apply to triligostats have been used with great success in silicon chemistry.[7]

Chart I outlines the most quoted example of the Walden inversion cycle

$$(+)\text{-III} \xleftarrow{\text{I}} (-)\text{-I} \xrightarrow{\text{R}} (-)\text{-II} \xrightarrow{\text{R}} (-)\text{-III}$$

This three-reaction stereochemical cycle is antipodal and triligostatic. A different type of cycle that involves carbon was closed by Bernstein and Whitmore[26] and is illustrated in Chart XI. The cycle is large and is composed of many elegant interconversions such as a semipinacolic deamination[27] and conversion of a phenyl ring to a carboxyl group.[28] This multireaction cycle is podal and diligostatic and contains one I and one LM. Although the deaminative rearrangement is a simultaneous double ligand substitution,[15] the character of the cycle is not affected. The sequence of retention reactions effects a ligand metathesis which may be counted as an additional inversion and results in a podal cycle.

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(26) H. I. Bernstein and F. C. Whitmore, *J. Amer. Chem. Soc.*, **61**, 1324 (1939).

(27) A. McKenzie, R. Roger, and G. O. Wills, *J. Chem. Soc.*, 779 (1926).

(28) W. Leithe, *Ber.*, **64**, 2827 (1931).

Intrinsic and Torsional Diastereomers. The Optical Purity of (+)-(*S*)-Deoxyephedrine[1]

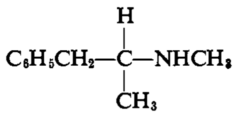
John Jacobus and Taylor B. Jones

Contribution from the Department of Chemistry, Clemson University,
Clemson, South Carolina 29631. Received January 6, 1970

Abstract: The optical purity of (+)-(*S*)-deoxyephedrine (**1**) has been determined by an nmr method. A combination of intrinsic and torsional diastereomerism, which precludes a reliable determination of the enantiomeric homogeneity of **1** at room temperature, leads to deceptively complex nmr spectra of the O-methylmandelamide of **1**. At sufficiently elevated temperatures only intrinsic diastereomerism is observed and the optical purity of **1** can be determined.

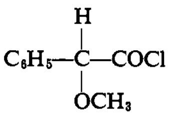
Both intrinsic[2] and torsional[3] diastereomerism[4] of amides have been reported; the nuclear magnetic resonance (nmr) consequences of both types of isomerism have been discussed.[2,3] In the determination of the optical purity of (+)-(*S*)-deoxyephedrine (**1**) by an nmr technique[2] *both* types of isomerism are encounted simultaneously, leading to deceptively complex nmr spectra at room temperature.

Thus, reaction of optically pure (*vide infra*) **1** with optically pure (*S*)-O-methylmandelyl chloride (**2**) afforded N-methyl-N-((*S*)-1-phenyl-2-propyl)-(*S*)-O-methylmandelamide (**3**), which exhibited the nmr spectrum depicted in Figure 1. Similarly, reaction of excess optically pure **1** with racemic **2** afforded an equimolar mixture of **3** and its intrinsic diastereomer **4**. The nmr spectrum of this mixture and an expanded scale spectrum of the C-methyl ($\text{HCC}H_3$) signals of both samples are depicted in Figures 2 and 3, respectively.



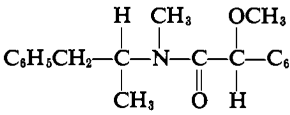
$C_6H_5CH_2\text{—}\overset{\text{H}}{\underset{\text{CH}_3}{\text{C}}}\text{—}NHCH_3$

1



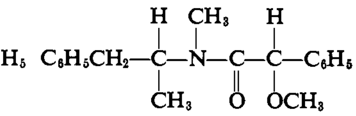
$C_6H_5\text{—}\overset{\text{H}}{\underset{\text{OCH}_3}{\text{C}}}\text{—}COCl$

2



$C_6H_5CH_2\text{—}\overset{\text{H}}{\underset{\text{CH}_3}{\text{C}}}\text{—}\overset{\text{CH}_3}{\text{N}}\text{—}\underset{\overset{\|}{\text{O}}}{\text{C}}\text{—}\overset{\text{OCH}_3}{\underset{\text{H}}{\text{C}}}\text{—}C_6H_5$

