Enantiomer Discrimination Arising from Solute–Solute Interactions in Partially Resolved Chloroform Solutions of Chiral Carboxamides

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Enantomer discrimination is revealed in the ^{1}H-NMR spectra of partially resolved samples of seven chiral carboxamides. Signal separation is temperature and concentration dependent, and it varies smoothly with enantiomer composition, being a maximum when the difference in enantiomer content is also a maximum and coalescing to one signal in racemic material. These effects are interpreted in terms of linear hydrogen-bonded arrays of amide molecules, which undergo exchanges of the end units at rates that give rise to two different averaged environments when the enantiomer composition is different.

Introduction

Enantiomers at the molecular level, when isolated from other nonracemic chiral influences, are isoenergetic, displaying identical chemical and physical properties. When associated with another nonracemic chiral agent, however, the initial enantiomeric condition changes to a diastereomeric one, frequently displaying discernibly different properties. Sometimes this can be very subtle, particularly when the interacting nonracemic chiral influence is represented by aggregations of the same enantiomer. For example, chiral substances crystallize in several modifications—two of which exhibit enantiomer discrimination owing presumably to strong crystal forces which can bring about diastereomeric interactions in the aggregate.[1] Highly structured chiral monolayers may also exhibit enantiomer discrimination in the aggregate.[2] But similar effects in solutions of enantiomeric solutes are few, probably because of the lack of sufficiently stable aggregations in solution. The fact that each of the small number of known or suspected cases[3] shares the likelihood of pronounced solute–solute hydrogen-bonding appears to support this view. Because of the well-known ability of carboxamides to form intermolecular hydrogen bonds, enantiomer discrimination in carboxamides might be expected to be a fairly common occurence, but heretofore only two examples were reported.[4,5] The present work, however, supports the expectation, for we have examined seven partially resolved carboxamides and found them all to manifest enantiomer discrimination in their ^{1}H-NMR spectra.

Results and Discussion

Chloroform solutions of partially resolved samples of each of the chiral amides, **1–7**, display separate signals in their proton NMR spectra owing to each enantiomer. The ratios of intensities of these signals correspond to the molar ratios of enantiomers present in the sample. The signal separations ($\Delta\delta$) are directly related to enantiomer compositions, being maximums when the differences in enantiomer contents are also maximums. The signal differences smoothly narrow as the enantiomers approach equimolarity, finally coalescing to single signals in the racemic samples. A representative set of these data are shown in Figure 1, where the doublet owing to the methyl group in **3** is followed from samples containing 5:95 *R*:*S*, through 50:50 *R*:*S* to 95:5 *R*:*S*. The magnitude of $\Delta\delta$ is also dependent on temperature and overall solution concentration. These dependencies, which are consistent with the idea of strong solute–solute hydrogen bonding, are illustrated again with compound **3** in Figures 2 and 3, respectively.

Also supporting the need for stable solute–solute structures is the fact that in solvents like DMSO-d_6 and CD_3OD, which interact strongly with polar solutes, the amides do not show any enantiomer discrimination.

Harger was the first to observe enantiomer discrimination, which he found in the ^{1}H-NMR spectra of partially resolved samples of chiral phosphinamides **8**[6] and then in the spectra determined from nonracemic samples of chiral phosphoinothioic acids **9**.[7] He postulated formation of the diastereomeric cyclic dimers, **10** and **11**, to account for the effect, while at about the same time, Cung, Marraud, and Neel[4] observed differences between aggregations (solutions) of L-leucine diamides and D,L-leucine diamides, which they also attributed to diastereomeric cyclic dimers (**12** and **13**). But cyclic dimeric associations are not appropriate models for monocarboxamides because the amide

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(2) Stewart, M. V.; Arnett, E. M. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1982; Vol. 13, p 220 ff.
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(4) Cung, M. T.; Marraud, M.; Neel, J. *Biopolymers* **1978**, *17*, 1149–1173.
(5) Dobashi, A.; Saito, N.; Motoyama, Y.; Hara, S. *J. Am. Chem. Soc.* **1986**, *108*, 307–308.
(6) Harger, M. J. P. *J. Chem. Soc., Perkin Trans. II* **1977**, 1882–1887.
(7) Harger, M. J. P. *J. Chem. Soc., Perkin Trans. II* **1978**, 326–331.

