Use of Liquid Crystal Induced Circular Dichroism for Absolute Configurational Assignments of β-Amino Alcohols

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Dissolution of small quantities of chiral β-amino alcohols in liquid crystalline *N*-(*p*-methoxybenzylidene)-*p*-*n*-butylaniline (MBBA) results in induced rotations due to the formation of a cholesteric (chiral) liquid crystal phase. The induced rotations are several orders of magnitude larger than those observed for β-amino alcohols in isotropic solutions, and the signs of these rotations can be correlated with the absolute configurations of the chiral amino alcohols when standard conformational analysis arguments and the preference of elongated molecules to align with MBBA are considered.

A new technique has recently been developed that is useful for correlating the absolute configurations of chiral β-amino alcohols. The method uses liquid crystal induced circular dichroism (LCICD) and offers the advantage of many orders of magnitude greater sensitivity than "normal" optical activity measurements. For the limited number of examples cited here, it also appears more reliable than classical optical activity measurements.

The most common method for absolute configurational assignments of chiral compounds has historically been correlation with the rotation sign of plane-polarized light at 589 nm (α_D). One of the disadvantages of this method is its relative insensitivity. When the substituents on the chiral center have a high degree of electronic symmetry, gram quantities of material may be needed for a determination of the rotation sign. This is clearly out of line with the modern analytical techniques used for the elucidation of chemical structure, where IR, NMR, MS, and UV allow structural assignments using submilligram quantities of material.

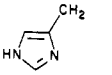
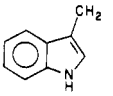
Application of single-wavelength rotation measurements is also complicated by the fact that the signs of α_D often are not correlated with absolute configurations of compounds in a homologous series. Examples of this difficulty can be observed for β-amino alcohols as shown in column 4 of Table I. The sign change from methyl to ethyl to propyl for β-substituted-β-amino alcohols is particularly indicative of the complications that may arise in polarimetric determinations of absolute configurations.

More reliable results can be obtained with circular dichroism (CD) or optical rotatory dispersion (ORD) measurements, which also are superior to polarimetry with respect to sensitivity.[1,2] When applied to relatively rigid compounds such a cyclic ketones, reliable configurational correlations can be made with the sign of the Cotton effect. However, when the chromophore whose Cotton effect is to be related to the absolute configuration is in an inaccessible region of the electronic spectrum, the sign of the Cotton effect must be inferred from the plain curve. This is also unreliable in many instances.

Configurational assignments using NMR in conjuction with chiral shift reagents has gained in popularity in recent years. Fourier transform ^1H NMR methods alleviate the sensitivity problem, allowing configurational assignments to be made by using submilligram quantities of unknown. In most cases, however, both enantiomers of the compounds are needed for comparison of relative shifts. Additionally, sharp, well-resolved resonances from substituents in the vicinity of the chiral center are required, so that they experience the greatest stereochemically dependent shift perturbation by the chiral NMR reagent. Predictable interactions such as conformational preferences or chelate formation are also desirable to minimize uncertainty due to rotational perturbations. These difficulties necessarily limit the number of classes of compounds to which NMR techniques can be applied.

The liquid crystal technique described here was shown to be very useful in configurational assignments for chiral alcohols.[3,4] Dissolution of the chiral alcohol in a nematic liquid crystal such as *N*-(*p*-methoxybenzylidene)-*p*-*n*-butylaniline (MBBA) results in the formation of a cholesteric,

Table I. Liquid Crystal Induced Optical Activity for Chiral β-Amino Alcohols

compd	R	enantmr	sign of $[\alpha]_D$ (in EtOH)	sign of LCICD[a] (1% in MBBA)
1a	CH_3	*S*	+	−
1b	CH_3CH_2	*S*[b]	−	+
1c	$CH_3CH_2CH_2$	*S*	+	+
1d	$(CH_3)_2CH$	*S*	+	+
1e	$CH_3(CH_2)_3$	*S*	+	+
1f	$(CH_3)_2CHCH_2$	*S*	+	−
1g	$CH_3CH_2(CH_3)CH$	*S*	+	+
1h	$CH_3SCH_2CH_2$	*S*	−	+
1i	$CH_3CH_2SCH_2CH_2$	*S*[c]	−	+
1j	$PhCH_2SCH_2$	*R*[d]	−	+
1k	Ph	*S*[c]	+	+
1l	$C_6H_5CH_2$	*S*	−	+
1m	*p*-$HOC_6H_4CH_2$	*S*	−	+
1n	*p*-$CH_3OC_6H_4CH_2$	*S*	−	+
1o	*p*-$PhCH_2OC_6H_4CH_2$	*S*	−	+
1q		*S*	−	+
		*S*	−	+
1r	PhCH(OH)	1*R*,2*R*[e]	−	+

[a] Determined from the sign of the Cotton effect in the CD spectrum of the MBBA chromophore between 380 and 400 nm. [b] Both enantiomers were studied, giving opposite signs. [c] *R* enantiomer was actually studied, giving the opposite sign. [d] Derived from the L-amino acid. [e] 1*S*,2*S* enantiomer actually studied, derived from the D-amino acid.

(1) Crabbe, P. "ORD and CD in Chemistry and Biochemistry"; Academic Press: New York, 1972.
(2) Kagan, H. B. "Stereochemistry Fundamentals and Methods"; Georg Thieme; Stuttgart, West Germany, 1977; Vol 2.
(3) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1980**, *45*, 1379.
(4) Gottarelli, G.; Samori, B.; Marzochi, S.; Stremmenos, C. *Tetrahedron Lett.*, **1975**, 1981.