3



$C_6H_5CH_2\text{—}\overset{\text{H}}{\underset{\text{CH}_3}{\text{C}}}\text{—}\overset{\text{CH}_3}{\text{N}}\text{—}\underset{\overset{\|}{\text{O}}}{\text{C}}\text{—}\overset{\text{H}}{\underset{\text{OCH}_3}{\text{C}}}\text{—}C_6H_5$

4

Discussion

In general, the determination of the optical purity of a compound A by the nmr technique[2] requires that it be converted to a mixture of diastereomers ($\text{AB}/\text{A}\overline{\text{B}}$) with a second chiral substance ($\text{B}/\overline{\text{B}}$). The nmr spectrum of the resultant mixture of diastereomers generally exhibits "resonance doubling" since the corresponding groups in the compounds in the mixture are diastereotopic by external comparison and, consequently, are anisochronous in the nmr spectrum.[6] If a pure enantiomer A is allowed to react with a second optically pure substance B, only a single diastereomer (AB) is produced and the absence of resonance doubling is indicative of the enantiomeric homogeneity of both A and B.[7] This technique has recently been discussed[2] and has received wide application.[2,8]

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(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) (a) M. Raban and K. Mislow, *Top. Stereochem.*, **2**, 199 (1967); (b) J. Jacobus, M. Raban, and K. Mislow, *J. Org. Chem.*, **33**, 1142 (1968); (c) J. Jacobus and M. Raban, *J. Chem. Educ.*, **46**, 351 (1969).

(3) (a) J. A. Pople, W. J. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 366 ff; (b) Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban, *J. Amer. Chem. Soc.*, **89**, 4910 (1967), and references cited therein.

(4) The extension of the term "diastereomer" to include all stereoisomers which are not enantiomers has been advocated by Mislow.[5]

(5) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, N. Y., 1966, p 50 ff.

(6) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1966).

(7) This statement is correct if and only if resonance doubling has been demonstrated for an optically impure sample of either A or B.

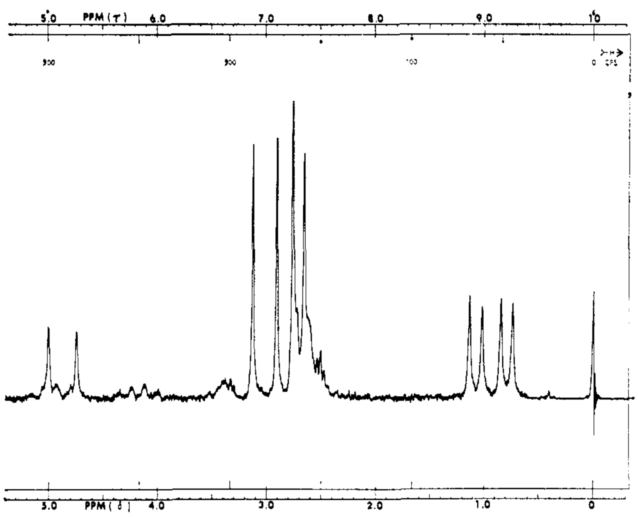


Figure 1. The 60-MHz pmr spectrum of **3**: solvent, DMSO-d_6 containing 1% TMS, temperature 37°.

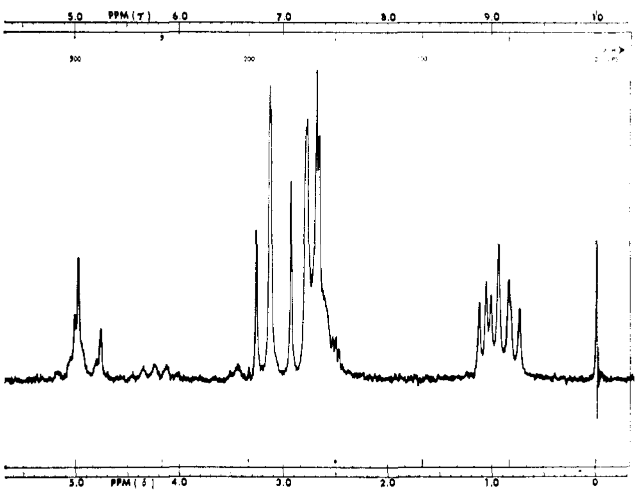


Figure 2. The 60-MHz spectrum of the mixture of **3** and **4**: solvent, DMSO-d_6 containing 1% TMS, temperature 37°.