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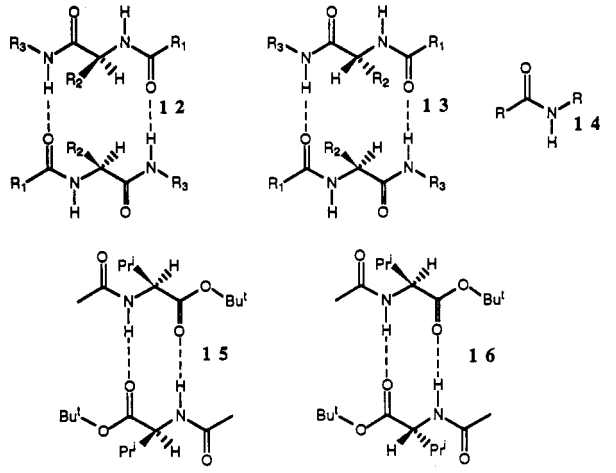
function prefers the anti conformation, 14,[8] and cannot



form a cyclic dimer. This fact was apparently why Dobashi et al.[5] did not include participation of the amide carbonyl group in the hydrogen-bonded dimers **15** and **16**, invoked to explain the enantiomer discrimination they observed in the ^{1}H-NMR spectra obtained from partially resolved samples of *N*-acetylvaline *tert*-butyl ester.

The hydrogen-bonded associations in simple carboxamides, therefore, must be linear. This may be the case for phosphinamides as well as since the three phosphinamide crystal structures[9-11] determined subsequent to Harger's 1978 work all show the phosphinamide linkage in the anti conformation.

While there is no information available on the sizes of the carboxamide (and perhaps phosphinamide) linear associations, the following model appears to work for dimers, trimers, and perhaps even tetramers. These are inventoried in Figure 4, where the general monomeric enantiomer is represented as R (or S) and hydrogen bonds are shown as solid lines. Thus **D-1** and **D-2** are enantiomers, while R_1--R_2 and R_2--R_1 are indentical. Under conditions of slow exchange, for example, R_1 and R_2 in **D-1** would act as if they are constitutionally distinct, however, R_1 and R_2 (in **D-1**) would exist effectively in an averaged environment and display identical chemical shifts. The proposed exchange process for the dimers is represented in Figure 5, where the monomer R_3 adds to the R_2 end while R_1 is lost. Thus, in the presence of only R (the completely resolved sample), there would be only one NMR signal owing to an averaging of what would be the constitutionally different environments under slow exchange on the NMR time scale. The same exchange process can create a second averaged environment, one involving **D-3** and **D-4** and different from the first, when a small amount of S (partially resolved sample) is present. As [R] and [S] approach equality, the two averaged environments also approach a single or global averaged environment, which is reached when [R] = [S] (the racemic sample), and the two NMR signals coalesce to one. Similar rapid additions and losses of end groups in larger associations (trimers and tetramers, if they are formed) could also result in the averaging of environments