0022-3263/83/1948-2141$01.50/0

and therefore chiral, mesophase due to asymmetric interactions between the liquid crystal solvent and the chiral solute.[5] In the case of chiral alcohol solutes, (*S*)-1-phenylethanol, for example, was found to induce a right-handed helical arrangement in liquid-crystal solvent. In the chiral matrix, chromophores exhibit optical activity regardless of whether or not they are on the chiral molecule. For the MBBA solutions described, the sense of the helix can be determined by observation of the amplified optical activity resulting from the conjugated imine chromophore of the solvent (380–400 nm) with positive and negative Cotton effects corresponding to right- and left-handed helices, respectively. Very intense CD/ORD bands result from 10 to 20 μm films of 0.05–1% solutions of chiral solutes in MBBA. This optical activity is referred to as liquid crystal induced circular dichroism (LCICD) and has been used to correlate the configurations of the previously mentioned alcohols, oxaziridines,[3] oxiranes,[3] and more recently, α-substituted benzylamines,[6] where it has been particularly reliable.

In light of the success with chiral amines, studies with chiral β-amino alcohols were undertaken. These compounds are easily prepared with known configuration from chiral α-amino acids.

Result and Discussion

The β-amino alcohols reported here were synthesized by direct reduction of the corresponding α-amino acids or their esters. The signs of the LCICD and of the rotation at 589 nm for these compounds are presented in Table I. The relative disposition of substituents are identical for all entries, and any change in *R* or *S* designation results from artifacts due to priority of substituents in the Cahn, Ingold, Prelog system of nomenclature (e.g., **1j** and **1r**).

Before any discussion of the LCICD, the results of the more classical methods should be evaluated. Some correlations can be observed for the α_D signs of ethanolic solutions (Table I, column 4). Within the aliphatic series (**1a–g**) a positive rotation is consistently observed with the exception of **1b** where the substituent is ethyl. The thioethers (**1h, 1i, 1j**) exhibit a consistent negative rotation. While the α_D sign inversion for **1j** might be predicted from consideration of substituent polarizabilities,[7] the inversion of **1h** or **1i** is not as easily anticipated. Similarly, the sign obtained by substituting an aryl ring for an aliphatic group might be predicted, but interposition of a methylene between the aryl ring and the chiral center usually produces rotational data analogous to the aliphatic compound. This is not observed when the rotational data for entries **1l–q** are compared with those for **1a–g**. In this series the signs of the plain ORD curves, which can be inferred from rotational data at several wavelengths (see Experimental Section), are in complete agreement with the signs of α_D.

On the Cary 60 ORD-CD instrument, the lower detection limit is ca 5 mg when rotation data is obtained in isotropic solution. By comparison, consider the LCICD data shown in the last column of Table I. Reliable LCICD measurements can be obtained with 1–10 μg of actual sample. The LCICD data presented in Table I were obtained with 15–25-μm films of 1% solutions and required approximately 5 μg of chiral solute for the measurement. The sensitivity of the technique is indicated by the fact that these samples exhibited ellipticities typically greater than 2° (see Experimental Section).

Table II. Liquid Crystal Induced Optical Activity of *N*-*p*-Methoxybenzilidene Derivatives, 2

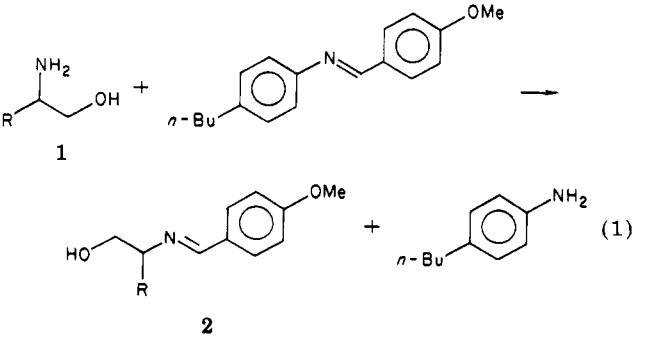
compd	R	enantmr	sign of $[\alpha]_D$ (in EtOH)	sign of LCICD (1% in MBBA)
2a	CH_3	*S*	+	−
2b	CH_2CH_3	*S*	+	+
2d	$CH(CH_3)_2$	*S*	−	+
2f	$CH_2CH(CH_3)_2$	*S*	−	−
2k	C_6H_5	*S*[a]	−	+

[a] *R* enantiomer actually studied, giving the opposite rotational sign.

Measurements were obtained with MBBA and MBBA/EBBA (*N*-(*p*-ethoxybenzylidene)-*p*-*n*-butylaniline) mixtures as solvent with identical results. The latter mixture offers advantages over pure MBBA. Its liquid crystalline temperature range is much greater, and a larger amount of solute can be dissolved while still maintaining liquid crystalline behavior at room temperature. Mixtures of MBBA and EBBA are liquid crystalline over a temperature range of approximately 0–70 °C, depending on the relative concentrations of the two solvents and the amount of solute. MBBA itself has a liquid crystal range of 21–46 °C, while EBBA is liquid crystalline between 35 and 79 °C. Pure MBBA remains liquid crystalline at solute concentration up to ca. 1.5%, but MBBA/EBBA mixtures can be used with solute concentrations of 5% or higher, depending upon the nature of the solute. This can be advantageous for solute–solvent systems in which interactions are very weak or in cases where the ambient sample compartment temperature of the instrument is high.

A good correlation exists between the absolute configuration at the chiral center of the amino alcohol and the LCICD sign, regardless of the nature of the R substituent. In fact only two exceptions, entries **1a** and **1f**, are found in the data. While no explanation for the deviation of **1f** can be offered at the present time, **1a** is the member with the smallest R substituent in the series, and its behavior can be explained (see below).

It was found during research with chiral benzylamines that a facile transamination reaction occurred upon dissolution of the amine in the liquid crystal.[6] The same reaction was expected for β-amino alcohols as shown by eq 1, so that the actual species giving rise to the helix



formation would be the *p*-methoxybenzylidene derivative, **2**, rather than the β-amino alcohol itself.

