135.72, 135.41, 133.44, −2.02; LRMS *m/z* 232 (M^+, 19.9), 217 (3.7), 189 (9.8), 159 (4.4), 105 (9.6); HRMS calcd for $C_{13}H_{16}O_2Si$ 232.0919, found 232.0917.

2-(4-Methoxybenzoyl)-2,4,6-cycloheptatrienone (Table II, entry 3): tan solid; mp 132–133 (EtOAc); TLC (2:1 hexanes–EtOAc) R_f 0.07; IR (KBr) 1665, 1600, 1570, 1420, 1255, 1240, 1170, 1020, 845 cm^{-1}; ^1H NMR (270 MHz) δ 7.84 (d, J = 8.8 Hz, 2 H), 7.27–7.17 (m, 3 H), 7.13–7.07 (m, 2 H), 6.91 (d, J = 9.0 Hz, 2 H), 3.86 (s, 3 H); ^{13}C NMR (68 MHz) δ 194.11, 185.69, 163.97, 151.83, 142.98, 135.80, 135.49, 134.30, 133.74, 131.63, 128.86, 113.90, 55.38. Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.98; H, 5.03. Found: C, 74.78; H, 5.13. A second fraction, **2-(4-Methoxyphenyl)-2,4,6-cycloheptatrienone**, was isolated as small yellow crystals; mp 51–52 °C (1:1 hexanes–cyclohexane); TLC (2:1 hexanes–EtOAc) R_f 0.20; IR (KBr) 1620, 1600, 1565, 1495, 1455, 1250, 1170, 1025, 830, 780, 680 cm^{-1}; ^1H NMR (270 MHz) δ 7.48 (d, J = 8.9 Hz, 2 H)8 7.34 (d, J = 8.2 Hz, 1 H), 7.20–6.95 (m, 4 H), 6.92 (d, J = 8.7 Hz, 2 H), 3.82 (s, 3 H); ^{13}C NMR (68 MHz) δ 186.44, 160.09, 151.80, 141.69, 135.23, 134.65, 133.39, 132.38, 132.26, 130.62, 113.62, 55.24. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.03; H, 5.78.

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Chiral Discrimination in the Structures and Energetics of Association of Stereoisomeric Salts of Mandelic Acid with α-Phenethylamine, Ephedrine, and Pseudoephedrine

S. P. Zingg,[†] Edward M. Arnett,*[‡] Andrew T. McPhail,[‡] Aksel A. Bothner-By,[§] and W. R. Gilkerson[⊥]

Contribution from the Departments of Chemistry, Duke University, Durham, North Carolina 27706, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213, and University of South Carolina, Columbia, South Carolina 29208.

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Abstract: A carefully coordinated study of the relations between structure and energetics of association in the crystalline state and solution is reported here. Hydrogen-bonded ion pairs formed from reaction between the enantiomers of mandelic acid, α-phenethylamine, ephedrine, and pseudoephedrine have been studied in dimethyl sulfoxide, dioxane, and water and as solid salts. Single-crystal X-ray analysis, performed on four unique diastereomeric pairs of (±)-ephedrinium and (±)-pseudoephedrinium (±)-mandelates yielded details of the solid-state hydrogen-bonding schemes for all eight diastereomeric salts. ^1H NMR spectra (at 300 and 600 MHz) over a wide concentration range were determined and indicated a simple two-state equilibrium between ion pairs and free ions in dimethyl sulfoxide. The dissociation equilibria in dimethyl sulfoxide were examined more quantitatively by conductance and the results treated by the Fuoss–Justice, Fuoss-1977, and Onsager methods to yield calculated dissociation constants, equivalent conductances, and mean activity coefficients over a wide concentration range. Thermochemical properties determined by various techniques were (1) the heat of fusion by differential scanning calorimetry, (2) heats of solution of the crystalline salts to high dilution by isoperibolic batch calorimetry, and (3) heats of protonation and heats of dissociation from thermometric titration of solutions of mandelic acid with the bases. Extensive use was made of cross-chiral checks (e.g., *R,R′* vs *S,S′*) to prove that observed chiral discrimination factors were real and accurate. Significant chiral discrimination factors were found for all properties of diastereomeric combinations. In several cases the largest differences in thermochemical properties and ^1H NMR spectra of diastereomeric pairs could be related reasonably to differences in hydrogen-bonding schemes in their crystals.

One of the most important unresolved problems in chemistry is the quantitative understanding and control of stereospecific reactions. This must ultimately come down to a detailed analysis of the strengths and geometrical requirements of the forces that attract and hold molecules together in complexes, aggregates, or transition states. Intermolecular forces range from weak nondirectional dispersion forces to hydrogen bonds that have enough strength and direction to provide a good starting point for the understanding and prediction of stereochemistry.

The goal of this research was to explore the relationship between the geometry and strength of intermolecular interactions for a series of closely related chiral ion pairs in solution. Because the energetic differences are small and the geometry of molecular interactions is not easily defined, it is difficult to relate observed energy variations to changes in the shapes of the aggregates. One partial resolution of this problem lies in the use of chiral molecules and stereochemical methodology to study intermolecular interactions.[1–4]

The interactions of chiral molecules produce complexes that are related as enantiomers or as diastereomers. Comparison of

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[†] The experimental work reported here was all done by S.P.Z. at the University of Pittsburgh and Duke and appears in her doctoral dissertation, University of Pittsburgh, 1982. Present address: Oak Ridge National Laboratories, Oak Ridge, TN.

[‡] Duke University.

[§] Carnegie-Mellon University.

[⊥] University of South Carolina.

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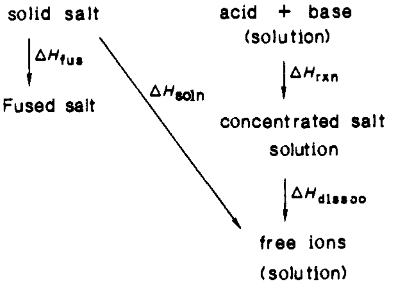
0002-7863/88/1510-1565$01.50/0

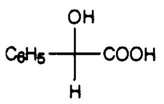
Scheme I

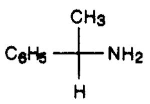


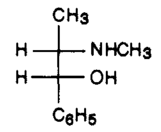
enantiomeric pairs affords an absolute check that instrumental errors and impurities are not producing anomolous results. Any phenomenological differences between diastereomeric complexes are ultimately due to their differences in geometrical requirements and the strength of the intermolecular forces that hold them together.

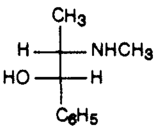
Ion pairs formed from chiral carboxylic acids and amines were chosen for this study since they have strong, specific sites of interaction, i.e., the hydrogen bonds between the carboxylate and ammonium ions. It is reasonable to believe that diastereomeric differences between the physical properties of ion pairs in solution might be detectable, since it is well-known that diastereomeric salts often have quite different crystalline properties.[5-16] These properties form the basis for the most common method of resolving chiral acids or bases.[17-19] Furthermore, the opportunity to approach the structures of the ion pairs in solution through those in the crystalline phase offers some promise.

Our choice of compounds for this study (α-phenethylamine, ephedrine, pseudoephedrine, mandelic acid) was prompted primarily by their accessibility in high optical purity, by their known configurations,[20] and by a number of other studies to which we could relate this work.[21]


(*R*)-(−)-mandelic acid


(*R*)-(+)-phenethylamine


(1*R*, 2*S*)-(−)-ephedrine


(1*S*,2*S*)-(+)-pseudoephedrine

Ephedrine, α-phenethylamine, and mandelic acid have been utilized extensively in stereochemical investigations. Chiral discrimination has been observed in a variety of different systems including solids,[8,22,23] solid–liquid,[24-26] gas–liquid,[27] gas–solid,[28] and homogeneous[29-32] and heterogeneous[33] solutions. For example, the diastereomeric mandelate salts of α-phenethylamine and ephedrine have melting points that differ by ~50 °C. All of these phenomena are consistent with structural and energetic differences in the diastereomeric aggregates formed by mandelic acid and these bases in solution as well as in the solid state. None of these investigations have, however, attempted to relate the observed chiral discrimination in physical properties to the structures of the species involved in a systematic way. That is the aim of this study, which has coordinated a variety of techniques for investigating the interactions between ion pairs in solution. Thermochemical measurements and conductance studies were used to elucidate the energetics of the diastereomeric ion pairs. Structures of the crystalline salts were determined by single-crystal X-ray analysis. Examination of the salt solutions by NMR spectroscopy through the range of concentrations where ion pairing occurs provided structural information about the ion pairs in solution.