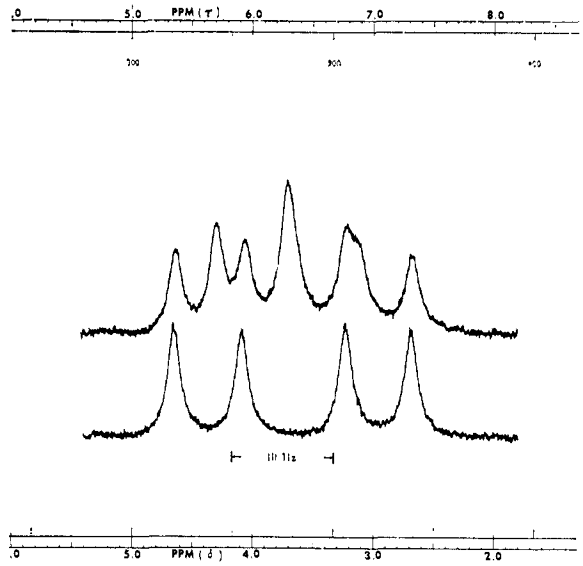
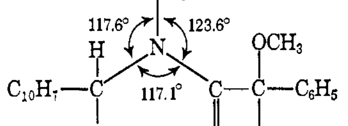


Figure 3. The 60-MHz pmr spectrum of the C-methyl region of (a) **3** and (b) **3** and **4**; temperature 37°.

The resonance doubling observed for **3** alone (Figure 1) signalizes that the *s-cis-* and *s-trans*-torsional diastereomers (**5** and **6**, respectively),[9] resulting from hindered rotation about the carbonyl–nitrogen bond, are present, and the intensities of the doubled resonances indicate that the *s-cis* and *s-trans* forms are present in approximately equal amounts. The additional resonance doubling displayed by a mixture of **3** and **4** (Figure 2) relative to that of **3** alone (Figure 1) indicates that both intrinsic and torsional diastereomers are being observed.

It is well known that torsional diastereomers of amides can be detected by nmr spectroscopy and that appreciable barriers (10–20 kcal mol^{-1}) to their interconversion may exist.[3a] An alternative explanation as to the observed resonance doubling, slow inversion at nitrogen and rapid rotation about the amide bond, has been judged unlikely.[3b] Barriers to pyramidal inversion at nitrogen in amides generally have activation energies of only *ca.* 1–2 kcal mol^{-1}.[11] Further, at least in the solid phase, a structurally related mandelamide, N-methyl-N-(1-(1-naphthyl)ethyl)-O-methylmandelamide (**7**), is essentially planar about nitrogen, the sum of the angles about the nitrogen atom being 358.3°.[12]

At 140° in DMSO-d_6 interconversion of the *s-cis* (**5**) and *s-tran* (**6**) diastereomers is rapid and the original spectra have collapsed to the spectra depicted in Figures 4 and 5. At this temperature the methine (HC-OCH$_3$), methoxyl (HCOCH_3), and benzyl (C$_6$H$_5$CH_2–) signals in the mixture of **3** and **4** are still perceptibly anisochronous, while the C-methyl signals are accidently coincident. Inspection of either the methine region (τ 5.0) or the methoxyl region (τ 6.8) for **3** alone indicates that both the acid and the amine are optically pure since signals attributable to **4** are absent. As judged by the coalesence of the methyl and methoxyl signals, the barrier to interconversion (ΔG_c*) of the torsional diastereomers is *ca.* 17 kcal mol^{-1} in DMSO-d_6.[13] The failure to observe simultaneous intrinsic and



7

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[8] (a) M. Raban and K. Mislow, *Tetrahedron Lett.*, 4249 (1965); 3961 (1966); (b) M. Axelrod, P. Bickart, J. Jacobus, M. M. Green, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4835 (1968); (c) R. A. Lewis, O. Korpiun, and K. Mislow, *ibid.*, **90**, 4847 (1968); (d) J. Jacobus and K. Mislow, *Chem. Commun.*, 253 (1968); (e) J. P. Casey, R. A. Lewis, and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 2789 (1969).

[9] For convenience, N-methyl and carbonyl oxygen *cis* about the amide bond are termed *s-cis*. Attempts to assign configuration about the carbonyl–nitrogen bond by utilization of the aromatic solvent induced shift (ASIS) technique[3b,10] failed since the N-methyl resonances in both diastereomers are shifted upfield in changing solvent from carbon tetrachloride to benzene.

[10] (a) P. Laszlo and D. H. Williams, *J. Amer. Chem. Soc.*, **88**, 2799 (1966); (b) R. M. Moriarty, *J. Org. Chem.*, **28**, 1296 (1963); (c) R. M. Moriarty and J. M. Kliegman, *Tetrahedron Lett.*, 891 (1966).

