_3CO_2D to a 75:25 mixture of enammonium salts *trans*-**6**:*cis*-**6**, each of which rearranged stereospecifically to give a 75:25 mixture of iminium salts *cis*-**7**:*trans*-**7**. Rate data for this rearrangement were acquired and computationally analyzed. The dehydration of free base **5b** in CF_3CO_2D was also studied. In this case, we were able to characterize the rate of disappearance of **5b**, as well as the rate of the stereospecific enammonium–iminium rearrangement. We also address slow, "post-rearrangement" epimerization at ring position 7, H/D exchange at ring position 6, and mechanistic aspects of the overall process.

Recently, we identified an unusual stereospecific 1,3 proton migration from nitrogen to carbon in the context of an enammonium–iminium rearrangement (Scheme I).[1] This process, which appears to occur substantially through a tight solvent cage, is crucial to the high stereoselectivity obtained in the deoxygenation of pyrroloisoquinoline **1a** or **1b** with borane–THF/trifluoroacetic acid to a mixture of **2a** and **2b** highly enriched in **2b**.[1] In this reduction a mixture of enammonium salts **3**, strongly biased to the cis-fused form (*cis*-**3**), rearranges to a mixture of iminium salts **4**, highly enriched in the trans diastereomer (*trans*-**4**), regardless of the stereochemistry of the original amino alcohol. The stereospecificity was reflected by virtually identical isomer ratios at the enammonium and iminium stages of the reaction (*trans*-**3**:*cis*-**3** = *cis*-**4**:*trans*-**4**; by ^1H NMR). As far as the independent diastereomeric pathways are concerned, we deemed the rearrangement of the major diastereomers, *cis*-**3** → *trans*-**4**, to be >98% stereospecific, but we were only able to estimate a level of stereospecificity of >80% for the minor rearrangement, *trans*-**3** → *cis*-**4**, because of the small populations involved. By the same token, we could only measure reaction rates for the major pathway, not the minor one.

To address these issues further, we required a related system in which the ratio of trans- and cis-fused enammonium salts would be closer to 50:50. Consequently, we explored the corresponding benzo[*a*]quinolizidine system, represented by amino alcohols **5a** and **5b** (Scheme II). The derived enammonium salts, *cis*-**6** and *trans*-**6**, now have a junction of two six-membered rings at the nitrogen bridgehead, reducing the thermodynamic preference for the cis-fused form.[2] As a valuable side benefit, we expected this endeavor to test our explanation for the origin

Scheme I

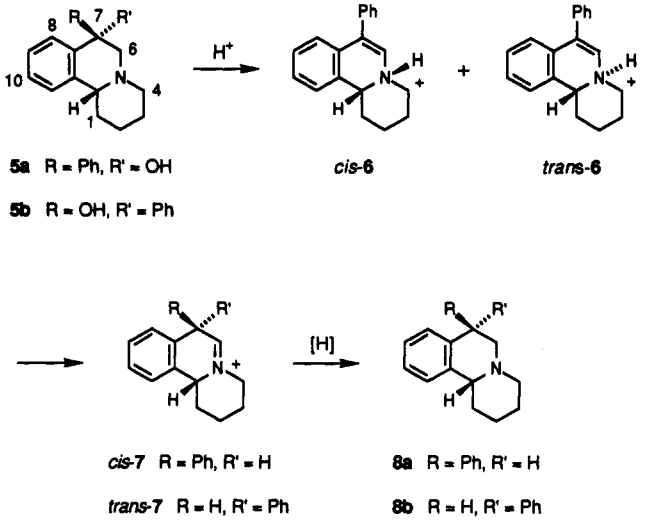


(1) (a) Maryanoff, B. E.; McComsey, D. F.; Mutter, M. S.; Sorgi, K. L.; Maryanoff, C. A. *Tetrahedron Lett.* **1988**, *29*, 5073. (b) Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 3567. (Please note that the stereochemical descriptors used in these papers are consistent with the descriptors used herein: "cis-fused" and "trans-fused" for the ring fusion in **3** and **6**, and "cis" and "trans" for the relative stereochemistry between the phenyl substituent and the angular proton in **2**, **4**, **7**, and **8**.)

(2) Maryanoff, B. E.; McComsey, D. F.; Inners, R. R.; Mutter, M. S.; Wooden, G. P.; Olofson, R. A. *J. Am. Chem. Soc.* **1989**, *111*, 2487.

0022-3263/92/1957-1190$03.00/0

Scheme II



of high stereoselectivity in the reductive deoxygenation. For the pyrroloisoquinoline series we proposed that an intrinsic, strong preference for the cis-fused enammonium salt, *cis*-**3**, over the trans-fused form, *trans*-**3**, is a key determinant in the stereoselection process.[1] The different ratio of enammonium salts (*trans*-**6**:*cis*-**6**) anticipated for the benzo[*a*]quinolizidine system[2] would yield a correspondingly different product ratio (*cis*-**7**:*trans*-**7** or **8a**:**8b**) and thereby corroborate this concept. We report herein the results of this study.

Results and Discussion

Rearrangement Reactions. Reduction of **5a**·HBr or **5b**·HBr with borane–THF in CF_3CO_2H produced a 68:32 mixture of amines **8a**:**8b** (cis/trans),[3] in a stereoconvergent fashion (Scheme II).[1] This ratio was a significant departure from the highly trans-biased 8:92 ratio seen with the corresponding pyrroloisoquinoline reaction,[1] supplying the first suggestion that the benzo[*a*]quinolizidine reaction would meet our needs. The 68:32 product ratio is consistent with our expectation, with control of stereoselectivity being dictated by the original diastereomeric composition of enammonium salts **6** (i.e., *trans*-**6**:*cis*-**6**). As such, we sought to verify this point by conducting the necessary NMR experiments.