A number of *p*-methoxybenzylidene derivatives were prepared and characterized with results presented in Table II. It can be seen that although the sign of α_D has changed in most cases, the sign of the LCICD remained identical upon derivatization of the amino alcohol. In addition, Korte and Schrader recently reported infrared LCICD studies of compounds **2a** and **2b**.[8] It is possible to relate

(5) Stegemeyer, H.; Mainusch, K. J.; Steigner, E. *Chem. Phys. Lett.* **1970**, *6*, 5.
(6) Rinaldi, P. L.; Naidu, M. S. R.; Conaway, W. E. *J. Org. Chem.* **1982**, *47*, 3987.
(7) Brewster, J. H. *Top. Stereochem.* **1967**, *2*, *1*.

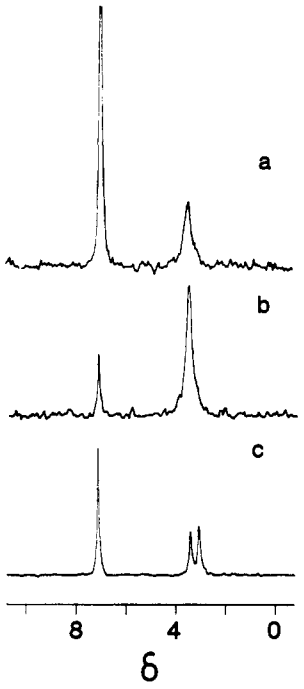


Figure 1. 30.7-MHz ^2H NMR spectra of deuterated samples in $CHCl_3$ (with 1% $CDCl_3$) obtained with proton decoupling: (a) 5% 2-amino-1,1-dideuterio-4-methyl-1-pentanol in MBBA was heated to 50 °C for 5 min, then dissolved in chloroform, and the spectrum recorded; (b) authentic *N*-(*p*-methoxybenzylidene)-2-amino-1,1-dideuterio-4-methyl-1-pentanol; and (c) authentic 2-amino-1,1-dideuterio-4-methyl-1-pentanol.

infrared LCICD measurements to those obtained in the ultraviolet region.[9] In both cases their infrared LCICD studies confirmed the helix senses inferred for these compounds from the UV–vis LCICD.

To verify that **2** was indeed the species giving rise to the observed LCICD, a deuterated sample of alcohol **1f** was dissolved in MBBA and the ^2H NMR spectrum of this sample was compared to that of its authentic *p*-methoxybenzylidene derivative. The results in Figure 1 indicate that the *p*-methoxybenzylidene is in fact obtained in essentially quantitative yield upon dissolution of the amino alcohol in MBBA.

While this reaction might at first appear to be an annoying complication, the formation of **2** simplifies the prediction of solute–solvent interactions that might give rise to the LCICD effect observed for these systems. The formation of a derivative with a more elongated liquid crystal like shape results in a more predictable molecular orientation and possibly in larger twisting powers (with a concomitant increase in the magnitude of the LCICD). It is expected that the phenyl ring will intercalate between the phenyl rings of the solvent molecules and that a hydrogen-bonding interaction between the hydroxyl hydrogen and imine nitrogen will exist. Adjacent solvent molecules will then skew to avoid interaction with the R substituent. Hydrogen bonding can be either intra- or intermolecular in nature. Several reasonable models for solute orientation can be predicted as shown in Figures 2 and 3. When large R substituents are involved, the interactions described by Figure 2 are most probable. Those in Figure 3 are insignificant since this involves projection of a large group perpendicular to the long axis of the solute, a very unfavorable conformation in the presence of long, orienting,

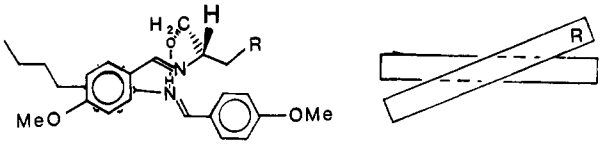


Figure 2. Normal model for the interaction of MBBA with the *N*-*p*-methoxybenzylidene derivatives of amino alcohols. The preferred conformation in liquid crystal solution will orient the R substituent such that an elongated molecule will align with its director axis approximately parallel to the MBBA. Intermolecular hydrogen bonding will cause the solute to skew relative to the MBBA solvent, resulting in the formation of a segment of a right-handed helix, when the absolute configuration is as shown.

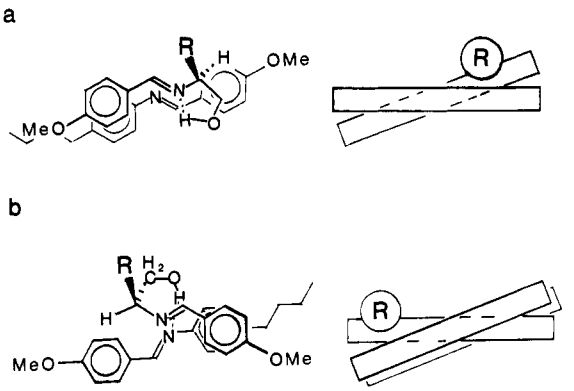


Figure 3. Other possible models for the interaction of MBBA with *N*-*p*-methoxybenzylidene derivatives of amino alcohols. These conformations will only be populated to a significant degree when the R substituent of the amino alcohol is small (e.g., methyl), since they result in projection of the substituent perpendicular to the long axis of the solvent, a very unfavorable orientation in nematic liquid crystals. The intramolecular hydrogen-bonded conformer (a) forms a relatively flat molecule with the R and H substituents directed above and below the plane of the solute, respectively. Interaction of the MBBA solvent with the R group above the plane is more severe than the corresponding interaction with H, below the plane. The result is skewing to form a segment of a left-handed helix, illustrated schemically at the right. A second model consisting of intermolecular hydrogen bonding can be envisaged (b). Although hydrogen bonding will cause a skewing of the solute relative to the MBBA below the plane of the solute, this is largely cancelled by a compensating interaction of MBBA with the R substituent above the plane of the solute as illustrated schematically at the right. This model is not expected to contribute significantly to the net LCICD observed.

liquid crystal solvent molelcules. However, the orientations described by Figure 3 may be significantly populated when the R substituent is small (e.g., CH_3 in **2a**).