[11] (a) C. C. Costain and J. M. Dowling, *J. Chem. Phys.*, **32**, 158 (1960); (b) P. G. Lister and J. K. Tyler, *Chem. Commun.*, 152 (1966).

[12] M. G. B. Drew, *Acta, Crystallogr.*, **B25**, 1320 (1969).

[13] Methyl ($\Delta\nu$ 17.5 Hz, slow exchange, T_c 63°), methoxyl ($\Delta\nu$ 13.5 Hz, slow exchange, T_c 52°); rate constants at coalescence calculated according to methods presented in ref 3a, Chapter 10; ΔG_c* calculated from the Eyring equation with $K = \frac{1}{2}$.

Table I. Nmr Spectral Data of 3 and 4[a]

Compd	Solvent	Temp,[c] °C	Resonance[b] H—CCH_3	NCH_3	OCH_3	HCO
3[d]	$CDCl_3$	37	9.14, d, 6.5	7.12, s	6.85, s	5.38, s
			8.87, d, 6.5	7.38, s	6.83, s	5.11, s
4[e]	$CDCl_3$	37	9.23, d, 6.5	7.36, s	6.70, s	5.12, s
			8.92, d, 6.5	7.36, s	6.63, s	5.12, s
3[d]	DMSO-d_6	37	9.20, d, 6.5	7.25, s	7.12, s	5.27, s
			8.93, d, 6.5	7.35, s	6.86, s	5.02, s
4[e]	DMSO-d_6	37	9.11, d, 6.5	7.32, s	6.86, s	5.05, s
			8.88, d, 6.5	7.25, s	6.75, s	5.05, s
3	DMSO-d_6	140	9.00, d, 6.5	7.28, s	6.83, s	5.10, s
4[e]	DMSO-d_6	140	9.00, d, 6.5	7.28, s	6.77, s	5.05, s

[a] Spectra at 60 MHz as *ca.* 10% solutions with internal TMS. [b] Data reported as chemical shift (τ), multiplicity (d = doublet, s = singlet), and coupling constant (*J* in hertz). [c] Determined by temperature chemical shift dependence of ethylene glycol. [d] *s-cis* and *s-trans* isomers not determined (see ref 9). [e] Determined from mixtures of **3** plus **4** by consideration of lines present in spectrum of **3** alone.

torsional diastereomerism in the nmr determination of the optical purity of amines as amides previously[2] is attributable to a thermodynamic restriction to rotation about the amide bond which favors one of the two possible isomers to the virtual exclusion of the other.[3b,14]

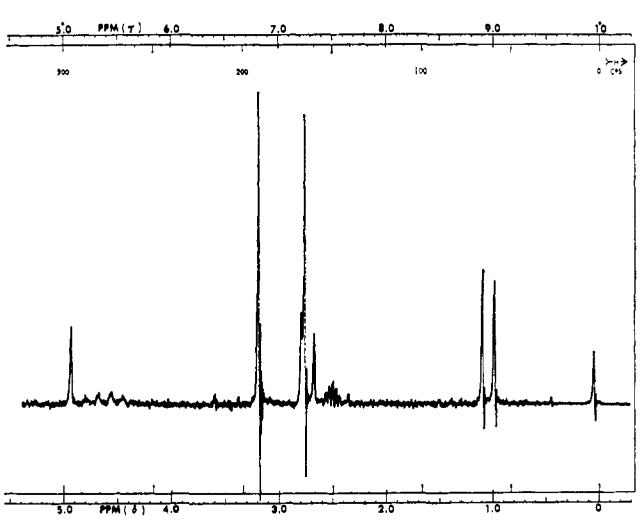

Figure 4. The 60-MHz pmr spectrum of **3**: solvent, DMSO-d_6 containing 1% TMS, temperature 140°.

(+)-(*S*)-**1** has itself recently been employed in the determination of the optical purity of chlorofluoroacetic acid.[15,16] However, at that time, uncertainty[17] about the specific rotation of the optically pure amine precluded any plausible conclusions concerning the optical purity of the material in question.

Experimental Section[18]

(+)-(*S*)-**O-Methylmandelic acid** was obtained by a previously reported procedure;[19] mp 65–67°, $[\alpha]^{23}D$ +163.5° (*c* 1.566, water) (lit.[2b] mp 65–67°, $[\alpha]^{23}D$ −161.9° (*c* 1.66, water)).