Thus, **5a**·HBr was dissolved in CF_3CO_2D at 0 °C and the solution was monitored by 360-MHz ^1H NMR at 24 °C. The initial spectrum (t = 0.25 h) depicted a mixture of enammonium salts *trans*-**6** and *cis*-**6** in a 75:25 ratio. Spectra were collected at 30-min intervals to follow the course of rearrangement to iminium salts *cis*-**7** and *trans*-**7**, and these rate data are presented in Table I. A sample spectrum from the 1.75-h time point is presented in Figure 1. The ^1H NMR data indicate that the rearrangement of enammonium salts *trans*-**6** and *cis*-**6** (75:25) to iminium salts *cis*-**7** and *trans*-**7** (ca. 75:25) occurred with >98% stereospecificity. *Now, this principle is established within each diastereomeric set.* The half-life of this rearrangement ($t_{1/2}$) was approximately 1.83 h (110 min). Although the ratios of *trans*-**6** to *cis*-**6** did not change with time (ca. 75:25), the ratios of *cis*-**7** to *trans*-**7** changed very slowly, such that the ratio at 11.25 h was 67:33. We noted this previously and attributed it to *post-rearrangement isomerization* of the iminium diastereomers.[1] After 228 h (9 days) at room temperature, the ratio of *cis*-**7**/*trans*-**7** had shifted to 65:35. The ^1H NMR spectrum of **7** showed little proton incorporation (almost entirely D) at C_7 because of expected H/D exchange between the salts (**6** and/or **7**) and the deuterated solvent.[1b] Interestingly, we noticed (see Table I) that the hydrogen at C_6 was slowly replaced with deuterium from the medium to a significant degree; e.g., at 11.25 h, 39% of H had exchanged.[4] The issue of deuterium incorporation into C_6 will be addressed later. On reduction of the 228-h NMR sample with BH_3·THF, we obtained amines **8a** and **8b** in an identical 65:35 ratio, consistent with the final iminium salt ratio in situ.

Table I. Data for the Rearrangement of 6 to 7 (Bromide Salts) at 24 °C over Time

time[a] (h)	6:7[b]	% *trans*-6	% *cis*-6	% *cis*-7	% *trans*-7	*cis*-7: *trans*-7	% H at C_6 in 7[c]
0.25	90:10	67.0	23.0	7.7	2.3	75:25	100
0.75	71:29	52.5	18.5	20.7	8.0	73:27	95
1.25	57:43	41.7	15.3	31.3	11.6	72:28	90
1.75	47:53	34.6	12.7	37.9	14.8	70:30	82
2.25	40:60	28.9	10.6	43.0	17.5	70:30	80
2.75	33:67	24.4	8.7	47.5	19.4	68:32	76
3.25	28:72	20.4	7.5	51.2	20.9	71:29	76
3.75	23:77	16.8	6.3	53.8	23.1	70:30	72
4.25	19:81	14.0	5.4	55.6	25.0	70:30	68
4.75	16:84	12.0	4.0	57.1	26.9	68:32	69
5.25	14:86	10.0	4.0	60.2	25.8	69:31	67
5.75	12:88	8.4	3.6	60.7	27.3	68:32	65
6.75	8:92	5.2	2.8	63.5	28.5	69:31	65
7.75	5:95	*d*	*d*	65.5	29.5	69:31	62
11.25	0:100	*d*	*d*	67.0	33.0	67:33	61

[a] The best fit of the data was obtained with a lag time of 0.13 h. The time points shown here are actual experimental values (i.e., uncorrected). [b] The amounts of **6** and **7** were established by ^1H NMR integration. The quantitation of *trans*-**6** and *cis*-**6**, respectively, is based on the signals for H_{11b} (pair of dd at δ 4.90 and 4.60); for the first four half-lives the trans/cis ratio remained essentially constant at 3:1. The quantitation of *cis*-**7** and *trans*-**7**, respectively, is based on the signals for H_{11b} (pair of dd at δ 5.30 and 5.22), and H_{3e} (pair of dd at δ 2.72 and 2.83); the cis/trans ratios changed slightly over the course of rearrangement (0–11 h). [c] Integral of the total of H_6 in *cis*-**7** and *trans*-**7**. [d] Integrals were too small to measure or no starting material remained.