Our strategy for investigating the energetics and structures of a series of diastereomeric ion pairs is outlined by Scheme I. Conversion of the crystalline salt to a fused salt (ΔH_{fus}) at the melting point, and also various premelting phase transitions, was determined by differential scanning calorimetry. The enthalpy change for taking fully associated ions in the crystal to dissociated ions in solution (ΔH_{soln}) was determined by solution calorimetry.

A second pathway to fully dissociated ions begins with equally concentrated solutions of the acid and base in separate syringes. The acid and base are pumped at the same rate into a calorimeter containing pure solvent or a concentrated solution of the corresponding salt to yield a concentrated salt solution (0.01 or 0.20 M, respectively). The heat of reaction (ΔH_{rxn}) resulting from this thermogram[34-36] reflects the heat of dilution of acid, base, and salt as well as the heat of proton transfer (ΔH_{pt}) to form the ion pair and the heat of dissociation (ΔH_{dissoc}) of a portion of the ion pairs into free ions.

The heats of dissociation and of proton transfer are clearly the most significant thermochemical properties within the present discussion of ion-pairing energetics. These are accessible from the observed heats of reaction at two concentrations and the degree of dissociation to free ions calculated from the conductance dissociation constant. The heat of dissociation may also be obtained from the titration of a concentrated salt solution into a calorimeter containing pure solvent. The resulting thermogram reflects the

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Table I. DSC Data for Ammonium Mandelate Salts

	isomer		mp, °C		
amine	base	acid	capillary	DSC	ΔH_{fus}, kcal mol^{-1}
α-phenethylamine	(*S*)-(−)	(*R*)-(−)	107.9–108.7	107.6 ± 0.3	6.10 ± 0.19
	(*R*)-(+)	(*S*)-(+)	108.0–108.8	107.9 ± 0.4	6.38 ± 0.29
	(*S*)-(−)	(*S*)-(+)	166.0–169.8	173.3 ± 0.3	11.1 ± 0.3
	(*R*)-(+)	(*R*)-(−)	166.0–169.8	172.7 ± 0.5	11.4 ± 0.5
ephedrine	(1*S*,2*R*)-(+)	(*S*)-(+)	165.4–167.0	165.4 ± 0.4	12.5 ± 0.5
	(1*R*,2*S*)-(−)	(*R*)-(−)	165.6–167.4	164.9 ± 0.1	12.3 ± 0.4
	(1*S*,2*R*)-(+)	(*R*)-(−)	111.2–111.9	110.8 ± 0.2	6.71 ± 0.26
	(1*R*,2*S*)-(−)	(*S*)-(+)	110.9–111.9	110.4 ± 0.3	6.52 ± 0.07
pseudoephedrine	(1*S*,2*S*)-(+)	(*S*)-(+)	110.5–111.3	109.6 ± 1.5	5.87 ± 0.12
	(1*R*,2*R*)-(−)	(*R*)-(−)	110.2–111.2	110.1 ± 0.3	5.77 ± 0.11
	(1*S*,2*S*)-(+)	(*R*)-(−)	115.9–116.7	107.4 ± 1.0	4.01 ± 0.64
	(1*R*,2*R*)-(−)	(*S*)-(+)	116.0–116.9	107.9 ± 0.3	3.57 ± 0.91

heat of dilution of the various species in solution and the change in the degree of dissociation (from conductance data) of the ion pair from a concentrated to a dilute solution.

Finally, we have chosen dioxane, dimethyl sulfoxide (DMSO), and water as media for our studies. Dioxane is a low dielectric (ϵ 2.2) solvent that is a poor hydrogen bond acceptor and donor, so interionic association through hydrogen bonding should be strong with very little competition from the solvent. DMSO (ϵ 46.7) is a good hydrogen bond acceptor but a poor anion solvator[37-40] and so should allow a different perspective on the balance of ion pairing and solvation factors than dioxane alone can provide. Water is an important reference solvent because of its ability to dissociate salts. The lack of chiral discrimination between diastereomeric salts in this solvent provides a trivial but useful check on the purity of the salts and the validity of the various techniques described above.

Results

Differential Scanning Calorimetry. The thermograms were all prepared under the same conditions and were clearly different for the diastereomeric mandelate salts. The melting point and enthalpy of fusion for each salt are given in Table I. The melting points obtained from the DSC method are also compared with the capillary melting points. As expected, large differences were observed in the enthalpies of fusion for those diastereomeric salts that had large differences in their melting points.

Enthalpies of Solution. The amount of salt added for each measurement was small so that the final concentration after dissolution of the salt in 40.00 mL of DMSO was $\simeq 10^{-3}$ M. Conductance results indicated that each of the salts was at least 90% dissociated into free ions at this concentration (eq 1). The

$$\mathrm{AHB_{solid}} \xrightarrow{\Delta H_{soln}} \mathrm{A^-{}_{soln}} + \mathrm{HB^+{}_{soln}} \underset{\Delta H_{dissoc}}{\overset{\Delta H_{assoc}}{\rightleftharpoons}} \mathrm{A^-\cdots HB^+{}_{soln}} \quad (1)$$

heat change observed upon solution of the solid salts in DMSO was corrected for the amount of association of the ions into ion pairs by using the heat of association (ΔH_{assoc}) obtained from dilution studies (see below) and the mole fraction of ion pairs present in solution calculated from the conductance data. The enthalpies of solution for the mandelate salts in DMSO were, therefore, the molar heats produced by dissolution of the solid salt to give free solvated ions. All of the observed heats were endothermic, and large differences were observed between each of the diastereomeric pairs of salts (see Table II). The uncertainty in the measurements was due primarily to the difficulties in weighing small samples ($\simeq$10 mg) into glass ampules and in preventing the powdered salt from filling the neck of the ampule where it would not dissolve rapidly.

Table II. Enthalpies of Solution of Ammonium Mandelate Salts in DMSO at 25 °C

	isomer		
amine	base	acid	ΔH_{soln}, kcal mol^{-1}
α-phenethylamine	(*R*)-(+)	(*S*)-(+)	7.19 ± 0.08
	(*S*)-(−)	(*R*)-(−)	7.21 ± 0.07
	(*R*)-(+)	(*R*)-(−)	8.86 ± 0.02
	(*S*)-(−)	(*S*)-(+)	8.74 ± 0.04
ephedrine	(1*S*,2*R*)-(+)	(*S*)-(+)	9.50 ± 0.08
	(1*R*,2*S*)-(−)	(*R*)-(−)	9.51 ± 0.03
	(1*S*,2*R*)-(+)	(*R*)-(−)	6.49 ± 0.03
	(1*R*,2*S*)-(−)	(*S*)-(+)	6.54 ± 0.09
pseudoephedrine	(1*S*,2*S*)-(+)	(*S*)-(+)	5.89 ± 0.02
	(1*R*,2*R*)-(−)	(*R*)-(−)	5.78 ± 0.05
	(1*R*,2*R*)-(−)	(*S*)-(+)	7.15 ± 0.02
	(1*S*,2*S*)-(+)	(*R*)-(−)	7.29 ± 0.09

Enthalpies of Dissociation. In order to measure the heat changes upon dissociation of the ion pairs, concentrated solutions of the salts (0.1–0.4 M) were titrated into 40.00 mL of pure solvent. The mole fraction of ion pairs present in solution decreases upon dilution of the salt solution. From the molar change in ion-pair concentration (calculated from the conductance data) and the heat change Q, the enthalpy of dissociation was calculated by eq 2,

$$\Delta H_{dissoc} = Q/(\alpha_f - \alpha_i)n \quad (2)$$

where α_f and α_i are the fractions of salt present as free ions at the final and initial concentrations, respectively, and n is the total number of moles of salt added to the pure solvent during the titration. Conductance data were used to calculate α_f; however, the degree of dissociation of the salts at concentrations greater than 0.02 M is outside the range of the conductance data. Therefore, α_i values were calculated by using the conductance K's and eq 3 and 4 where

$$K_a = (1 - \alpha)/\gamma_\pm{}^2\alpha^2 C \quad (3)$$

$$\ln(\gamma_\pm{}^2) = -2\kappa q/(1 + \kappa R) \quad (4)$$

$$q = e^2/2DkT \quad (5)$$

$$\kappa = \frac{e^2}{DkT}\frac{4\pi N}{1000}\sum(C_i z_i)^2 \quad (6)$$

and R was taken to be equal to Bjerrum's q, which for the mandelate salts was 6 Å.