(+)-(*S*)-**Deoxyephedrine** (bp 68° at 0.3 mm (kugelrohr); $[\alpha]^{26}D$ +2.24 ± 0.02° (neat, *l* 1)) was obtained from (+)-(*S*)-deoxyephedrine hydrochloride (mp 175.5–177°, $[\alpha]^{26}D$ +17.9 ± 0.1° (*c* 1.086, water)) (lit.[17b] $[\alpha]^{20}D$ +17.91° (*c* 2.7643, water)) by ether extraction of the free amine which has been liberated from the hydrochloride with aqueous potassium hydroxide. The ether extract was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under reduced pressure prior to the final distillation.

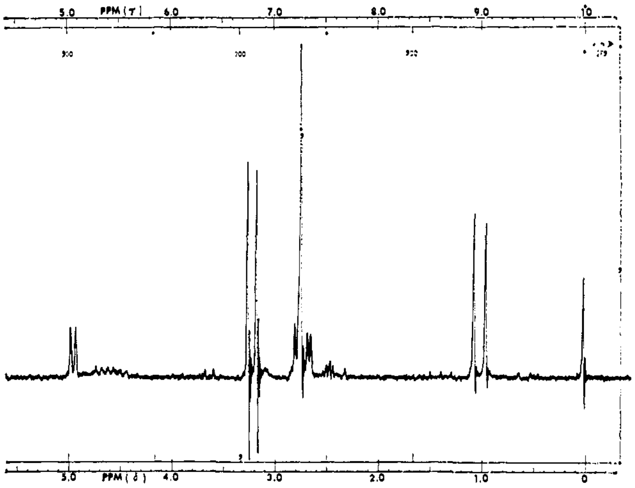

Figure 5. The 60-MHz pmr spectrum of the mixture of **3** and **4**: solvent, DMSO-d_6 containing 1% TMS, temperature 140°.

O-Methylmandelamide 3 was prepared in an analogous manner to that described[2b] for the amides of α-phenylethylamine; **3** exhibited bp 165° at 0.45 mm (kugelrohr), mp 97.5–99°, $[\alpha]^{23}D$ +54.7° (*c* 1.30, ethanol). Nmr data are presented in Table I.

Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.75; H, 7.75; N, 4.72. Found: C, 76.60; H, 7.85; N, 4.93.

O-Methylmandelamides 3 and 4 were prepared from racemic O-methylmandelyl chloride and (+)-**1** in an analogous manner to that previously described for the preparation of the amides of α-phenylethylamine.[2b] This mixture exhibited bp 170° at 0.5 mm (kugelrohr) and partially solidified on standing, $[\alpha]^{24}D$ +45.9° (*c* 3.10, ethanol). Nmr data are collected in Table I.

Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.75; H, 7.75; N, 4.72. Found: C, 76.87; H, 7.64; N, 4.62.

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[14] T. H. Sidall, III, *J. Org. Chem.*, **31**, 3719 (1966).

[15] Absolute configuration of (+)-**1**: (a) P. Karrer and K. Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951); (b) W. Leithe, *Chem. Ber.*, **65**, 660 (1932).

[16] G. Bellucci, G. Berti, A. Borraccini, and F. Macchia, *Tetrahedron*, **25**, 2979 (1969).

[17] Various values for the specific rotation of the amine and the amine hydrochloride have been reported; see, for example, (a) E. Schmidt, *Arch. Pharm.* (Weinheim), **252**, 136 (1914); (b) H. Emde, *Helv. Chim. Acta*, **12**, 365 (1929); (c) K. Freudenberg and F. Nikolai, *Justus Liebigs Ann. Chem.*, **510**, 223 (1934); (d) S. Senoh, *J. Pharm. Soc. Jap.*, **72**, 1098 (1952); (e) O. Cervinka and L. Dub, *Collect. Czech. Chem. Commun.*, **32**, 2295 (1967); (f) J. C. Craig, R. P. K. Chan, and S. K. Roy, *Tetrahedron*, **23**, 3573 (1967).

[18] Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Nmr spectra were measured on a Varian A-60A spectrometer and refer to approximately 10% solutions with tetramethylsilane as internal standard. Rotations were measured on a Rudolph Model 70 polarimeter.

[19] D. G. Neilson and D. A. V. Peters, *J. Chem. Soc.*, 1519 (1962).