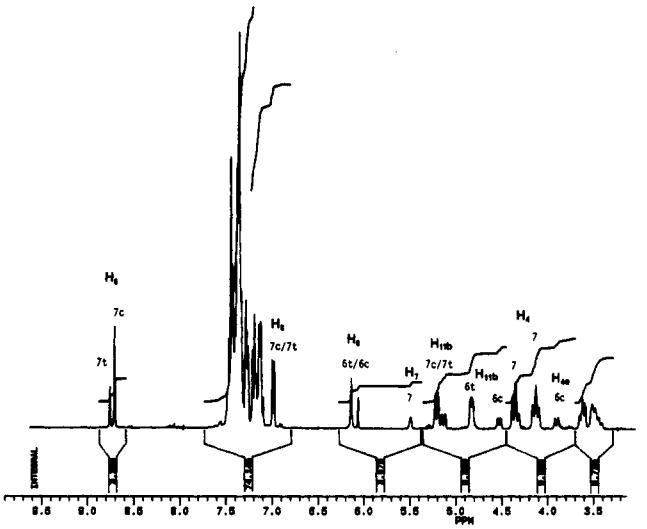
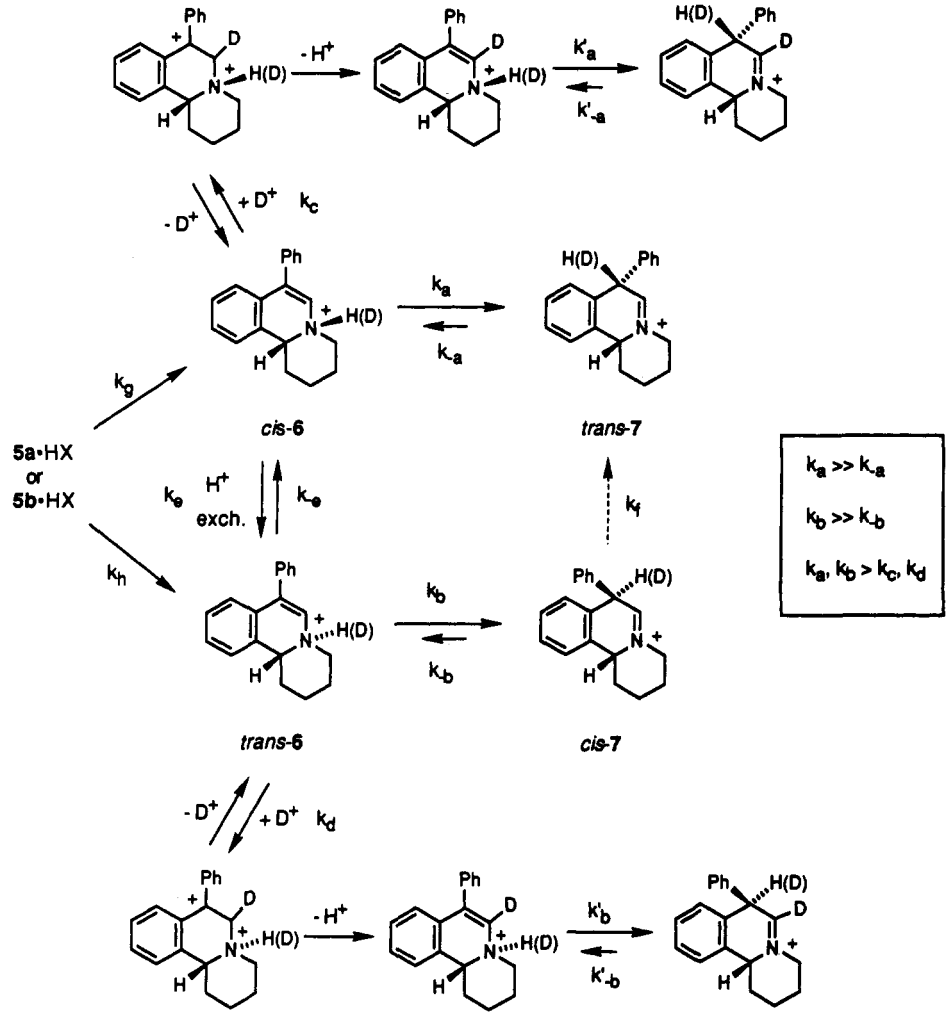


Figure 1. Section of a representative 360-MHz ^1H NMR spectrum for a time point in the reaction of **5a**·HBr with CF_3CO_2D (t = 1.75 h; 6:7 = 47:53; see Table I). Abbreviations for resonance assignments: 6c = *cis*-**6**, 6t = *trans*-**6**, 7c = *cis*-**7**, and 7t = *trans*-**7**.

(3) 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.

(4) In our previous study of **1a** and **1b** (HBr salts in CF_3CO_2D), we noted only a minor amount of deuterium incorporated at C_5 (5–20% depending on duration).[1b]

Scheme III



We attempted to fit the NMR rate data (Table I) to a kinetics model consisting of three equilibria between *cis*-**6**, *trans*-**6**, *cis*-**7**, and *trans*-**7** (Scheme III; k_a, k_{-a}, k_e, k_{-e}, k_b, k_{-b}). This showed that the reverse reaction of *trans*-**7** to *cis*-**6** (k_{-a}) was too small for detection even though k_{-b} was significant. The kinetic constants for the isomerization of **6** (k_e, k_{-e}) are so strongly correlated with each other and with the initial isomer ratio that they cannot be independently determined under these conditions. Consequently, a model of three first-order reactions (k_a, k_b, and k_f) was used, from which the enammonium–iminium rearrangement rates the were found to be equivalent for both diastereomeric pathways ($k_a = k_b = 0.38 \pm 0.02$ h^{-1}). The other constant, $k_f = 0.016 \pm 0.004$ h^{-1}, represents the net isomerization of *cis*-**7** to *trans*-**7**, undoubtedly via a route involving k_{-b}, k_{-e}, and k_a. The results from our computational treatment of the kinetic data are displayed in Figure 2 (see the Experimental Section for details).

A similar ^{1}H NMR experiment was performed on free base **5b** at 25 °C with data being collected at intervals of 1.35 min (over a 1.28-min period for each point). Since the half-life was very short ($t_{1/2}$ = ca. 8.3 min),[5] the accuracy of the data was deemed to be severely limited. Consequently, this reaction was repeated at 5 °C, furnishing a more useful half-life of 0.75 h (Table II).[6] We found that the initial ratio of *trans*-**6**:*cis*-**6** was 73:27, nearly the same as that for the HBr salt; this ratio was maintained over the first four half-lives of the rearrangement. In this case, relative to the HBr salt, the ratio of *cis*-**7**:*trans*-**7** was constant during the rearrangement and approximately the

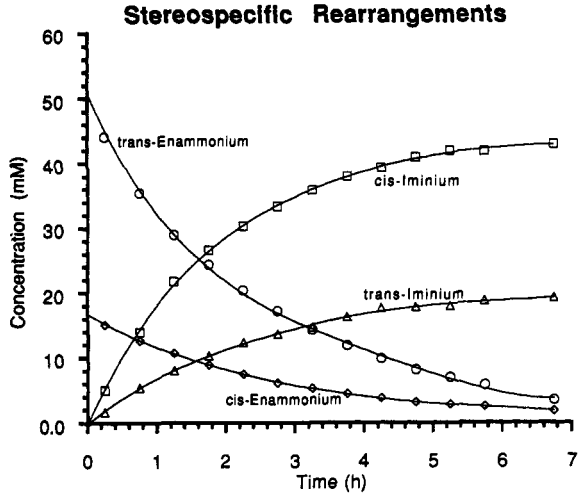


Figure 2. Experimental data and calculated curves for the rate study of the reaction of **5a**·HBr with CF_3CO_2D. Symbols are as follows: (○) *trans*-**6**, (◇) *cis*-**6**, (△) *trans*-**7**, (□) *cis*-**7**.