There was some uncertainty in the absolute values of the heats of dissociation calculated by the above methods due to the inaccessibility of the separate heats of dilution for either the ion pairs or the free ions needed to correct the observed heat change.

In addition, activity coefficients for the ions may not behave in a predictable manner at higher concentrations. However, the heats of dilution and the mean activity coefficients for enantiomeric ions will be identical so that any error introduced into the calculations should be identical for a given pair of diastereomeric salts. Any chiral discrimination in the heats of dissociation of the diastereomeric ion pairs will, therefore, not be obscured.

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Table III. Enthalpies of Dissociation for Ammonium Mandelate Ion Pairs in DMSO at 25 °C

amine	isomer base		isomer acid	titrant concn, M	final concn ($\times 10^2$), M	Δn^a ($\times 10^4$), mol	ΔH_{dissoc},^{b} kcal mol^{-1}
α-phenethylamine	(*R*)-(+)		(*S*)-(+)	0.127	0.597	1.06	4.06
		or		0.254	1.20	2.05	3.89
	(*S*)-(−)		(*R*)-(−)	0.400	1.88	3.06	3.93
	(*R*)-(+)		(*R*)-(−)	0.127	0.597	1.06	4.62
		or		0.254	1.20	2.05	4.44
	(*S*)-(−)		(*S*)-(+)	0.400	1.88	3.06	4.42
ephedrine	(1*R*,2*S*)-(−)		(*R*)-(−)	0.218	1.03	1.77	3.74
		or		0.400	1.88	2.98	3.65
	(1*S*,2*R*)-(+)		(*S*)-(+)				
	(1*S*,2*R*)-(+)		(*R*)-(−)	0.218	1.03	1.77	3.36
		or					
	(1*R*,2*S*)-(−)		(*S*)-(+)				
pseudoephedrine	(1*R*,2*R*)-(−)		(*R*)-(−)	0.218	1.03	1.79	3.47
		or		0.400	1.89	3.20	3.38
	(1*S*,2*S*)-(+)		(*S*)-(+)				
	(1*R*,2*R*)-(−)		(*S*)-(+)	0.218	1.03	1.79	3.75
		or		0.400	1.88	3.20	3.67
	(1*S*,2*S*)-(+)		(*R*)-(−)				

[a] Δn: change in the number of moles of free ions [$\Delta n = (\alpha_f - \alpha_i)$ (number of moles added)] where α_i and α_f (from conductance data) are the fractions of the salt present as the free ions at the initial titrant concentration and at the final concentration after the titration, respectively. [b] ΔH_{dissoc}: molar enthalpy of dissociation of the ion pair to free ions ($\Delta H_{\text{dissoc}} = A/\Delta n$).

Typical data for calculation of enthalpies of dissociation are presented in Table III.

Enthalpies of Reaction of Mandelic Acid with the Stereoisomeric Bases. The enthalpies of reaction for mandelic acid with α-phenethylamine, ephedrine, and pseudoephedrine were measured in dioxane, DMSO, and water under a variety of conditions. The interaction of a base and acid in solution may be described by a series of equilibria (eq 7). Each step in the equilibrium has

$$\underset{\text{free acid and base}}{\text{AH} + \text{B}} \overset{K_1.\Delta H_1}{\rightleftharpoons} \underset{\text{H-bonded complex}}{\text{AH}\cdots\text{B}} \overset{K_2.\Delta H_2}{\rightleftharpoons}$$

$$\underset{\text{H-bonded ion pair}}{\text{A}^-\cdots\text{HB}^+} \overset{K_3.\Delta H_3}{\rightleftharpoons} \underset{\text{free ions}}{\text{A}^- + \text{HB}^+} \quad (7)$$

associated with it an equilibrium constant and an enthalpy for that process. The overall enthalpies of reaction are thus dependent upon which of these processes occur and to what extent. In all of the following results the enthalpies are corrected for the heats of dilution of the base and acid in the corresponding solvent.

Work by other investigators[40,41] as well as our conductance and PMR studies show that the equilibrium in DMSO lies between the hydrogen-bonded ion pair and the free ions. The heats of reaction of mandelic acid with α-phenethylamine, ephedrine, and pseudoephedrine in DMSO were measured under two experimental regimes: (1) By use of two burets, concentrated solutions of the acid and base were titrated simultaneously into pure DMSO. The final concentration in the reaction vessel was $\simeq 10^{-2}$ M. At this concentration, the equilibrium should favor formation of the free ions. The measured enthalpies of reaction are thus composed of the heats of proton transfer from the acid to the base plus the heat changes due to dissociation of some fraction α of the hydrogen-bonded ion pairs into free ions (eq 8). (2) Concentrated solutions

$$\Delta H_{\text{rxn}} = \Delta H_{\text{pt}} + \alpha \Delta H_{\text{dissoc}} \quad (8)$$

(0.40 M) of the acid and base were titrated simultaneously into a concentrated solution (0.20 M) of the corresponding salt. This method insured that the concentration of salt in the Dewar was constant (0.20 M) throughout the titration. At this concentration, proton transfer should still be complete as in the first experiment. However, the equilibrium should now be displaced toward the ion pair. Any difference between the heats of reaction obtained from these two types of experiments should be due to the differing degrees of dissociation of the ion pairs.

The enthalpies of reaction for titration into pure DMSO are given in Table IV. Chiral discrimination ($\delta\Delta H$) was observed in the heats of reactions with mandelic acid for all of the amines: α-phenethylamine, $\delta\Delta H$ = 0.22 kcal/mol; ephedrine, $\delta\Delta H$ = 0.22 kcal/mol; pseudoephedrine, $\delta\Delta H$ = 0.22 kcal/mol.

Table IV. Enthalpies of Reaction from the Dual Titration of the Amines and Mandelic Acid into Pure DMSO at 25 °C[a]

amine	isomer base	isomer acid	$-\Delta H^1{}_{\text{rxn}}$, kcal mol^{-1}
α-phenethylamine[b]	(*R*)-(+)	(*S*)-(+)	7.43 ± 0.01
	(*S*)-(−)	(*R*)-(−)	7.37 ± 0.02
	(*R*)-(+)	(*R*)-(−)	7.63 ± 0.01
	(*S*)-(−)	(*S*)-(+)	7.61 ± 0.03
ephedrine[c]	(1*R*,2*S*)-(−)	(*R*)-(−)	7.63 ± 0.01
	(1*S*,2*R*)-(+)	(*S*)-(+)	7.62 ± 0.01
	(1*S*,2*R*)-(+)	(*R*)-(−)	7.41 ± 0.01
	(1*R*,2*S*)-(−)	(*S*)-(+)	7.38 ± 0.01
pseudoephedrine[d]	(1*R*,2*R*)-(−)	(*R*)-(−)	6.67 ± 0.03
	(1*S*,2*S*)-(+)	(*S*)-(+)	6.69 ± 0.02
	(1*S*,2*S*)-(+)	(*R*)-(−)	6.88 ± 0.02
	(1*R*,2*R*)-(−)	(*S*)-(+)	6.91 ± 0.02

[a] $\Delta H_{\text{rxn}} = Q/\text{moles added} = \Delta H_{\text{pt}} + \alpha_f \Delta H_{\text{dissoc}}$, where α_f is the fraction of the salt present as free ions at the final concentration calculated from conductance data. [b] [Titrant] = 0.300 M; [salt] = 1.41×10^{-2} M; α_f = 0.675. [c] [Titrant] = 0.400 M; [salt] = 1.54×10^{-2} M; α_f = 0.634. [d] [Titrant] = 0.400 M; [salt] = 1.54×10^{-2} M; α_f = 0.728.