With use of the model described by Figure 2, the LCICD signs of all the amino alcohols except **1a** and **1f** are predicted; L-amino acid derived amino alcohols will orient to form right-handed helices, resulting in a positive LCICD band between 380 and 400 nm. The LCICD sign inversion for **1a** is explained by the significant population of conformers described in Figure 3. The skew sense for the orientation in Figure 3a is left handed, causing a negative LCICD. However, the prediction of the net skew sense from the model in Figure 3b is zero, resulting in little or no contribution to the observed LCICD.

From examination of space-filling models, it is expected that the conformer described in Figure 3a will have a larger twisting ability than that described in Figure 2. Therefore, the LCICD signs might not reflect the skew sense induced by the major conformer populated. This might cause complications, since qualitative judgements must be made regarding the relative amounts of left- and right-handed skew-inducing conformers and the relative importance of the conformers in contributing to the net LCICD sign.

(8) Korte, E. H.; Schrader, B. *Adv. Infrared Raman Spectrosc.* **1981**, *8*, 226.
(9) Dudley, R. J.; Mason, S. F.; Peacock, R. D. *J. Chem. Soc., Faraday, Trans. 2*, **1975**, 997.

However, for the amino alcohols studied, the only exception for which the models in Figure 3 appear to be reasonable is the case with the smallest substituent, methyl. Therefore, no judgment is necessary; only the skew sense for **1a** (**2a**) is predicted by these models. Any larger substituent will necessitate the use of the models in Figure 2.

We currently have no rationalization for the exception of compound **1f** (**2f**). An explanation for this anomaly must await results from NMR studies currently being performed to determine the orientations of these solutes in liquid crystals.

Conclusion

LCICD is a useful chirality amplification technique that increases the detection limit by several orders of magnitude over the more classical techniques of optical activity measurement in isotropic solution. Additionally, for the β-amino alcohols studied, absolute configurational correlations using LCICD data are obtained more directly. The right- or left-handed cholesteric mesophase can be related to positive or negative LCICD effect in the region of 400 nm. From the interaction models for β-amino alcohols' *N*-(*p*-methoxybenzylidene) derivatives described in Figures 2 and 3, it is possible to relate the helix sense to the unknown's absolute configuration. While the use of CD is described here, in principle, ORD or single-wavelength polarimetric methods can also be used to obtain the sign of the LCICD. These measurements are less reliable, however, due to the magnitude of the rotations involved, particularly in the case of single-wavelength rotational measurements.[6] Although the technique can be extended to the determination of optical purity,[8] the sensitivity of LCICD magnitude to temperature and film thickness, as well as impurities present in the solute and solvent, make such measurements difficult at this time.

Experimental Section

Optical rotations were measured on a Perkin-Elmer Model 141 automatic polarimeter. CD and ORD spectra were obtained on a Cary Model 60 ORD instrument with a CD accessory. NMR spectra were recorded on Varian A-60, EM-360, and XL-200 instruments, and IR spectra were recorded on a Beckman IR8A spectrophotometer.

Compounds **1a**, **1b**, **1h**, **1k**, and **1r** were purchased from Aldrich Chemical Co. and used without further purification. Optical rotations for the compounds described are provided in Table III.

Preparation of β-Amino Alcohols. Method A: Typically 3–5 g of amino acid were suspended in 30–50 mL of dry diethyl ether or tetrahydrofuran and added dropwise to a stirred suspension of $LiAlH_4$ (6.8 equiv/mol of amino acid) in 50–70 mL of the same solvent under a nitrogen atmosphere. After the addition was complete, the reaction mixture was heated at reflux for 3 h and cooled to room temperature. Unreacted $LiAlH_4$ was quenched with a minimum of water, typically 10 equiv, and with 0.23 equiv of NaOH (15% aqueous solution). The mixture was stirred for 0.5 h and filtered with trituration of the filter cake. The solvent was removed under vacuum, and the residue was distilled or recrystallized from a suitable solvent. Yields were in the range of 70–85%.

Method B:[10] Two to three grams of amino acid in approximately 50 mL of dry THF were placed in a flame-dried one-neck flask and sealed with a septum cap. After a nitrogen purge, an equimolar amount of $BF_3{\cdot}Et_2O$ was added dropwise at room temperature with stirring. A 1:1 molar ratio of 0.98 M $BH_3{\cdot}THF$

Table III. Properties of Chiral β-Amino Alcohols 1a–q

	$[\alpha]^{20}$ [a], deg							literature		
compd	589	578	546	436	365	bp, °C (mm)	method of synthesis	$[\alpha]_{589}^{max}$ [b], deg	bp, °C (mm)	ref [d]
1a	19.3	20.1	22.6	36.3	52.1			22.0 (*c* 6.5)	84 (23)	*4*, IV, 1615
1b	−7.8	−8.1	−9.0	−14.7	−21.7			−9.8 (neat)	80 (11)	*4*, III, 771
1c	7.3	7.4	8.6	13.8	20.0	91–93 (11)	C		194–195 (760)	*4*, III, 794
1d	14.4	15.0	16.9	27.1	39.1	105–115 (30)	B	15.6 (*c* 7.85)	88 (11)	*4*, III, 805
1e	3.9	3.9	4.3	6.9	9.9	65–70 (0.7)	C		111–113 (21)	*4*, III, 809
1f	2.7	2.7	3.1	5.3	*c*	108–109 (11)	A	4.15 (*c* 11)	100–105 (10)	*4*, IV, 1797
1g	4.1	4.1	4.5	5.8	4.9	111–115 (20)	B	3.6 (*c* 1.776)	87–89 (10)	11
1h	−11.9	−12.3	−13.8	−22.2	−27.3			−14.1 (neat)	115–120 (12)	*4*, IV, 1879
1i	6.8	7.1	8.0	13.3	19.6	102–105 (1)	B			
1j	−2.5	−2.6	−3.0	−5.3	*c*	(mp)	C			
1k	−26.5	−27.6	−31.3	−51.7	*c*	72–74 (mp)	B	−25.4 (*c* 9, MeOH)	78–79 (mp)	*13*, III, 1681
1l	−24.0	−25.2	−29.0	−41.8	*c*	77–80 (mp)	B	−24.4 (*c* 3)	91–93 (mp)	*13*, III, 1757
1m [e]	−7.4	−7.7	−8.4	−10.4	*c*	93–94 (mp)		−26.1 (*c* 4)	94 (mp)	*12*, III, 2263
1n	−11.2	−12.5	−14.4	−27.7	*c*	96–97 (mp)	C			
1o	−10.1	−10.0	−11.1	−20.9	*c*	96–97 (mp)	C			
1p	−1.6	−1.8	−2.0	−3.8	−6.8			−3.7 (*c* 10, H_2O)	198–199 (mp dec)	*25*, 3/4, 3329
1q	[g]							−18.7 (*c* 5.4)	155–165 (0–0035)	22, 3/4, 5691
1r	20.6	21.4	24.5	43.7	71.5			16.9 (*c* 15, H_2O)	115–117 (mp)	12