(5) Our previous study[1b] demonstrated that the enammonium–iminium rearrangement was subject to a significant anion effect: the bromide ion caused a 25-fold decrease in rate compared with the trifluoroacetate ion.

(6) Concerning Table II, see the paragraph at the end of this paper regarding supplementary material.

same as for **6** (ca. 72:28), reflecting little epimerization on the time scale of this faster reaction. Also, there was essentially no deuterium incorporation at C_6. To follow up on this, we allowed the NMR sample to stand at room temperature. At 190 h (ca. 8 days), we found (1) less than 5% deuterium incorporated into C_6 (compared to 47% with the HBr salt) and (2) an isomer ratio that now favored *trans*-**7** (*cis*-**7**:*trans*-**7** = 43:57). Reduction of this sample with BH_3·THF gave a 42:58 ratio of amines **8a** and **8b**, which had very little, if any, deuterium incorporated at C_6, as determined by ^1H and ^2H NMR. Thus, isomerization of *cis*-**7** trifluoroacetate salt occurred more rapidly than isomerization of *cis*-**7** bromide, which was negligible.[5] Deuterium introduction at C_6 of the iminium trifluoroacetate was much less than that for the iminium bromide.

The rate data for this reaction (Table II)[6] were analyzed with a similar set of first-order and pseudo-first-order steps, **5b** → *cis*-**6** → *trans*-**7** and **5b** → *trans*-**6** → *cis*-**7**, to furnish the following rate constants: $k_g = 0.84 \pm 0.03$, $k_a = 1.03 \pm 0.03$, $k_h = 2.11 \pm 0.07$, and $k_b = 1.08 \pm 0.02$ h^{-1}. Again, the reverse reactions could not be uniquely determined; however, in this case no measurable isomerization occurred during the rate study (i.e., $k_f = 0$).

A ^1H NMR experiment with **5b**·HBr in CF_3CO_2D at 23 °C behaved just like that involving **5a**·HBr and serves to illustrate the stereoconvergence that we mentioned for the pyrroloisoquinoline series.[1] After 144 h (6 days), we noted a 62:38 ratio of *cis*-**7** to *trans*-**7** and about 50% deuterium incorporated at C_6. At 21 days, the ratio changed to 47:53 and ca. 0.40 hydrogen remained at C_6 (ca. 60% D). The sample was then reduced with BH_3·THF to yield **8a** and **8b** in a ratio of 45:55. The ^1H NMR spectrum of the mixture showed that C_7 was completely deuterated as expected and C_6 was partially deuterated as indicated by less than 50% of the normal proton integrals for C_{6a} in both **8a** and **8b**. The ^2H NMR showed the C_7 deuterium at 4.42 and 4.01 ppm in a 43:57 ratio, while the C_{6a} deuteriums of **8b** and **8a** appeared at 2.90 and 2.60 ppm and integrated for ca. 0.33 and 0.31 D, respectively. Thus, deuterium was again incorporated at C_6 when the bromide anion was present.

H/D Exchange and Mechanistic Aspects. Enammonium salt *trans*-**6** rearranges to iminium salt *cis*-**7**, and enammonium salt *cis*-**6** rearranges to iminium salt *trans*-**7**, with very high stereoselectivity (>98%). This supplements the observation on the pyrroloisoquinoline system, where we were able to show high stereoselectivity only for the rearrangement of the major species, *cis*-**3** to *trans*-**4**, due to the strong predominance of that isomeric set.[1] The stereospecificity for this rearrangement process is remarkable, indeed, especially when one considers that there is a slow, underlying equilibrium that epimerizes the product iminium salts. This slow equilibrium presumably entails deprotonation (or dedeuteration) of the iminium salts, in a reverse reaction, to regenerate enammonium salts (Scheme III). This mixture of *cis*-**6** and *trans*-**6** would isomerize in favor of the thermodynamically more stable cis isomer, rearrange again, and so on to enhance the population of *trans*-**7**.

Our previous paper[1b] mentioned the propensity for intramolecular transfer of H (or D) from nitrogen to carbon amidst the rearrangement, although we could only establish a lower limit for this. In the present study, when **5a**·HBr was reduced with borane–THF in CF_3CO_2D, proton incorporation was evident at C_7 to the extent of 40–50%. Thus, once again the reaction manifests a *significant intramolecular component in the proton-transfer mechanism*. However, in the rearrangement experiment involving the HBr salt, monitored by ^1H NMR, the proton originally present on nitrogen was almost completely exchanged for D (>80%) of C_7 of **7** (vide supra). This contrasts with our study of the pyrroloisoquinoline system wherein the proton was still substantially present at C_6 (to the extent of ca. 40%) after 16 h. In the prior work, however, the rearrangement that we monitored was almost exclusively one involving a cis-fused enammonium ion going to a trans iminium ion. In the present case, both diastereomeric rearrangements are significant, with the major pathway actually being the trans-fused enammonium species going to the cis iminium species. Perhaps, the trans-fused enammonium salt *trans*-**6** undergoes relatively more rapid exchange of N–H with the medium, resulting in much greater deuterium incorporation.