When equimolar acid and base solutions are titrated into a concentrated solution of the salt in DMSO, less dissociation of the ion pair should occur than when pumped into pure solvent. Since the heat of dissociation is endothermic, the net result is that the measured heat of reaction is more exothermic when the titrate is a concentrated solution of the salt rather than pure DMSO. The results of these titrations are given in Table V. Chiral discrimination was again observed for all of the heats of reaction: α-phenethylamine, $\delta\Delta H$ = 0.35 kcal/mol; ephedrine, $\delta\Delta H$ = 0.38 kcal/mol; pseudoephedrine, $\delta\Delta H$ = 0.35 kcal/mol. The relative magnitude of the enthalpies for diastereomeric pairs of salts was consistent with that observed in the preceding experiments.

Free ions are not well solvated electrostatically in dioxane. BH^+ can hydrogen bond to dioxane; however, the anion A^- cannot interact with this solvent. Studies by Derevyanka and associates[42] suggest that the equilibria in carboxylic acid–amine systems in dioxane lie between hydrogen-bonded complexes, ion pairs, and secondary associations of the ion pairs into dimers. Conductance studies by Maryott[43] indicate that homo-hydrogen bonding to the

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(41) DeTar, D. F.; Novak, R. W. *J. Am. Chem. Soc.* **1970**, *82*, 1361.

(42) Derevyanka, L. I.; Fialkov, Y. Y.; Tsarevskaya, M. N. *Z. Obshch. Khim.* **1976**, *47*, 1444. Derevyanka, L. I.; Tsarevskaya, M. N.; Khlevnyuk, V. S. *Z. Obshch. Khim.* **1972**, *42*, 2083.

Table V. Enthalpies of Reaction from the Dual Titration of 0.40 M Amines and 0.40 M Mandelic Acid into an 0.20 M Salt Solution in DMSO at 25 °C[a]

amine	isomer: base	isomer: acid	$-\Delta H^2_{rxn}$, kcal mol^{-1}
α-phenethylamine	(*R*)-(+)	(*S*)-(+)	9.03 ± 0.03
	(*S*)-(−)	(*R*)-(−)	9.04 ± 0.02
	(*R*)-(+)	(*R*)-(−)	9.48 ± 0.03
	(*S*)-(−)	(*S*)-(+)	9.49 ± 0.02
ephedrine	(1*R*,2*S*)-(−)	(*R*)-(−)	9.13 ± 0.06
	(1*S*,2*R*)-(+)	(*S*)-(+)	9.20 ± 0.01
	(1*S*,2*R*)-(+)	(*R*)-(−)	8.77 ± 0.02
	(1*R*,2*S*)-(−)	(*S*)-(+)	8.79 ± 0.03
pseudoephedrine	(1*R*,2*R*)-(−)	(*R*)-(−)	8.09 ± 0.05
	(1*S*,2*S*)-(+)	(*S*)-(+)	8.09 ± 0.01
	(1*S*,2*S*)-(+)	(*R*)-(−)	8.47 ± 0.01
	(1*R*,2*R*)-(−)	(*S*)-(+)	8.42 ± 0.01

[a] The concentration of salt in the titrate was constant (0.20 M) throughout the titration; therefore, the degree of dissociation into free ions, α_f, was also constant: α-phenethylamine, 0.316; ephedrine, 0.292; pseudoephedrine, 0.374. $\Delta H_{rxn} = Q/\text{moles added} = \Delta H_{pt} + \alpha_f \Delta H_{dissoc}$, where moles added = 7.95×10^{-4}.

Table VI. Enthalpies of Reaction for the Dual Titration of α-Phenethylamine and Mandelic Acid into Dioxane at 25 °C[a]

base	acid	$-\Delta H_{rxn}$, kcal mol^{-1}: 1A–1B	1A–2B	2A–1B
(*R*)-(+)	(*R*)-(−)	8.76 ± 0.03	11.40 ± 0.06	11.60 ± 0.02
(*S*)-(−)	(*S*)-(+)	8.76 ± 0.02	11.37 ± 0.05	11.58 ± 0.04
(*R*)-(+)	(*S*)-(+)	8.42 ± 0.03	11.13 ± 0.03	11.35 ± 0.02
(*S*)-(−)	(*R*)-(−)	8.41 ± 0.02	11.18 ± 0.03	11.36 ± 0.05

[a] Acid–base stoichiometry was as follows. 1A–1B: [acid] = 0.20 M; [base] = 0.20*M*. 1A–2B: [acid] = 0.20 M; [base] = 0.40*M*. 2A–1B: [acid] = 0.40 M; [base] = 0.20*M*.

anion may also occur when an excess of the carboxylic acid is present.

Thermochemical data were obtained only for α-phenethylamine in dioxane, since the ephedrinium and pseudoephedrinium mandelates were too insoluble to study in this solvent. The results of the dual titration of α-phenethylamine and mandelic acid (0.20 M each) into dioxane are given in Table VI. In contrast to the thermograms for titrations in DMSO, those in dioxane were curved, which is consistent with the presence of an equilibrium that is not fully displaced in either direction. The enthalpy of the reaction was calculated from the latter half of the titration, where the change in heat was apparently linear. The absolute values of the calculated enthalpies (presumably) for formation of the ion pairs may be in error; however, the differences in the enthalpies were real and can only be accounted for by differences in the enthalpies of reaction for the diastereomeric acid–base pairs. A difference in the association constant for ion-pair formation seems unlikely, since no difference was observed in DMSO. The observed chiral discrimination $\delta\Delta H$ was 0.35 kcal/mol.

To examine the effects of homo-hydrogen bonding on the acid–base reaction in dioxane, titrations in which the stoichiometry was maintained at 2 equiv of base to 1 equiv of acid (1A–2B) and 2 equiv of acid to 1 equiv of base (2A–1B) were performed. These results are also shown in Table VI. The thermograms were similar to those obtained for the 1A–1B titrations except that the heat rise was much steeper. The discrimination observed in the enthalpies for the 1A–2B titration was 0.22 kcal/mol, while a discrimination of 0.24 kcal/mol was observed for the 2A–1B titrations. In all three types of titrations, 1A–1B, 2A–1B, and 1A–2B, the enthalpy was more exothermic for the *R,R′* and *S,S′* enantiomeric interactions.

The addition of excess acid or base may have two effects, which cannot be differentiated by solution calorimetry. First, the excess acid or base may favor the formation of homo-hydrogen-bonded complexes or ion pairs (e.g., $A^-HB^+ + HA \rightleftharpoons AHA^-HB^+$).

Table VII. Experimental Conductance Data for (*R*)-(+)-α-Phenethylammonium (*R*)-(−)-Mandelate in DMSO

concn ($\times 10^3$), M	(concn)$^{1/2}$ ($\times 10^2$), M	conductance, mmho	spec conductance, mmho cm^{-1}	equiv conductance, mho cm^2 equiv^{-1}
1.001	3.163	23.68	18.72	18.71
2.000	4.473	44.53	35.21	17.60
3.000	5.477	63.41	50.14	16.71
4.001	6.325	80.71	63.82	15.95
5.000	7.071	96.91	76.62	15.32
7.500	8.660	133.87	105.84	14.11
10.000	10.000	166.82	131.90	13.19
20.001	14.142	275.43	217.77	10.89
40.000	20.000	437.70	346.08	8.652
60.000	24.495	559.74	442.57	7.376
80.000	28.284	661.30	552.87	6.536
100.000	31.623	747.96	591.39	5.914

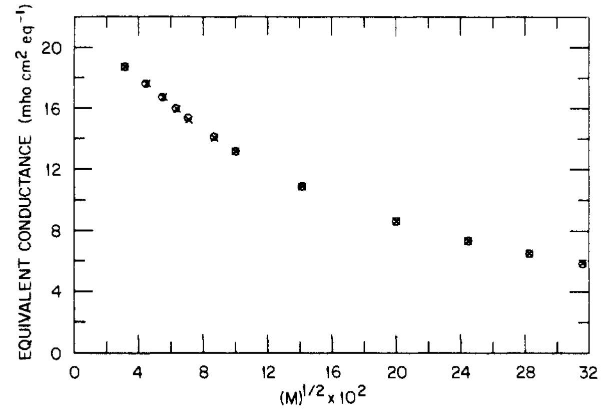

Figure 1. Plot of the equivalent conductance versus the square root of the concentration for the α-phenethylammonium mandelates: ×, (*R*)-(+)-α-phenethylammonium (*R*)-(−)-mandelate; O (*R*)-(+)-α-phenethylammonium (*S*)-(+)-mandelate.