[a] 10% (w/w) ethanolic solutions (*c* 8.7) unless otherwise specified. [b] Ethanolic solutions unless otherwise specified. [c] Optical density too large to measure optical activity. [d] Beilstein Handbuch der Organische Chemie (volume, part, page), unless otherwise noted. [e] *c* 2.4, ethanol. [f] Measured as the dihydrochloride salt. [g] Rotational data not obtained.

(10) Anhoury, M. L.; Aricks, M.; Crooy, P.; DeNeys, R.; Eliaers, J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 191.
(11) Seki, H.; et al. *Chem. Pharm. Bull*, **1965**, *13*, 995.
(12) Newman, P. "Optical Resolution Procedures for Chemical Compounds"; Optical Resolutions Information Center: Manhattan College, Riverdale, N.Y., 1978; Vol. 1, p 148.

complex was added, and the mixture was allowed to stir for approximately 12 h under a nitrogen atmosphere. The mixture was acidified with 10% aqueous H_2SO_4, made basic with 10% aqueous $NaHCO_3$, and extracted with diethyl ether. The ether layer was dried over anhydrous K_2CO_3, and the solvent was removed under vacuum. The residue was distilled or recrystallized. Yields were in the range of 50–60%.

Method C: A suspension of 2–3 of amino acid in 20–25 mL of absolute ethanol was treated with anhydrous HCl until the amino acid dissolved. The solution was heated at reflux for 1 h, and the ethanol was then removed. The residue was suspended in CH_2Cl_2, treated with anhydrous NH_3, and filtered. The filter cake was suspended in CH_2Cl_2 and treated as above two more times combining filtrates. The combined filtrates were evaporated under vacuum, and the residue was distilled or recystallized to yield the ethyl ester of the amino acid, which was reduced as in method A with overall yields of 60–80% based on starting amino acid.

L-**Norvalinol (1c)** was prepared by method C and isolated as a colorless liquid: bp 91–93 °C (11 mm); ^{1}H NMR ($CDCl_3$) δ 3.0–3.8 (m, 2 H, CH_2OH), 2.6–3.0 (m, 1 H, $CHNH_2$), 2.1 (s, 3 H, OH, NH_2), 1.1–1.6 (m, 4 H, CH_2CH_2), 0.94 (t, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 66.03, 52.24, 35.77, 18.96, 13.82; IR (neat) 3550, 3300, 1590, 1460, 1370, 1140, 1050, 940, 890, 830, 745 cm^{-1}.

L-**Norleucinol (1e)** was prepared by method C and isolated as colorless liquid: bp 65–70 °C (0.7 mm); ^{1}H NMR ($CDCl_3$) δ 3.0–3.8 (m, 2 H, CH_2OH), 2.4–3.0 (m, 1 H, $CHNH_2$), 2.1 (s, 3 H, NH_2, OH) 0.9–1.6 (m, 6 H, $CH_3CH_2CH_2CH_2$), 0.92 (t, 3 H, CH_3); IR (neat) 3350, 2950, 2900, 1600, 1475, 1400, 1130, 1070 cm^{-1}.

D-**Ethioninol (1i)** was prepared by method B and isolated as a colorless liquid: bp 102–105 °C (1 mm); ^{1}H NMR ($CDCl_3$) δ 3.8–3.0 (m, 2 H, CH_2OH), 2.85 (m, 1 H, $CHNH_2$), 2.3–2.8 (m, 4 H, CH_2SCH_2), 2.5 (s, 3 H, NH_2, OH), 1.9–1.4 (m, 2 H, CH_2CHNH_2), 1.3 (t, J = 7.5, 3 H, CH_3CH_2S); ^{13}C NMR ($CDCl_3$) δ 65.95, 51.71, 33.27, 28.10, 26.65, 14.47; IR (neat) 3350, 2825, 1620, 1470, 1390, 1280, 1065, 980, 870 cm^{-1}.

***S*-Benzyl-L-cysteinol (1j)** was prepared by method C and purified by molecular distillation: ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 5 H, C_6H_5), 3.48 and 3.34 (s, 2 H, $PhCH_2S$), 3.46 (**ABX**, J_{AB} = 11, J_{AX} = 4, J_{BX} = 7, 2 H, CH_2OH), 3.02–2.84 (m, 1 H, $CHNH_2$), 2.58 (s, 3 H, OH, NH_2) 2.52 and 2.32 (**ABX**, J_{AB} = 12.5, J_{AX} = 4.5, J_{BX} = 8.5, 2 H, $PhCH_2SCH_2$); IR (neat) 3350, 2925, 1600, 1500, 1460, 1050, 750 cm^{-1}.