There is significant incorporation of deuterium at C_6 (i.e., α to nitrogen) in the HBr case, but not in the free base (trifluoroacetate) case (Tables I and II).[6] This is a slow and steady exchange process, which probably entails addition of D^+ to the alkene unit of the enammonium salts to generate a transient carbocation that loses H^+ to give iminium salts labeled at C_6 with deuterium (Scheme III). This deuteration process, which imparts an additional complication to the rearrangement reaction although it does not interfere with the stereospecificity of the rearrangement, may or may not compete effectively, depending on relative rates. Deuterium incorporation is slow relative to rearrangement of the free base (k_c, $k_d \ll k_a$, k_b), but it has a rate comparable to that for rearrangement of the HBr salt. It is interesting that this side pathway appears to require the presence of a strong acid like HBr, even though this acid is only present at the level of 1 mol equiv. Since the olefin in an enammonium salt is expected to be very weakly basic, the requirement for a strong acid is not unreasonable. Indeed, trifluoroacetic acid is a weaker acid than HBr by almost 9 orders of magnitude on the basis of pK_a.[1b] The fact that equilibration of iminium salt diastereomers occurs with or without D incorporation at C_6 points to deprotonation (dedeuteration) at C_7 as a sufficient mechanism.

Conclusions

We have now studied reductive deoxygenations and enammonium–iminium rearrangements for both pyrrolo[2,1-*a*]isoquinoline[1] and benzo[*a*]quinolizidine systems. The stereoselectivity of our reductive deoxygenation process is governed by the ring-fusion preference at the stage of the enammonium salts. Subsequent 1,3 proton migration from nitrogen to carbon in the enammonium–iminium rearrangement occurs with high stereospecificity. We have now demonstrated that *this stereospecificity is associated with both diastereomeric rearrangement pathways*. Although related enammonium–iminium rearrangements had been reported[7] prior to our investigations, the stereochemical ramifications are just now becoming more fully appreciated.

Interestingly, significant deuterium incorporation at C6 was detected. This results from the addition of D^+ to the α carbon (C6) of the olefin in the enammonium species,

(7) (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. (c) Cook, A. G. In *Enamines*, 2nd ed.; Cook. A. G., Ed.; Marcel Dekker: New York, 1988; Chapter 1, p 1. (d) Paukstelis, J. V.; Cook, A. G. In *Enamines*, 2nd ed.; Cook. A. G., Ed.; Marcel Dekker: New York, 1988; Chapter 6, p 275. (e) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975. (f) Matsushita, H.; Tsujino, Y.; Noguchi, M.; Yoshikawa, S. *Chem. Lett.* **1976**, 1087; (g) *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1513. (h) Matsushita, H.; Tsujino, Y.; Noguchi, M.; Saburi, M.; Yoshikawa, S. *Ibid.* **1978**, *51*, 201. (i) Barthelemy, M.; Bessière, Y. *Tetrahedron* **1976**, *32*, 1665.

which constitutes an unusual example of electrophile attack *at an enamine α carbon*. This process requires the presence of a strong acid, such as HBr or DBr, and probably is accentuated by stabilization of the carbocation at C7 by the presence of the two aromatic rings.

Post-rearrangement isomerization of the iminium species intervened in rearrangement reactions that were allowed to stand for a prolonged time. However, this side process is generally not a problem in a synthetic sense, such as for diastereoselective reductive deoxygenation in the pyrroloisoquinoline series.[1] This isomerization turned out to be much faster with the trifluoroacetate anion than with the bromide anion.

Experimental Section

General Methods. Melting points are corrected. ^{1}H NMR spectra were recorded on a 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 rate studies followed the sum of deuterated and nondeuterated species. ^{2}H NMR spectra were obtained at 55.3 MHz on the Bruker AM-360WB. Chemical-ionization (methane) mass spectral data were recorded on a Finnigan 3300 spectrometer. TLC analyses were performed on Whatman 250-μm 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. HPLC separations were effected on a Waters Prep 500A instrument. Trifluoroacetic acid (99%), trifluoroacetic acid-*d*, and 1 M BH_3·THF were purchased from Aldrich Chemical Co. and used as received.

***cis*- and *trans*-1,3,4,6,7,11b-Hexahydro-7-hydroxy-7-phenyl-2*H*-benzo[*a*]quinolizin-6-one.** 2-Phenylpiperidine[8] (12.2 g, 0.076 mol) and *rac*-mandelic acid (11.5 g, 0.076 mol) were condensed[3] to give a crude mixture of amido alcohols, which were cyclized with polyphosphoric acid (170 g) to give a crude mixture of lactams (11.3 g). This product was purified by preparative HPLC (ethyl acetate/hexane (1:2)) to give the lactams as an ca. 50:50 mixture (GLC; CI-MS (CH_4): MH^+ = 278): ^{1}H NMR δ 1.50–2.72 (m, 8 aliph), 4.48 (d, J = 11.6 Hz, trans H_{11b}), 4.61 (d, J = 11.6 Hz, cis H_{11b}), 4.74 (s, trans H_7), 4.86 (s, cis H_7), 6.80–7.35 (m, arom). This mixture (1.92 g, 6.9 mmol) in DMSO (15 mL) with 40% NaOH (0.69 g, 6.9 mmol) was oxygenated in the usual manner[1b] to give a mixture of *cis*- and *trans*-1,3,4,6,7,11b-hexahydro-7-hydroxy-7-phenyl-2*H*-benzo[*a*]quinolizin-6-ones (CI-MS (CH_4): MH^+ = 294).