Second, if formation of the hydrogen-bonded complex (AH···B) was not complete then the excess acid or base would serve to shift the equilibrium. Either process would result in a more exothermic heat change for the 1A–2B and 2A–1B titrations than observed for the equimolar titrations.

In water no difference should be observed in the heats of neutralization of diastereomeric acid–base pairs, and none was found for the enthalpy of neutralization of α-phenethylamine by mandelic acid by any of the thermometric methods employed.

Conductance. The conductance of DMSO solutions of the α-phenethylammonium, ephedrinium, and pseudoephedrinium mandelate salts was measured for a series of concentrations ranging from 10^{-3} to 10^{-1} M. Typical data for one of these salts are presented in Table VII. The measured conductance was found to be the same (within the limits of the measurement) for each pair of diastereomers. The appropriate cross-chiral checks, performed for each of the compounds at selected concentrations, were consistent with those reported for the other isomers. A plot of the equivalent conductance versus the square root of the concentration (Figure 1) illustrates the deviation of the conductance behavior at higher concentrations for the mandelate salts.

The concentration-dependent parameters were treated by means of two theoretical equations, the Fuoss–Justice equation[44,45] and the Fuoss-1977 equation,[46] and are given for (*R*)-(+)-α-phenethylammonium (*R*)-(−)-mandelate in Table VIII. Fuoss has set an upper limit on the salt concentration beyond which ion–ion interactions involving three or more ions begin to become important,[47] $C_{max} \simeq 2 \times 10^{-7} D^3$, where *D* is the solvent dielectric

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Table VIII. Concentration-Dependent Parameters Calculated from the Conductance Data for (*R*)-(+)-α-Phenethylammonium (*R*)-(−)-Mandelate in DMSO[a]

concn ($\times 10^4$), M	mho cm^2 equiv^{-1}	Fuoss–Justice calcn			Fuoss-1977 calcn		
		$\Lambda_{calcd} - \Lambda$	α	$\gamma_\pm^2$	$\Lambda_{calcd} - \Lambda$	α	$\gamma_\pm^2$
200.0	10.89	0.063	0.6248	0.6411	0.107	0.6145	0.6429
100.0	13.19	0.008	0.7247	0.6994	0.001	0.7153	0.7007
75.00	14.11	−0.010	0.7632	0.7231	−0.026	0.7545	0.7242
50.00	15.32	−0.017	0.8129	0.7555	−0.036	0.8053	0.7564
40.01	15.95	−0.032	0.8375	0.7727	−0.048	0.8305	0.7734
30.00	16.71	−0.055	0.8661	0.7940	−0.065	0.8600	0.7946
20.00	17.60	−0.031	0.9001	0.8222	−0.028	0.8953	0.8226
10.01	18.71	0.082	0.9424	0.8645	0.109	0.9394	0.8647

[a] Parameters: $\Lambda \equiv$ experimentally observed equivalent conductance; $\Lambda_{calcd} \equiv$ calculated equivalent conductance; $\alpha \equiv$ degree of dissociation of the ion pair into free ions; $\gamma_\pm^2 \equiv$ mean activity coefficient for the free ions.

Table IX. A comparison of Λ_0, K_a, and ΔG_a Calculated by Different Conductance Equations for the Stereoisomeric Mandelate Salts in DMSO[a]

		Fuoss–Justice equation	Fuoss-1977 equation	Onsager limiting law
(*R*)-(+)-α-phenethylammonium (*S*)-(+)-mandelate	Λ_0	21.19 ± 0.08	21.27 ± 0.10	20.85 ± 0.06
	K_a	73.5 ± 2.0	78.0 ± 2.8	49.5 ± 1.5
	ΔG_a	−2.55 ± 0.02	−2.58 ± 0.02	−2.31 ± 0.02
(*R*)-(+)-α-phenethylammonium (*R*)-(−)-mandelate	Λ_0	21.21 ± 0.06	21.29 ± 0.09	20.88 ± 0.06
	K_a	75.0 ± 1.6	79.4 ± 2.4	50.6 ± 1.5
	ΔG_a	−2.56 ± 0.01	−2.59 ± 0.02	−2.32 ± 0.02
(1*R*,2*S*)-(−)-ephedrinium (*S*)-(+)-mandelate	Λ_0	19.48 ± 0.06	19.56 ± 0.09	19.13 ± 0.07
	K_a	89.2 ± 1.8	96.2 ± 3.0	62.2 ± 2.3
	ΔG_a	−2.66 ± 0.01	−2.71 ± 0.02	−2.45 ± 0.02
(1*R*,2*S*)-(−)-ephedrinium (*R*)-(−)-mandelate	Λ_0	19.52 ± 0.03	19.56 ± 0.09	19.29 ± 0.07
	K_a	88.6 ± 1.0	93.9 ± 1.5	66.7 ± 1.3
	ΔG_a	−2.66 ± 0.01	−2.69 ± 0.01	−2.49 ± 0.01
(1*R*,2*R*)-(−)-pseudoephedrinium (*S*)-(+)-mandelate	Λ_0	19.15 ± 0.05	19.23 ± 0.09	18.83 ± 0.06
	K_a	50.9 ± 1.3	57.2 ± 2.2	28.4 ± 1.4
	ΔG_a	−2.33 ± 0.02	−2.40 ± 0.02	−1.98 ± 0.02
(1*S*,2*S*)-(+)-pseudoephedrinium (*S*)-(+)-mandelate	Λ_0	19.24 ± 0.05	19.32 ± 0.09	18.92 ± 0.06
	K_a	51.2 ± 1.3	57.4 ± 2.2	28.8 ± 1.5
	ΔG_a	−2.33 ± 0.02	−2.40 ± 0.02	−1.99 ± 0.02

[a] Parameters: $\Lambda_0 \equiv$ limiting equivalent conductance at infinite dilution (mho cm^2 equiv); $K_a \equiv$ equilibrium constant for ion-pair formation, where $K_a = (1 - \alpha)/\gamma_\pm^2\alpha^2C$; $\Delta G_a \equiv$ free energy of ion-pair formation (kcal mol^{-1}), $\Delta G_a = -1.364 \log K_a$.

Table X. Concentration Dependence of the Proton Chemical Shifts (±0.001 ppm) in DMSO-d_6 at 300 MHz for the α-Phenethylammonium Mandelates $C_6H_5CH^B(CH_3)^ANH_3^+C_6H_5CH^C(OH)COO^-$

assgnt	concn, M							
	0.01	0.02	0.05	0.10	0.20	0.30	0.40	0.50
(*R*)-(+)-α-Phenethylammonium (*R*)-(−)-Mandelate and (*S*)-(−)-α-Phenethylammonium (*S*)-(+)-Mandelate								
A[a]	1.431	1.432	1.432	1.431	1.430	1.430	1.429	1.429
B[b]	4.302	4.296	4.288	4.281	4.273	4.266	4.261	4.257
C[c]	4.522	4.532	4.545	4.558	4.575	4.588	4.598	4.606
(*R*)-(+)-α-Phenethylammonium (*S*)-(+)-Mandelate and (*S*)-(−)-α-Phenethylammonium (*R*)-(−)-Mandelate								
A[a]	1.424	1.424	1.423	1.424	1.423	1.423	1.421	1.421
B[b]	4.307	4.302	4.296	4.293	4.286	4.282	4.278	4.275
C[c]	4.522	4.531	4.545	4.557	4.572	4.584	4.592	4.601

[a] Doublet, $J_{CH} = 6.73 \pm 0.10$ Hz. [b] Quartet, $J_{CH_3} = 6.73 \pm 0.10$ Hz. [c] Singlet.

constant. Here $C_{max} = 2 \times 10^{-2}$ M; therefore, the experimental data were truncated at that value for the calculations. The deviation of the calculated values of the equivalent conductance Λ from the experimental data was consistently smaller with the Fuoss–Justice equation; however, the calculated value of the mean activity coefficient $\gamma_\pm^2$ and the degree of dissociation of the ion pair α were comparable for the two equations. The calculated values of the limiting equivalent conductance Λ_0 and the equilibrium constant K_a for ion-pair formation along with the free energy of ion-pair formation ($\Delta G_a = -1.364 \log K_a$) are compared in Table IX for the various stereoisomeric ammonium mandelate salts. The Onsager limiting law[48] results are also included. One should note the similarity in the parameters calculated by the more sophisticated equations, whereas the limiting law results were not consistent with the other methods used to treat the data. Utilization of the Fuoss–Justice equation to analyze the conductance data resulted in less uncertainty in the calculated equilibrium constants as well as a smaller deviation of the calculated equivalent conductances Λ_{calcd} from the observed values than those obtained via the Fuoss-1977 calculation. Therefore, the results obtained from the Fuoss–Justice calculation were used to analyze the calorimetry data in the preceding section.