***O*-Methyl-L-tyrosinol (1n)** was prepared by method C. Recsytallization from ethyl acetate/hexane provided a white solid: mp 96–97 °C; ^{1}H NMR ($CDCl_3$) δ 7.1 and 6.8 (AA'BB', 4 H, $C_6H_4OCH_3$), 3.78 (s, 3 H, OCH_3), 3.2–3.8 (m, 2 H, CH_2OH), 2.9–3.2 (m, 1 H, $CHNH_2$), 2.1–2.8 (m, 2 H, $ArCH_2CH$), 2.0 (s, 3 H, NH_2 and OH); IR (Nujol) 3200, 2950, 2850, 1625, 1475, 1395, 1250, 1185, 1125, 1065, 1030, 970, 955, 905, 810, 755 cm^{-1}.

***O*-Benzyl-L-tyrosinol (1o)** was obtained by method C as a beige solid from ethyl acetate/hexane: mp 95–97 °C; ^{1}H NMR ($CDCl_3$) δ 7.3 (s, 5 H, C_6H_5CH), 7.2 and 6.9 (AA'BB', 4 H, $C_6H_4OCH_2Ph$), 4.9 (s, 2 H, $PhCH_2O$), 2.7–3.8 (m, 3 H, $CH(NH_2)CH_2O$), 2.5 (m, 2 H, $ArCH_2CH$), 1.8 (s, 3 H, NH_2, OH); IR (Nujol) 3200, 1625, 1540, 1320, 1260, 1195, 1030, 1005, 995, 960, 855, 810, 790, 750, 705 cm^{-1}.

General Procedure for the Preparation of *p*-Methoxybenzylidene Derivatives. Equimolar amts. of β-amino alcohol and *p*-*n*-butylaniline were dissolved in methylene chloride and allowed to stand at room temperature over $MgSO_4$ for approximately 12 h. The solution was filtered, the solvent was removed under vacuum, and the residue was distilled or recrystallized.

***(S)*-*N*-(*p*-Methoxybenzylidene)-2-amino-1-propanol (2a)** was isolated as white solid from hexane: mp 83–83.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.2 (s, 1 H, HC=N), 7.6 and 6.9 (AA'BB', 4 H, $C_6H_4OCH_3$) 3.8 (s 3 H, OCH_3), 3.75–3.2 (m, 3 H, CH_2OH, CHN=C), 2.55 (s br, 1 H, OH), 1.2 (d, J = 6, 3 H, CH_3CHN=C); ^{13}C NMR ($CDCl_3$) δ 161.46, 160.67, 129.69, 128.64, 113.67, 67.33, 67.17, 55.13, 18.22; IR (Nujol) 3275, 1660, 1590, 1550, 1535, 1325, 1270, 1180, 1065, 1035, 915, 895, 845, 815 cm^{-1}; $[\alpha]^{20}_{\lambda}$ (*c* 8.7, EtOH) $+43.7_{589}$, $+45.7_{578}$, $+52.8_{546}$, $+101.7_{436}$.

***(S)*-*N*-(*p*-Methoxybenzylidene)-2-amino-1-butanol (2b)** was isolated as a white oil: bp 141–143 °C (1.4 mm); ^{1}H NMR ($CDCl_3$) δ 8.0 (s, 1 H, HC=N), 7.6 and 6.9 (AA'BB', 4 H, $C_6H_4OCH_3$), 3.8 (s, 3 H, OCH_3), 3.75–3.65 (m, 2 H, CH_2OH), 3.4–2.9 (m, 1 H, CHN=C), 2.7 (s 1 H, OH), 1.8–1.3 (m, 2 H, CH_2CH_3), 0.8 (t, J = 7, 3 H, CH_2CH_3); IR (neat) 3400, 2950, 2850, 1660, 1640, 1600, 1540, 1480, 1320, 1270, 1180, 1065, 1040, 910, 840, 790, 770 cm^{-1}; $[\alpha]^{20}_{\lambda}$ (*c* 8.7, EtOH) $+17.1_{589}$, $+18.0_{578}$, $+21.2_{546}$, $+45.4_{436}$.

***(S)*-*N*-(*p*-Methoxybenzylidene)-2-amino-3-methyl-1-butanol (2d)** was isolated as a white viscous liquid: bp 132–133 °C (0.45 mm); ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 1 H, HC=N), 7.6 and 6.9 (AA'BB', 4 H, $C_6H_4OCH_3$), 3.78 (s, 3 H, OCH_3), 3.75–3.65 (m, 2 H, CH_2OH), 3.30 (m, 1 H, CHN=C), 2.4 (s, 1 H, OH), 1.89 (septet, J = 6.5, 1 H, $(CH_3)_2CH$), 0.97 and 0.85 (2d, J = 6.5, 6 H, $(CH_3)_2OH$); ^{13}C NMR ($CDCl_3$) δ 159.7, 159.4, 130.4, 127.5, 114.3, 84.0, 64.0, 55.5, 31.5, 18.8, 18.5; IR (neat) 3450, 2990, 2900, 2850, 1675, 1640, 1600, 1540, 1490, 1440, 1320, 1270, 1185, 1120, 1040, 910, 840, 770 cm^{-1}; $[\alpha]^{20}_{\lambda}$ (*c* 8.7, EtOH) -42.3_{589}, -44.6_{578}, -52.6_{546}, -115.6_{436}.

***(S)*-*N*-(*p*-Methoxybenzylidene)-2-amino-4-methyl-1-pentanol (2f)** was isolated as a yellow viscous liquid: bp 135–137 °C (0.5 mm); ^{1}H NMR ($CDCl_3$) δ 8.18 (s, 1 H HC=N), 7.6 and 6.9 (AA'BB', 4 H, $C_6H_4OCH_3$), 4.02 (s, 3 H, OCH_3), 3.8–4.0 (m, 2 H, CH_2OH), 3.64 (m, 1 H, CHN=C) 2.03 (s, 1 H, OH), 0.9–1.3 (m, 3 H, $(CH_3)_2CHCH_2$), 0.85 and 0.90 (2d, 6 H, $(CH_3)_2CHCH_2$); ^{13}C NMR δ 161.4, 161.1, 129.8, 128.8, 113.7, 70.8, 66.2, 55.1, 40.8, 24.2, 23.4, 21.5; IR (neat) 3400, 2990, 2900, 1660, 1640, 1600, 1540, 1490, 1440, 1320, 1260, 1180, 1070, 1050, 910, 840, 770 cm^{-1}; $[\alpha]^{20}_{\lambda}$ (*c* 8.7, EtOH) -61.8_{589}, -65.2_{578}, -76.3_{546}, -158.3_{436}.