***cis*- and *trans*-1,3,4,6,7,11b-Hexahydro-7-hydroxy-7-phenyl-2*H*-benzo[*a*]quinolizine (5a and 5b).** Reduction of the mixture of *cis*- and *trans*-1,3,4,6,7,11b-hexahydro-7-hydroxy-7-phenyl-2*H*-benzo[*a*]quinolizin-6-ones (1.40 g, 4.8 mmol) with BH_3·THF supplied a crude mixture of amino alcohols **5a** and **5b**,[1b,3] which was dissolved in 2-propanol (6 mL) and treated with 48% HBr (0.81 g, 4.8 mmol). A colorless crystalline mixture of HBr salts of **5a** and **5b** (0.97 g) was obtained and then partitioned between methylene chloride and 2 N NaOH. The organic solution was dried (K_2CO_3) and evaporated in vacuo to an oil (0.74 g), which was separated by preparative HPLC (ethyl acetate/hexane (1:3)). Fractions containing the first eluting isomer, **5a**, were combined, evaporated to an oil, and converted to a HBr salt, affording **5a**·HBr (0.28 g): mp 216–216.5 °C (intumescence); CI-MS (CH_4) MH^+ = 280; IR ν_{max} 3312, 2929, 2657 cm^{-1}; ^{1}H NMR δ 1.70–2.90 (m, 7), 3.40 (dd, H_{6a}, J = 11.0, 12.5 Hz), 3.67 (m, H_{4e}), 3.74 (d, H_{6e}, J = 12.9 Hz), 4.26 (ddd, H_{11b}, J = 10.5, 10.3, 2.6 Hz), 6.06 (s, OH), 7.20–7.50 (m, 9, arom). Anal. Calcd for $C_{19}H_{21}NO$·HBr: C, 63.34; H, 6.15; N, 3.89. Found: C, 63.50; H, 6.49; N, 4.10. The HPLC fractions containing the trailing isomer, **5b**, were combined, evaporated to an oil, and converted to a HBr salt, affording **5b**·HBr (0.40 g): mp 197.5–199 °C (intumescence); CI-MS (CH_4) MH^+ = 280; IR ν_{max} 3341, 2944, 2600 cm^{-1}; ^{1}H NMR δ 1.65–2.35 (m, 6), 3.35 (m, H_{4e}), 3.38 (d, H_{6e}, J = 13.0 Hz), 3.63 (ddd, H_{4a}, J = 13.4, 13.4, 3.0 Hz), 3.92 (bd, H_{6e}, J = 12.9 Hz), 5.32 (s, OH), 7.00–7.50 (m, 9, arom). Anal. Calcd for $C_{19}H_{12}NO$·HBr: C, 63.34; H, 6.15; N, 3.89. Found: C, 63.36; H, 6.52; N, 3.90.

Reductive Deoxygenation of 5a·HBr. General Procedure. Amino alcohol salt **5a**·HBr (17.1 mg, 0.047 mmol) was dissolved in trifluoroacetic acid (1 mL) under argon at room temperature and stirred for 40–60 min. The solution was cooled to 5 °C with an ice bath and 1 M BH_3 in THF (0.25 mL) was added. The reaction was stirred at 5 °C for 60 min, quenched with water, stirred for 60 min at room temperature, and partitioned between 1 N NaOH and methylene chloride. The organic solution was washed once with water and once with brine, dried (K_2CO_3), and evaporated to give a mixture of **8a** and **8b** (12.1 mg, 98%) in a 68:32 ratio (GLC). This ratio was verified by ^{1}H NMR: δ 4.00 (m, 0.34, H_7 of **8b**), 4.37 (dd, 0.66, H_7 of **8a**), 6.72 (d, J = 7.7 Hz, 0.65, H_8 of **8a**), 6.88 (d, J = 7.6 Hz, 0.35, H_8 of **8b**).

Likewise, **5b**·HBr (18.0 mg, 0.050 mmol) was reduced to give a mixture of amines **8a** and **8b** (12.8 mg, 97%) in a 68:32 ratio (GLC), which was substantiated by ^{1}H NMR (69:31).

Reductive Deoxygenation of 5b·HBr in Trifluoroacetic Acid-*d*. Amino alcohol **5b**·HBr (20.5 mg, 0.057 mmol) was dissolved in trifluoroacetic acid-*d* (1 mL) and reduced following the general procedure to give a mixture of amines **8a** and **8b** (14.6 mg, 97%) in a 72:28 ratio (GLC). ^{1}H NMR showed ca. 50% proton incorporation at C_7: δ 4.03 (m, 0.15, **8b**), 4.37 (dd, 0.35, **8a**).