Proton Magnetic Resonance. Diastereomeric complexes or ion pairs formed via nonbonding interactions between chiral molecules in solution have been shown to have nonequivalent ^{1}H NMR spectra in inert nonpolar solvents.[49] The spectral nonequivalence arises from the formation of short-lived solvates, which exist in different conformations. If, in addition, an equilibrium exists between the free and associated chiral species in solution, then

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Table XI. Concentration Dependence of the Proton Chemical Shifts (±0.001 ppm) in DMSO-d_6 at 300 MHz for the Ephedrinium Mandelates $C_6H_5CH^E(OH)CH^C(CH_3{}^A)^+NH_2CH_3{}^BC_6H_5CH^D(OH)COO^-$

	concn, M						
assgnt	0.01	0.02	0.05	0.10	0.20	0.30	0.40
(1*R*,2*S*)-(−)-Ephedrinium (*R*)-(−)-Mandelate and (1*S*,2*R*)-(+)-Ephedrinium (*S*)-(+)-Mandelate							
A[a]	0.864	0.855	0.856	0.849	0.848	0.848	0.847
B[b]	2.545	2.544	2.542	2.539	2.535	2.534	2.532
C[c]	3.212	3.229	3.235	3.244	3.246	3.244	3.247
D[d]	4.556	4.574	4.603	4.620	4.637	4.653	4.667
E[e]	5.002	5.028	5.056	5.078	5.094	5.104	5.114
(1*R*,2*S*)-(−)-Ephedrinium (*S*)-(+)-Mandelate and (1*S*,2*R*)-(+)-Ephedrinium (*R*)-(−)-Mandelate							
A[a]	0.864	0.859	0.862	0.855	0.854	0.854	0.853
B[b]	2.550	2.549	2.548	2.546	2.544	2.543	2.541
C[c]	3.222	3.231	3.235	3.243	3.245	3.244	3.246
D[d]	4.554	4.577	4.599	4.618	4.636	4.651	4.664
E[e]	5.001	5.026	5.049	5.069	5.086	5.095	5.104

[a] Doublet, J_{CH} = 6.73 ± 0.10 Hz. [b] Singlet. [c] Doublet of quartet, J_{CH_3} = 2.48, 6.73 ± 0.10 Hz. [d] Singlet. [e] Doublet, J_{CH} = 2.48 ± 0.10 Hz.

Table XII. Concentration Dependence of the Proton Chemical Shifts (±0.001 ppm) in DMSO-d_6 at 300 MHz for the Pseudoephedrinium Mandelates $C_6H_5CH^D(OH)CH^C(CH_3{}^A)^+NH_2CH_3{}^BC_6H_5CH^E(OH)COO^-$

	concn, M						
assgnt	0.01	0.02	0.05	0.10	0.20	0.30	0.40
(1*S*,2*S*)-(+)-Pseudoephedrinium (*R*)-(−)-Mandelate and (1*R*,2*R*)-(−)-Pseudoephedrinium (*S*)-(+)-Mandelate							
A[a]	0.858	0.852	0.847	0.841	0.834	0.833	0.833
B[b]	2.504	2.501	2.501	2.498	2.496	2.494	2.494
C[c]	3.113	3.111	3.125	3.129	3.138	3.142	3.142
D[d]	4.428	4.440	4.457	4.468	4.480	4.488	4.492
E[e]	4.546	4.565	4.585	4.602	4.622	4.638	4.651
(1*S*,2*S*)-(+)-Pseudoephedrinium (*S*)-(+)-Mandate and (1*R*,2*R*)-(−)-Pseudoephedrinium (*R*)-(−)-Mandelate							
A[a]	0.860	0.857	0.853	0.848	0.843	0.842	0.841
B[b]	2.500	2.500	2.501	2.498	2.497	2.494	2.492
C[c]	3.106	3.111	3.123	3.128	3.134	3.137	3.138
D[d]	4.429	4.442	4.461	4.473	4.486	4.495	4.500
E[e]	4.548	4.561	4.582	4.599	4.617	4.633	4.646

[a] Doublet, J_{CH} = 6.73 ± 0.10 Hz. [b] Singlet. [c] Doublet of quartets, J_{CH} = 9.20 ± 0.10 Hz, J_{CH_3} = 6.73 ± 0.10 Hz. [d] Doublet, J_{CH} = 9.20 ± 0.10 Hz. [e] Singlet.

Table XIII. Chiral Discrimination in the Proton Magnetic Resonance Spectra of 0.40 M α-Phenethylammonium, Ephedrinium, and Pseudoephedrinium Mandelate Salts in DMSO-d_6

salt	assgnt[a]	Δδ[b] (300 MHz)	concn effect[c]	mult[d] (600 MHz)	Δδ[b] (600 MHz)
α-phenethylammonium mandelates	A	−0.008	d	doubled	−0.008
	B	+0.018	d	doubled	+0.018
	C	−0.005	i	doubled	−0.006
ephedrinium mandelates	A	−0.006	d	doubled	−0.008
	B	−0.009	d	doubled	−0.009
	C	+0.001	i		
	D	+0.003	i		
	E	+0.010	i	doubled	+0.009
pseudoephedrinium mandelates	A	+0.008	d	doubled	+0.009
	B	−0.002	d		
	C	−0.004	i	doubled	−0.005
	D	+0.008	i	doubled	+0.007
	E	−0.005	i	doubled	−0.006

[a] The assignments are the same as those given in Tables X–XII for the alkyl protons. [b] The difference in the chemical shifts for the diastereomeric mandelate salts given in ppm. $\Delta\delta \equiv \delta_s - \delta_0$ where δ_s is the chemical shift for the salt in which the signs of rotation are the same and δ_0 is the chemical shift for the salts in which the signs of rotation are in the opposite direction. [c] The effects of increasing concentration on the position of the proton chemical shifts: d = decreases with increasing concentration; i = increases with increasing concentration. [d] The observed multiplicity for each signal at 600 MHz for mixtures of diastereomeric salts. For further discussion of this phenomenon see the text.

the chiral discrimination or magnetic nonequivalence in the ^1H NMR spectra of the diastereomeric solvates should be concentration dependent.

The concentration dependence of the chemical shifts at 300 MHz in DMSO-d_6 for the alkyl protons of α-phenethylammonium, ephedrinium, and pseudoephedrinium mandelate salts are given in Tables X–XII, respectively. The signals from the hydroxyl and ammonio protons were broad bands occurring at about 4.0 and 8.0 ppm, respectively, for all of the salts. The aromatic protons gave rise to complex multiplets (≃7.1–7.4 ppm), which were not easily analyzable at 300 MHz. Analysis of the 600-MHz spectra in this region will be discussed later in this section.

Enantiomeric mandelate salts gave identical chemical shifts; however, differences were observed between the diastereomers of all of the salts. A summary of the observed nonequivalences in the side-chain proton resonances for 0.40 M solutions of the mandelates as well as the effects of increasing concentration on the position of each of the resonances is given in Table XIII. The magnetic nonequivalence Δδ is defined as the chemical shift of the salt in which both the acid and the base rotate light in the same direction, i.e., the (+)B(+)A or (−)B(−)A salt, minus the chemical shift of the salt in which the signs of the rotations of the base and the acid are different, i.e., the (+)B(−)A or (−)B(+)A salt. The observed difference Δδ in the spectra of the diastereomeric salts increased as the concentration was increased for each of the observed discriminations in the proton chemical shifts.