***(R)*-*N*-(*p*-Methoxybenzylidene)-2-amino-2-phenylethanol (2k)** was isolated as white needles from hexane: mp 92–92.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.2 (s, 1 H, HC=N), 7.6 and 6.9 (AA'BB', 4 H, $C_6H_4OCH_3$), 7.3 (s, 5 H, C_6H_5CHN=C), 4.5 (m, 1 H, CHN=C), 4.1–3.8 (m 5 H, CH_2OH and OCH_3), 2.6 (s, br, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 162.26, 161.79, 140.90, 130.09, 128.70, 128.53, 128.46, 127.28, 113.86, 76.35, 67.69, 55.31; IR (Nujol) 3250, 1670, 1640, 1540, 1320, 1280, 1185, 1095, 1080, 1055, 1030, 980, 910, 830, 780, 755, 700 cm^{-1}; $[\alpha]^{20}_{\lambda}$ (*c* 8.7, EtOH) $+71.3_{589}$, $+75.4_{578}$, $+89.8_{546}$, $+202.4_{436}$.

Deuterated Material. Leucinol-d_2 was prepared by reduction with $LiAlD_4$ as described in method A and was isolated as a white liquid: bp 101–102 °C (11 mm); ^{1}H NMR ($CDCl_3$) δ 2.9 (t, J = 6.5, 1 H, $CHNH_2$), 2.1 (s, 3 H, OH, NH_2), 1.7 (septet J = 6.5, 1 H, $(CH_3)_2CH$), 1.2 (t, J = 6.5, 2 H, CH_2CHNH_2), 0.95 (d, J = 6.5, 3 H, CH_3), 0.88 (d, J = 6.5, 3 H, CH_3); IR (neat) 3300, 2950, 2200, 2100, 1600, 1480, 1400, 1390, 1125, 1100, 1000, 840, 770 cm^{-1}.

***N*-(*p*-Methoxybenzylidene)-2-amino-4-methyl-1-pentanol-d_2** was isolated as a yellow oil and used without purification: ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1 H, HC=N), 7.77 and 6.97 (AA'BB', 4 H, $C_6H_4OCH_3$), 3.85 (s, 3H, OCH_3), 3.4 (m, 1 H, CHN=C), 1.90 (s, br, 1 H, OH), 0.9–1.3 (m, 3 H, $(CH_3)_2CHCH_2$), 0.85 and 0.90 (2d, 6 H, $(CH_3)_2CH$); IR (neat) 3400, 2990, 2900, 2225, 2120, 1710, 1670, 1640, 1610, 1540, 1320, 1270, 1180, 1040, 990, 840, 765 cm^{-1}.

LCICD Measurement. Samples were prepared by adding 2.5–10 mg of chiral solute to 1 g of MBBA. The mixture was warmed to ca. 50 °C, at which point an isotropic liquid formed, and then was allowed to cool to room temperature. One drop (ca. 5 mg) of solution was placed between two quartz plates with a 15-μm silver spacer and mounted on a brass block. Care was taken not to mechanically twist the plates. A minimum of two measurements were performed on different sample preparations of each solution, and the CD signs were reliably reproduced in all cases, usually with an off-scale reading on the least sensitive setting of the instrument. The magnitudes of those readings that remained on scale could not be reproduced reliably due to variations in temperature and sample thickness.

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Registry No. **1a**, 2749-11-3; (*S*)-**1b**, 5856-62-2; *p*-*n*-butylaniline, 104-13-2; **1c**, 22724-81-8; **1d**, 2026-48-4; **1e**, 80696-29-3; **1f**,

7533-40-6; **1g**, 24629-25-2; **1h**, 2899-37-8; **1i**, 85803-42-5; **1j**, 85803-43-6; **1k**, 56613-80-0; **1l**, 3182-95-4; **1m**, 5034-68-4; **1n**, 20989-19-9; **1o**, 85803-44-7; **1p**, 4836-52-6; **1q**, 2899-29-8; **1r**, 46032-98-8; **2a**, 67928-34-1; **2b**, 67928-33-0; **2d**, 85879-93-2; **2f**, 85803-45-8; **2k**, 85803-46-9; leucinol-d_2, 76427-93-5; *N*-(*p*-methoxybenzylidene)-2-amino-4-methyl-1-pentanol-d_2, 85803-47-0; *N*-(*p*-methoxybenzylidene)-*p*-*n*-butylaniline, 26227-73-6; L-norvaline, 6600-40-4; L-norleucine, 327-57-1; D-ethionine, 535-32-0; *S*-benzyl-L-cysteine, 3054-01-1; *O*-methyl-L-tyrosine, 6230-11-1; *O*-benzyl-L-tyrosine, 16652-64-5; (*R*)-**1b**, 5856-63-3.

Comments on the Application of the Gassman–Fentiman Tool of Increasing Electron Demand to the Carbon-13 Nuclear Magnetic Resonance Spectroscopic Study of Substituted 2-Aryl-2-norbornyl Cations[1a]

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This paper is a rebuttal to the recent paper by Brown and co-workers entitled "Anomalous Carbon-13 Chemical Shifts with Increasing Electron Demand in the 2-Aryl-2-norbornyl Cations and Related Systems. Evidence That These Anomalous Shifts Are Not Diagnostic for the Onset of Nonclassical σ Bridging".[2] Our critical examination of all the available data clearly reveals that the deviation from linearity observed in the chemical shift plots of 2-aryl-2-norbornyl cations and related systems with more electron demanding substituents is uniquely consistent with the onset of nonclassical σ bridging. The Gassman–Fentiman tool of increasing electron demand, although coarse, is also capable of detecting the onset of enhanced π, $\pi\sigma$, and cyclopropyl conjugation in a wide variety of phenyl- and cyclopropyl-substituted cationic systems.