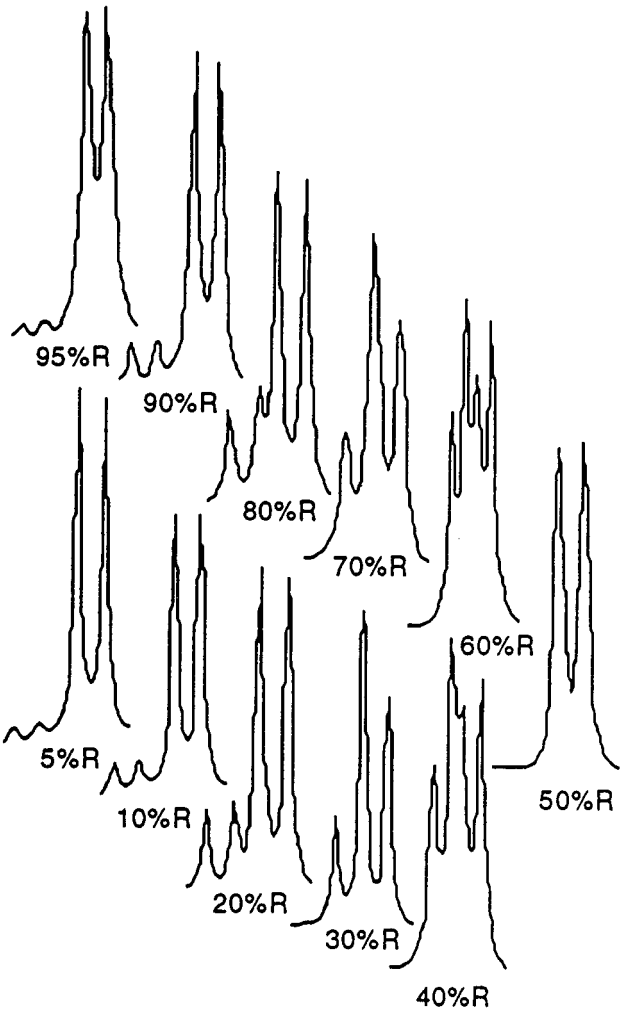


Figure 1.

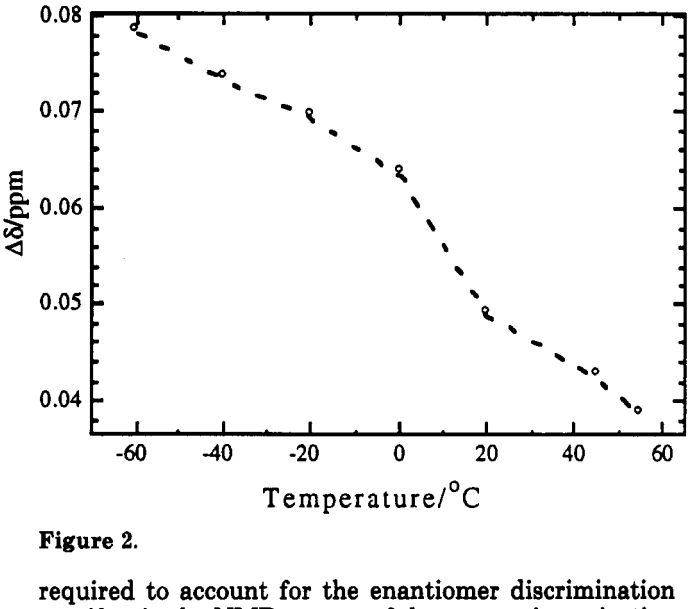


Figure 2.

required to account for the enantiomer discrimination manifest in the NMR spectra of the present investigation and the others cited herein.

Experimental Section

General. Melting points (uncorrected) were determined on an Electrothermal IA 9000 digital melting point apparatus. All FT-IR spectra were run on Nicolet 205 FT-IR as KBr plates. NMR spectra were recorded on a Varian Gemini 300 instrument with a hydrogen probe operating at 300 MHz. The deuterium signal of the solvent ($CDCl_3$) was used as the lock, and tetra-

(8) (a) Lister, D. G.; Macdonald, J. N.; Owen, N. L. *Internal Rotation and Inversion*; Academic Press: New York, 1978; pp 228–229. (b) Bassindale, A. *The Third Dimension in Organic Chemistry*; Wiley: New York, 1984; p 74 ff.

(9) *N*-(2-Phenylethyl)-*P,P*-diphenylphosphinamide: Cameron, A. F.; Duncanson, F. *Acta Crystallogr. Sect. B* **1981**, *B37*, 1604–608.

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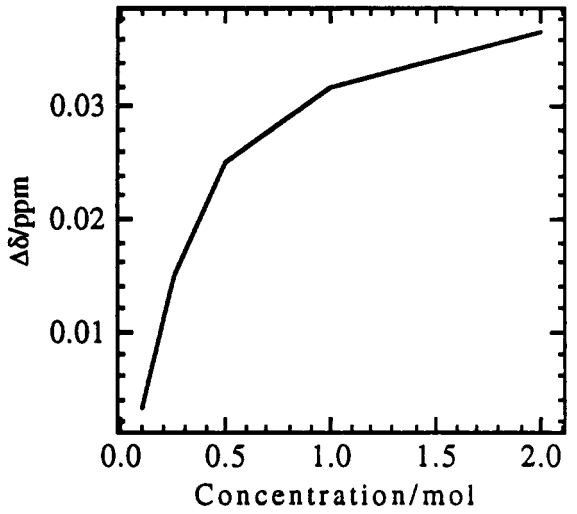

Figure 3.