^{1}H NMR Study of 5a·HBr in Trifluoroacetic Acid-*d*. The amino alcohol **5a**·HBr (26.0 mg, 0.072 mmol) was dissolved in trifluoroacetic acid-*d* (1 mL) at 0 °C and transferred to an NMR tube that had been purged with argon. The probe temperature was maintained at 24 °C, and spectra were accumulated every 30 min (see Table I). Initial ^{1}H NMR (15 min after mixing) showed mostly **6** (trans/cis = 3:1): δ 1.80–2.50 (m, 6), 3.50–3.70 (m, 2, H_{4e}/H_{4a}), 4.60 (bd, 0.25, H_{11b} of *cis*-**6**), 4.90 (m, 0.75, H_{11b} of *trans*-**6**), 6.13 (s, 0.25, H_6 of *cis*-**6**), 6.20 (s, 0.75, H_6 of *trans*-**6**), 7.00–7.60 (m, 9, arom.). ^{1}H NMR at 11.25 h (rearrangement complete): δ 1.90–2.40 (m, 5), 2.73 (m, 0.67, H_{3e} of *cis*-**7**), 2.84 (m, 0.33, H_{3e} of *trans*-**7**), 4.20 (m, 1, H_{4a}), 4.42 (m, 1, H_{4e}), 5.20 (bd, 0.33, H11b of *trans*-**7**), 5.29 (bd, 0.67, H_{11b} of *cis*-**7**), 7.00–7.60 (m, 9, arom), 8.78 (s, 0.42, H_6 of *cis*-**7**), 8.83 (s, 0.18, H_6 of *trans*-**7**). After standing at room temperature for a total of 228 h, the ^{1}H NMR showed that the ratio of isomers had shifted slightly and that deuterium incorporation at C_6 approached 50%: δ 2.72 (bd, J = 13.8 Hz, 0.62, H_{3e} of *cis*-**7**), 2.83 (bd, J = 13.7 Hz, 0.38, H_{3e} of *trans*-**7**), 5.21 (bd, J = 11.6 Hz, 0.35, H_{11b} of *trans*-**7**), 5.28 (bd, J = 11.2 Hz, 0.65, H_{11b} of *cis*-**7**), 8.78 (s, 0.33, H_6 of *cis*-**7**), 8.84 (s, 0.18, H_6 of *trans*-**7**). The sample was cooled to 5 °C and treated with 1 M borane·THF to give **8a** and **8b** (18 mg, 95%) in a 65:35 (GLC) ratio: ^{1}H NMR showed a mixture of four amines: δ 1.40–2.40 (m, 8), 2.61 (d, J = 11.6 Hz, 0.41, H_{6a} of **8a**), 2.77 (bd, J = 11.2 Hz, 0.41, H_{4e} of **8b**), 2.87/2.90 (2 s, 0.62, H_{6a} of **8b**/H_{6e} of **8b**), 2.99 (d, J = 11.0 Hz, 0.65, H_{4e} of **8a**), 3.09 (d, 0.62, H_{6e} of **8a**), 3.30 (m, 1.0 H, H_{11b}), 6.79 (d, J = 7.6 Hz, H_8 of **8a**), 6.96 (d, J = 7.6 Hz, H_8 of **8b**), 7.00–7.30 (m, 8 arom). ^{2}H NMR showed only four deuteriums present: δ 2.62 (0.26 D) and 2.90 (0.18 D) for the C_{6a} deuteriums of partially deuterated **8a** and **8b**, respectively, and 4.02 (0.34 D)/4.43 (0.66 D) for the C_7 deuterium of **8b** and **8a**.

Likewise, **5b**·HBr (26.0 mg, 0.072 mmol) was treated in the same way and let stand at room temperature. The ^{1}H NMR of the iminium salts at 144 h: δ 1.8–2.40 (m, 5 H), 2.73 (bd, J = 13.2 Hz, 0.62, H_{3e} of *cis*-**7**), 2.83 (bd, J = 13.7 Hz, 0.38, H_{3e} of *trans*-**7**), 4.21 (dd, J = 12.3 Hz, 1, H_{4a}), 4.43 (dd, J = 13.5 Hz, 1, H_{4e}), 5.21 (bd, J = 12.0 Hz, 0.35, H_{11b} of *trans*-**7**), 5.28 (bd, J = 11.8 Hz, 0.65, H_{11b} of *cis*-**7**), 7.0–7.6 (m, 9, arom), 8.79 (s, 0.28, H_6 of *cis*-**7**), 8.84 (s, 0.19, H_6 of *trans*-**7**). At 21 days the NMR showed a 47:53 ratio of *cis*-**7**:*trans*-**7** (based on H_{3e}), and now the H_6 resonance amounted to only 0.38, signifying ca. 60% deuterium incorporation at C_6. This sample was reduced employing the general procedure above to give a 45:55 (GLC) mixture of amines **8a** and **8b**, which by NMR were deuterated at C_7 (<5% H) and partially deuterated at C_6. ^{1}H NMR showed a mixture of four amines: δ 1.40–2.40 (m, 8), 2.60 (d, J = 11.7 Hz, 0.23, H_{6a} of **8a**), 2.76 (bd, J = 11.3 Hz, 0.62, H_{4e} of **8b**), 2.87/2.90 (2 s, 0.77, H_{6a} of **8b**/H_{6e} of **8b**), 2.97 (d, J = 11.2 Hz, 0.46, H_{4e} of **8a**), 3.05 (d, 0.38, H_{6e} of **8a**), 3.26 (dd, J = 9.0, 13.1 Hz, 1, H_{11b}), 6.70–7.30 (m, 9 arom). ^{2}H NMR showed only four deuteriums present: δ 2.59 (0.31 D) and 2.90 (0.33 D) for the C_{6a} deuteriums of partially deuterated **8a** and **8b**, re-

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spectively, and 4.01 (0.57 D)/4.41 (0.43 D) for the C_7 deuterium of **8b** and **8a**.