The concentration dependence for those resonances that displayed the largest changes in chemical shift with increasing

Table XIV. X-ray Crystallographic Parameters for Ephedrinium and Pseudoephedrinium Mandelate Salts[a]

salt	**1**	**2**	**3**	**4**
formula	$C_{18}H_{23}NO_4$	$C_{18}H_{23}NO_4$	$C_{18}H_{23}NO_4$	$C_{18}H_{23}NO_4$
fw	317.39	317.39	317.39	317.39
cryst syst	monoclinic	orthorhombic	orthorhombic	orthorhombic
space gp	C_2 (C_2^3)	$P2_12_12_1$ (D_2^4)	$P2_12_12_1$ (D_2^4)	$P2_12_12$(D_2^4)
unit cell dimens				
a, Å	18.158 (9)	8.898 (4)	13.394 (7)	8.808 (4)
b, Å	6.515 (3)	27.205 (14)	18.791 (9)	27.342 (14)
c, Å	13.913 (7)	7.241 (4)	7.028 (4)	7.261 (4)
α, deg	90.00	90.00	90.00	90.00
β, deg	92.14	90.00	90.00	90.00
γ, deg	90.00	90.00	90.00	90.00
V, Å^3	1645	1753	1769	1749
d, g·cm^{-3}	1.282	1.203	1.192	1.206
Z	4	4	4	4

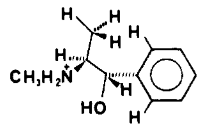
[a] **1**, (1*S*,2*R*)-(+)-ephedrinium (*S*)-(+)-mandelate; **2**, (1*S*,2*R*)-(+)-ephedrinium (*R*)-(−)-mandelate; **3**, (1*R*,2*R*)-(−)-pseudoephedrinium (*R*)-(−)-mandelate; **4**, (1*S*,2*S*)-(+)-pseudoephedrinium (*R*)-(−)-mandelate.

concentration is consistent with an equilibrium situation. At higher concentrations the chemical shifts approach individual limiting values, while at lower concentrations the chemical shifts for diastereomers converge. Significant curvature was also observed in the plots of concentration versus proton chemical shifts at lower concentrations. If indeed a simple two-species equilibrium exists in solution, then a plot of the concentration dependence of any two resonances versus one another for a specific salt should result in a straight line. Excellent linear correlations were found for the two most concentration-dependent chemical shifts for each of the mandelate salts, thus providing further evidence for a predominant two-species equilibrium in DMSO solutions of these salts. Attempts at obtaining the equilibrium constants for ion-pair formation from the curvature of the concentration dependence of the chemical shifts failed to yield meaningful results because of the small change in the chemical shifts with increasing concentration and because of the strong correlation between the chemical shifts for the ion pair and the free ions.

All of the observed differences in the chemical shifts of diastereomeric ion pairs at 300 MHz were small, albeit significant, given the standard deviation in the measurements (±0.001 ppm). As an important cross-check on these results, the following experiments were performed at 600 MHz in DMSO-d_6 for all of the salts. First, a spectrum of a single diastereomer of each of the salts was obtained at a concentration of 0.40 M. Second, the spectrum of a mixture of two diastereomeric salts was obtained. This mixture was composed of two diastereomers that contained different enantiomers of the base but the same enantiomer of the acid. For the third experiment, a mixture of two diastereomers was used in which only a single enantiomer of the base was present while both enantiomers of the acid were present in the sample. The second experiment should show a doubling of the multiplicity of those proton resonances of the base that display chiral discrimination, while the third experiment should show which resonances of the acid are doubled by chiral discrimination between diastereomeric ion pairs. The total concentration of salt present in each mixture was constant (0.40 M), but an unequal concentration of the two components was used in order to ascertain not only the degree of nonequivalence but also the relative position of the resonances for each diastereomeric salt. The chemical shifts (ppm) of the side-chain protons at 600 MHz were the same as those observed for a 0.40 M solution of the salt at 300 MHz. The proton resonances for which a doubling in the multiplicity of the signal was observed at 600 MHz when a mixture of two diastereomers was utilized are summarized in Table XIII. Even for those resonances that displayed no actual doubling of the signal for mixtures of diastereomers a distinct broadening of the resonance signal was observed. The degree and relative sense of the nonequivalence were in all cases consistent with those observed at 300 MHz.

The assignment of the particular resonances to either the acid or the base was accomplished by observing the effects of mixtures of diastereomers on the spectra. Those mixtures containing both enantiomers of the acid but only a single enantiomer of the base displayed a doubling of the resonances due to the phenyl protons of the acid. The same effect on the phenyl proton resonances of the base was observed in the mixture that contained both enantiomers of the base and only a single enantiomer of the acid. The observed chiral discriminations in the proton resonances of the phenyl rings are also indicative of an interaction between the π systems of the ammonium and mandelate ions in solution. These types of interactions are also observed in the crystal structures of the mandelate salts.

The aromatic region of the PMR spectra for ephedrine and pseudoephedrine could only be simulated with the LAOCOON III program by assuming that the ortho protons for these bases were not magnetically equivalent. This can be rationalized if a buttressing effect of the β-methyl group of the ephedrine bases prevented free rotation of the phenyl ring so that one of the ortho aromatic protons of the base is nested between the C–CH$_3$ protons.



Although such slow rotation is unprecedented, and is therefore unlikely, it corresponds to the orientation of the aromatic ring as observed in the crystal structures for the ephedrinium and pseudoephedrinium mandelates (see the following section).

X-ray Crystallography. Crystallographic data, unit-cell parameters, and space groups for the ephedrinium and pseudoephedrinium mandelates are provided in Table XIV. The densities of the unit cells, calculated from the molecular weights of the salts and the cell dimensions, are also given. The difference in the densities of the diastereomeric ephedrinium mandelates is noteworthy. The more densely packed (1*S*,2*R*)-(+)-ephedrinium (*S*)-(+)-mandelate also has a higher melting point (165.4–167.0 °C) and a more endothermic heat of fusion (ΔH_{fus} = 12.5 ± 0.5 kcal/mol) than its diastereomer (1*S*,2*R*)-(+)-ephedrinium (*R*)-(−)-mandelate (mp 111.2–111.9 °C; ΔH_{fus} = 6.71 ± 0.26 kcal/mol).

Very extensive and complex hydrogen-bonding interactions were found in all of the crystal structures.[50] The solid-state conformations, hydrogen-bonded interactions, and atom-numbering schemes for the ephedrinium and pseudoephedrinium mandelate ion pairs are shown in Figure 2–5. In addition to the interactions between ammonio and carboxylate groups, both the ephedrine bases and mandelic acid possess hydroxyl groups that may act as hydrogen bond donors or acceptors in the formation of intra- or intermolecular hydrogen bonds. A larger number of hydrogen-bonding interactions were found in the most densely packed (1*S*,2*R*)-(+)-ephedrinium (*S*)-(+)-mandelate, which has a much higher melting point and a more endothermic heat of fusion than any of the other salts. Another unusual feature of the crystal structure of this salt is the presence of a bifurcated hydrogen bond

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[50] Wallwork, S. C. *Acta Crystallogr.* **1962**, *15*, 758.

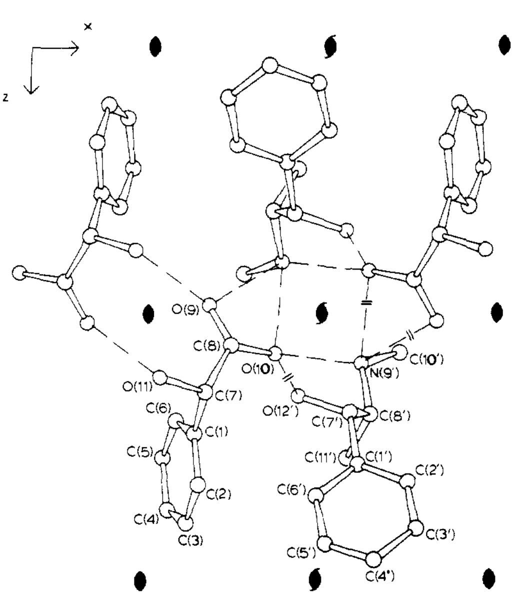

Figure 2. Atom-numbering scheme and solid-state conformation of a (1*S*,2*R*)-(+)-ephedrinium (*S*)-(+)-mandelate ion pair. Hydrogen bonds are denoted by broken lines where --- and || indicate interactions involving ions that differ by unit translation along *b*.