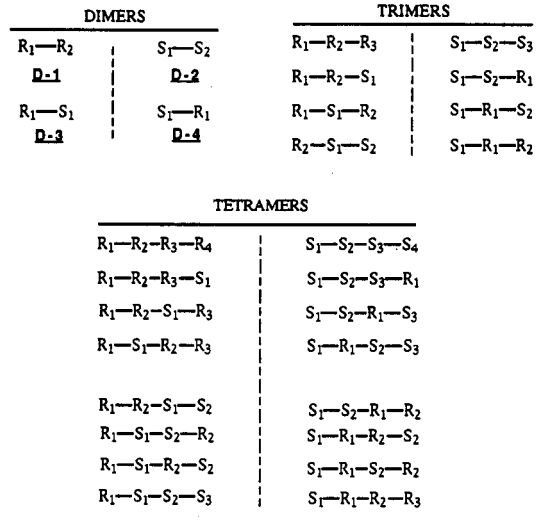

Figure 4.

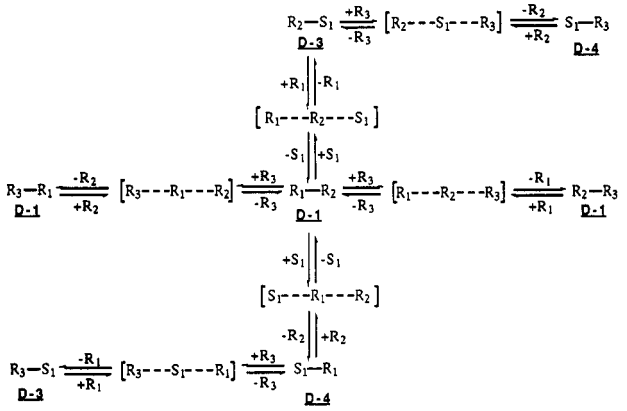

Figure 5.

methylsilane was the internal reference. GS and MS spectra were recorded on a Hewlett-Packard 5890 series II gas chromatograph with a Hewlett-Packard 5971 series mass selective detector.

Carboxamides. The amides **1–3** and **5–7** were each prepared by means of the following general procedure, while physical constants and spectral data are given below for the individual compounds. Preparation and characterization of compound **4** is described elsewhere.[12] In each of the other cases, the amine (10 mmol) and the acid chloride (10 mmol) were dissolved in pyridine (100 mL) and stirred at room temperature overnight before the solvent was evaporated. After the solid residue was partioned between chloroform (0.5 L) and water (0.3 L), and the separated chloroform solution was washed successively with 10% aqueous KOH solution (3 × 0.3 L), 10% aqueous HCl (3 × 0.3 L), and water (3 × 0.3 L), and finally dried, the chloroform was evaporated, leaving the crystalline amide product, which was recrystallized from a mixture of ethyl acetate and petroleum ether to give the pure amide ranging between 75 and 95% yield. In each case the use of enantiomerically pure reactant (either amine or acid chloride) gave the enantiomerically pure amide, the individual characterizations of which follow.

(*S*)-(−)-*N*-(1-Phenylethyl)acetamide (1): mp 101.4–101.7 °C (lit.[13] mp 101–102 °C); $[\alpha]^{20}$ −148° (*c* = 2.18, ethanol) (lit.[13] $[\alpha]^{20}$ −150° (ethanol)); IR (cm^{-1}) 3267, 3071, 2977, 1643, 1553, 1376, 759, 703, 533; ^1H NMR 1.41 (d, 3 H), 1.89 (s, 3 H), 5.05 (p, 1 H), 6.82 (d, 1 H), 7.2–7.3 (m, 5 H); ^{13}C NMR 21.6, 22.9, 48.6, 126.0, 127.0, 128.4, 143.4, 169.3; MS *m/z* (M^+), 120, 106, 104, 77.