Recently Brown and co-workers[2] published a paper entitled "Anomalous Carbon-13 Chemical Shifts with Increasing Electron Demand in the 2-Aryl-2-norbornyl Cations and Related Systems. Evidence That These Anomalous Shifts Are Not Diagnostic of the Onset of Nonclassical σ Bridging". In this paper we present a rebuttal of Brown's criticism of our previous work. It is our contention that a more comprehensive examination of the data and a proper understanding of the method render Brown's conclusions invalid.

The Gassman–Fentiman tool of increasing electron demand was first applied to chemical shifts by Gassman, Richey, and Winstein[4] to measure the electron demand of the electron-deficient cationic center of 7-aryl-7-norbornenyl cations. Subsequently, it has been extensively used (notably by Brown) to probe the onset of σ, π, and $\pi\sigma$ participation in the solvolytic transition states of a large number of systems.[5] Indeed, the application of this probe in solvolysis has confirmed the onset of π participation in 7-aryl-7-norbornenyl[4] and 2-aryl-5-norbornen-2-yl systems[6] and the onset of $\pi\sigma$ participation in Coates' 9-aryl-9-pentacyclo[4.3.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$]nonyl system.[7] The application of the same tool to the 2-aryl-2-norbornyl system in solvolytic studies failed to reveal the onset of σ participation[7,8] which led Brown to conclude that no such participation occurs in the parent 2-norbornyl system.

Extending the application of the same tool coupled with ^{13}C NMR spectroscopy as the structural probe under stable ion conditions allowed our groups to detect the onset of π, $\pi\sigma$, and σ delcoalization in a variety of systems.[9-15] The ^{13}C NMR chemical shifts of the cationic carbons of a series of arylcyclopentyl **2**, arylcyclohexyl **3**, 2-aryl-2-adamantyl **4**, 6-aryl-6-bicyclo[3.2.1]octyl **5**, and 7-aryl-7-norbornyl **6** cations (Chart I) correlate linearly with the observed cationic chemical shifts of substituted cumyl cations **1** over a range of substituents[16,17] (generally from the most electron releasing *p*-OCH_3 to the most electron withdrawing 3,5-$(CF_3)_2$ groups). However, systems such as the 7-norbornenyl **13**,[12] 5-norbornen-2-yl **14**,[10,11] 2-norbornyl **15**,[9] 8-tricyclo[5.2.1.$0^{2,6}$]decyl **16**,[11] and 9-aryl-9-pentacyclo[4.3.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$]nonyl **17**[13] cations show deviations from linearity in such chemical shift plots with electron demanding substituents or show negative slope throughout the range of substituents considered. Brown and coworkers[17] recently developed σ^{C^+} substituent constants (based on a modified Hammett–Brown equation) which

(1) (a) Stable Carbocations. 247. For part 246, see: Mertens, A. L.; Olah, G. A. *Chem. Ber.*, in press. (b) University of Southern California. (c) Michigan State University.

(2) Brown, H. C.; Periasamy, M.; Kelly, D. P.; Giansiracusa, J. J. *J. Org. Chem.* **1982**, *47*, 2089.

(3) Although Prof. Brown is kind enough to send us preprints of some of his articles, we were disappointed that we did not receive a preprint of this particular paper, nor were any of us selected as reviewers.

(4) (a) Gassman, P. G.; Fentiman, A. F., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 1545; **1970**, *92*, 2549. (b) Richey, H. G., Jr.; Nichols, D.; Gassman, P. G.; Fentiman, A. F., Jr.; Winstein, S.; Brookhart, M.; Lustgarten, R. K. *Ibid.* **1970**, *92*, 3783.

(5) Brown, H. C. "The Nonclassical Ion Problem"; Plenum: New York, 1977; Chapter 10.

(6) Brown, H. C.; Ravindranathan, M.; Peters, E. M. *J. Am. Chem. Soc.* **1975**, *97*, 2900.

(7) Coates, R. M.; Fretz, E. R. *J. Am. Chem. Soc.* **1975**, *97*, 2538; **1977**, *99*, 297. Brown, H. C.; Ravindranathan, M. *Ibid.* **1977**, *99*, 299.

(8) Brown, H. C.; Ravindranathan, M.; Takeuchi, K.; Peters, E. N. *J. Am. Chem. Soc.* **1975**, *97*, 2899. Brown, H. C.; Rei, M. H. *Ibid.* **1964**, *86*, 5008.

(9) Olah, G. A.; Prakash, G. K. S.; Liang, G. *J. Am. Chem. Soc.* **1977**, *99*, 5683.

(10) Farnum, D. G.; Botto, R. E. *Tetrahedron Lett.* **1975**, *46*, 4013.

(11) (a) Farnum, D. G.; Botto, R. E.; Chambers, W. T.; Lam, B. *J. Am. Chem. Soc.* **1978**, *100*, 3847. For preceding H^1 studies see: (b) Farnum, D. G.; Wolf, A. D. *J. Am. Chem. Soc.* **1974**, *96*, 5166.

(12) Olah, G. A.; Berrier, A. L; Arvanaghi, M.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1981**, *103*, 1122.

(13) Farnum, D. G.; Clausen, T. P. *Tetrahedron Lett.* **1981**, *22*, 549.

(14) For a comprehensive evaluation of the method see: Olah, G. A.; Berrier, A. L.; Prakash, G. K. S. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 1998.

(15) Olah, G. A.; Berrier, Al. L.; Prakash, G. K. S. *J. Org. Chem.* **1982**, *47*, 3903.

(16) Olah, G. A.; Porter, R. D.; Jeuell, C. L.; White, A. M. *J. Am. Chem. Soc.* **1972**, *94* 2044.

(17) Brown, H. C.; Kelly, D. P.; Periasamy, M. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 6956.

0022-3263/83/1948-2146$01.50/0