^{1}H NMR Study of 5b in Trifluoroacetic Acid-*d*. Amino alcohol **5b** (24.0 mg, 0.086 mmol) was dissolved in trifluoroacetic acid-*d* (1 mL) at 0 °C and monitored by ^{1}H NMR at 5 °C every 5 min (delay between spectra of 77 s, see Table II).[6] At 2.82 h, rearrangement was complete and ^{1}H NMR showed little epimerization had occurred (*cis*-**7**:*trans*-**7** = 72:28) and no deuterium was incorporated at C_6: δ 1.80–2.40 (m, ca. 5), 2.79 (bd, J = 13.9 Hz, 0.72, H_{3e} of *cis*-**7**), 2.88 (bd, J = 13.7 Hz, 0.28, H_{3e} of *trans*-**7**), 4.21 (m, 1, H_{4a}), 4.39 (m, 1, H_{4e}), 5.21/5.30 (2 d, 1, J = ca. 11.5 Hz, H_{11b}), 7.05–7.60 (m, 9.6, arom), 8.70 (s, 0.72, H_6 of *cis*-**7**), 8.77 (s, 0.28, H_6 of *trans*-**7**). After 190 h at room temperature, ^{1}H NMR showed epimerization had occurred to give a 43:57 ratio of *cis*-**7**:*trans*-**7**: δ 2.75/2.84 (2 d, J = 13.9/13.7 Hz, 0.43 and 0.57 for H_{3e} of *cis*-**7** and *trans*-**7**, respectively), 8.66/8.73 (2 s, 0.41/0.55 for H_6 of *cis*-**7**/*trans*-**7**). The H_6 integral showed little if any deuterium had been incorporated at C_6. This sample was reduced in the usual way to give amines **8a** and **8b** (19.5 mg, 85%) in a 42:58 ratio (GLC). ^{1}H NMR of the mixture showed complete deuteration at C_7 and virtually no deuteration at C_6: δ 1.40–2.40 (m, 6), 2.60 (d, J = 11.5 Hz, 0.46, H_{6a} of **8a**), 2.76 (d, J = 11.4 Hz, 0.60, H_{4e} of **8b**), 2.90 (s, 1.2, H_{6e}/H_{6a} of **8b**), 2.98 (bd, J = 11.0 Hz, 0.40, H_{4e} of **8a**), 3.06 (d, J = 11.5 Hz, 0.40, H_{6e} of **8a**), 3.25 (m, 1, H_{11b} of **8a** and **8b**), 6.80–7.30 (m, arom). ^{2}H NMR (CD_2Cl_2) showed only two deuterium signals, at δ 3.93 and 4.25 (55:45 = **8b**:**8a**) for the fully deuterated C_7; there was no detectable deuterium at C_6.

Kinetics Methods. The NMR data were fitted with the NONLIN84 program (V02-A) of C. M. Metzler and D. L. Weiner, Statistical Consultants, Inc. (462 High St., Lexington, KY 40508). The integral form of the model was used to permit estimation of a "lag time" to adjust for any uncertainty in zero time (t_0) because of mixing, transfer to the NMR probe, and thermal equilibration. The first-order constant k_f, which corresponds to a composite of the other constants in the pathway from *cis*-**7** to *trans*-**7** (Scheme III), was used because of the inability to ascertain k_e and k_{-e} individually. A lag time of 0.13 ● 0.05 h was determined for the rearrangement of **6** to **7** (bromide data; Table I), such that 0.25 h was treated as though it were 0.38 h for the calculated fit. The data from 0.25 through 6.75 h (with all four species measured) was used for the computational analysis. The data for the rearrangement in trifluoroacetic acid-*d* (Table II)[6] resulted in an optimum fit for a lag of 0.24 ± 0.01 h, such that 0.10 h was treated as 0.34 h for the calculated fit. Calculated rate constants (described in the Results and Discussion) are presented with their 95% confidence intervals.

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Registry No. **5a**·HBr, 137965-20-9; **5b**·HBr, 137965-21-0; **6**, 137965-22-1; *cis*-**7**, 138008-42-1; *trans*-**7**, 138008-43-2; **8a**, 87519-75-3; **8b**, 87519-77-5; 2-phenylpiperidine, 3466-80-6; (±)-mandelic acid, 611-72-3; *cis*-1,3,4,6,7,11b-hexahydro-7-phenyl-2*H*-benzo[*a*]quinolizin-6-one, 137965-16-3; *trans*-1,3,4,6,7,11b-hexahydro-7-phenyl-2*H*-benzo[*a*]quinolizin-6-one, 137965-17-4; *cis*-1,3,4,6,7,11b-hexahydro-7-hydroxy-7-phenyl-2*H*-benzo[*a*]-quinolizin-6-one, 137965-18-5; *trans*-1,3,4,6,7,11b-hexahydro-7-hydroxy-7-phenyl-2*H*-benzo[*a*]quinolizin-6-one, 137965-19-6.

Supplementary Material Available: Table II, containing data for the rearrangement of **6** to **7** as trifluoroacetate salts (2 pages). Ordering information is given on any current masthead page.

Substituent Effects on ^{33}S Chemical Shifts and Nuclear Quadrupole Coupling Constants in 4-Substituted Benzenesulfonates

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Both ^{33}S chemical shifts and line widths in 4-$XC_6H_4SO_3Na$ (X = NO_2, $COCH_3$, Cl, F, H, CH_3, OH, NH_2, NMe_2) are strongly dependent on the electronic properties of substituents. The occurrence of a "reverse" chemical shift effect has been observed. The dual substituent parameter analysis of ^{33}S chemical shifts suggests that (i) inductive contribution predominates over the resonance one, (ii) resonance effects operate without direct conjugation between the aromatic ring and the sulfonate group, and (iii) variations of ^{33}S chemical shift seem to be attributable to $-SO_3^-$ d–p π-polarization. Variations of ^{33}S line widths can be primarily ascribed to a change in the nuclear quadrupole coupling constant values. The dual substituent parameter analysis of the nuclear quadrupole coupling constants seems to indicate that in 4-substituted benzenesulfonates substituent effects on the ^{33}S nuclear quadrupole coupling constants and chemical shifts have the same origin.

Knowledge of the dependence of ^{33}S NMR parameters on the electronic properties of substituents may be particularly useful to organic chemists since ^{33}S NMR spectroscopy could provide structural information not available from ^{13}C and ^{1}H NMR experiments.

Unfortunately, the low receptivity and the relatively large nuclear quadrupole moment often make ^{33}S signals undetectable. ^{33}S NMR can provide useful spectra only in molecules with symmetrical electronic distribution around the sulfur atom.[1] In practice, only sulfones and sulfonates[2,3] display ^{33}S resonance lines narrow enough to permit an accurate measurement of CS and LW values and

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