(*R*)-(+)-*N*-(1-Phenylethyl)-2,2-dimethylpropanamide (2): mp 119.2–120.1 °C (lit.[14] mp 119–120 °C); $[\alpha]^{18}$ +101.9° (*c* = 4.21, $CHCl_3$) (lit.[14] $[\alpha]^{25}$ +107° (*c* = 5, $CHCl_3$)); IR (cm^{-1}) 3339, 3065, 3030, 2932, 2871, 1639, 1529, 1221, 1200, 755, 698; ^1H NMR 1.19 (s, 9 H), 1.46 (d, 3 H), 5.10 (p, 1 H), 6.00 (d, 1 H), 7.30 (m, 5 H); ^{13}C NMR 21.5, 27.4, 38.4, 48.3, 125.8, 127.0, 128.4, 143.5, 177.2; MS *m/z* 205 (M^+), 105, 77, 57.

(*R*)-(−)-*N*-(1-Phenylethyl)-4-nitrobenzamide (3): mp 140.6–140.9 °C (lit.[15] mp 140°); $[\alpha]^{18}$ −70.2° (*c* = 2.71, acetone) (lit.[15] *R*-enantiomer, $[\alpha]^{20}$ +62.7° (acetone)); IR (cm^{-1}) 3300, 3255, 3104, 3068, 3028, 2975, 2932, 1641, 1601, 1542, 1522, 1351, 868, 846, 700; ^1H NMR 1.57 (d, 3 H), 5.25 (p, 1 H), 7.07 (d, 1 H), 7.30 (m, 5 H), 8.01 (dd, 4 H); ^{13}C NMR 21.4, 49.6, 123.5, 126.1, 127.5, 128.1, 128.7, 140.0, 142.6, 149.3, 164.7; MS *m/z* 270 (M^+), 255, 150, 120, 104, 76.

(*S*)-(+)-*N*-Butylacetoxyphenylacetamide (5): mp 65.3–65.9 °C; $[\alpha]^{20}$ +98.5° (*c* = 2.71, $CHCl_3$); IR ($cm^{-}11$) 3320, 3065, 3038, 2956, 2934, 2871, 1737, 1660, 1542, 1377, 1230, 1033, 733; ^1H NMR 0.90 (t, 3 H), 1.31 (dt, 2 H), 1.48 (dt, 2 H), 2.17 (s, 3 H), 3.25 (q, 2 H), 6.05 (s, 1 H), 6.15 (s, br, 1 H), 7.40 (m, 5 H); ^{13}C NMR 13.6, 19.9, 21.1, 31.4, 39.1, 76.6, 127.3, 128.6, 128.8, 135.6, 168.2, 169.2; MS *m/z* 249 (M^+), 150, 149, 108, 107, 79, 57.

(*S*)-(+)-*N*-Phenylacetoxyphenylacetamide (6): mp 130.7–131.4 °C; $[\alpha]^{20}$ +74.9° (*c* = 3.65, $CHCl_3$); IR (cm^{-1}) 3320, 3065, 3035, 2938, 1741, 1676, 1600, 1536, 1446, 1375, 1227, 1054, 735, 732, 694; ^1H NMR 2.24 (s, 3 H), 6.20 (s, 1 H), 7.1–7.5 (m, 10 H), 8.05 (s, 1 H); ^{13}C NMR 21.0, 75.5, 120.1, 124.8, 127.4, 128.9, 129.0, 129.2, 135.1, 136.9, 166.4, 169.3; MS *m/z* 269 (M^+), 150, 108, 107, 93, 77.

(*S,S*)-(+)-1,3-Bis(acetoxyphenylacetamido)benzene (7). In its NMR spectra there are two sets of signals due to restricted amide bond rotation. Data for only major isomer are included: mp 211.3–211.9 °C; $[\alpha]^{20}$ +15.2° (*c* = 2.90, $CHCl_3$); IR (cm^{-1}) 3307, 3157, 3093, 3085, 3066, 3035, 2940, 1751, 1740, 1689, 1687, 1609, 1546, 1491, 1427, 1373, 1230, 1049, 697; ^1H NMR 2.24 (s, 6 H), 6.10 (s, 2 H), 7.3–7.6 (m, 10 H), 8.4–8.6 (m, 4 H); ^{13}C NMR 21.0, 76.0, 111.3, 116.1, 126.6, 127.4, 128.7, 129.2, 129.4, 134.7, 137.5, 166.8, 170.2.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **5**, **6** and **7** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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