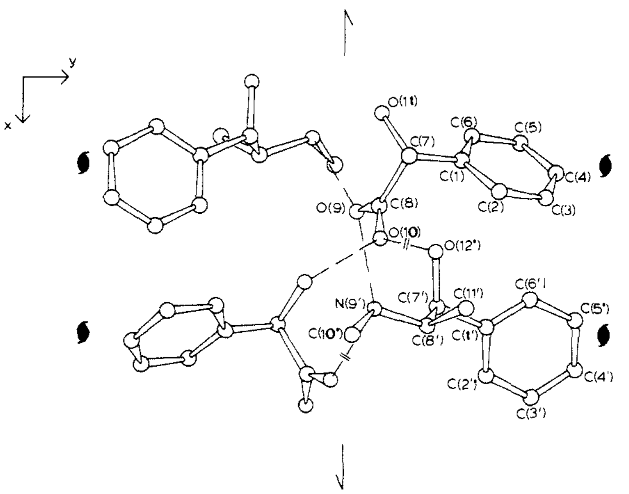

Figure 3. Atom-numbering scheme and solid-state conformation of a (1*S*,2*R*)-(+)-ephedrinium (*R*)-(−)-mandelate ion pair. Hydrogen bonds are denoted by broken lines where --- and || indicate interactions involving ions that differ by unit translation along *c*.

between the two carboxyl oxygens of a single mandelate ion and one of the ammonio protons of a neighboring ephedrinium ion.

Although all of the salts are formally capable of possessing intramolecular O(hydroxyl)···O(carboxyl) or O(hydroxyl)···N-(ammonium) hydrogen bonds, respectively, in the anions and cations, only the former was observed and was restricted to the pseudoephedrinium mandelate salts. Even for those salts that lack an OH···N hydrogen bond the hydroxyl oxygen consistently lay gauche to the N atom (the O–C–C–N dihedral angle range was 50–62°). Similarly, the acid hydroxyl atom is always rotated less than 40° out of the plane of the carboxylate group.

Discussion

This paper is concerned with the relationships between structure and energetics for various stages of aggregation of ions as probed by subtle variations in stereochemistry. In order to bring out the most significant effects of chiral discrimination on the different processes, the results will be discussed first in general terms for each thermodynamic property and then the structural evidence for each set of diasteromeric salts will be presented and related, wherever feasible, to the thermodynamic data.

Energetics of Association and Proton Transfer. The transfer of a proton from an acid (AH) to a base (B) in solvent (S)

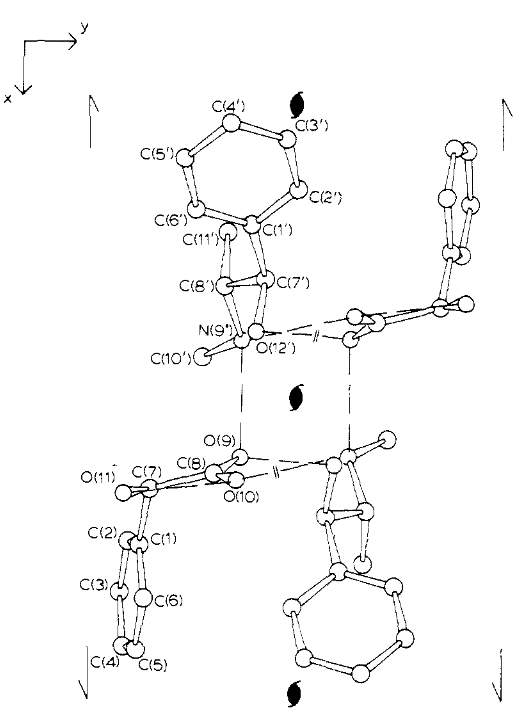

Figure 4. Atom-numbering scheme and solid-state conformation of a (1*R*,2*R*)-(−)-pseudoephedrinium (*R*)-(−)-mandelate ion pair. Hydrogen bonds are denoted by broken lines where --- and || indicate interactions involving ions that differ by unit translations along *c*.

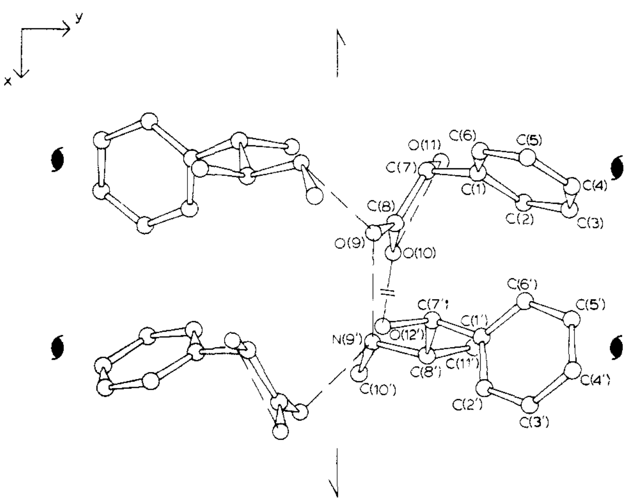

Figure 5. Atom-numbering scheme and solid-state conformation of a (1*S*,2*S*)-(+)-pseudoephedrinium (*R*)-(−)-mandelate ion pair. Hydrogen bonds are denoted by broken lines where --- and || indicate interactions involving ions that differ by unit translations along *c*.

proceeds through a series of equilibria (eq 7). The principal species in any solvent depend primarily on their hydrogen-bonding abilities and that of the solvent and also its dielectric constant. Triple ions ($A^-BH^+A^-$, $BH^+A^-BH^+$), dimers (or higher aggregates) of ion pairs ($2A^-BH^+ \rightleftharpoons (A^-BH^+)_2$), and homo-hydrogen-bonded ion pairs[39,43,51] ($AH + A^-BH^+ \rightleftharpoons AHA^-BH^+$ or $B + A^-BH^+ \rightleftharpoons A^-BH^+B$) may also be present in solvents of low ϵ depending on the dipole moment of the ion pairs, the ion size (aggregation involving one large and one small ion being especially favored), the concentration, and the presence of excess acid or base.

A representative energy–reaction coordinate diagram for the interaction of an acid and base is illustrated in Figure 6. The hydrogen-bonded complex and ion pair may exist separately, or a single species with a double minimum may occur. The enthalpies

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(51) Coetzee, J. F.; Padmanabhan, G. R.; Cunningham, H. P. *Tatlanta*, **1964**, *11*, 93. Coetzee, J. F.; Padmanabhan, G. R. *J. Am. Chem. Soc.* **1964**, *87*, 5005. Coetzee, J. F.; Padmanabhan, G. R. *J. Phys. Chem.* **1965**, *69*, 3193. Mooney, W. S.; Coetzee, J. F. *J. Phys. Chem.* **1962**, *66*, 89.

Table XV. Thermochemical Properties (kcal mol^{-1}) for Reaction of Chiral Bases with Mandelic Acid for Solutions in DMSO at 25 °C and Fusion of the Corresponding Salts[a]

	α-phenethylamine		ephedrine		pseudoephedrine	
	(*R*)-(+)/(*S*)-(+) or (*S*)-(−)/(*R*)-(−)	(*R*)-(+)/(*R*)-(−) or (*S*)-(−)/(*S*)-(+)	(1*R*,2*S*)-(−)/(*R*)-(−) or (1*S*,2*R*)-(+)/(*S*)-(+)	(1*R*,2*S*)-(−)/(*S*)-(+) or (1*S*,2*R*)-(+)/(*R*)-(−)	(1*R*,2*R*)-(−)/(*R*)-(−) or (1*S*,2*S*)-(+)/(*S*)-(+)	(1*R*,2*R*)-(−)/(*S*)-(+) or (1*S*,2*S*)-(+)/(*R*)-(−)
ΔH^1_{rxn}	−7.40 ± 0.04	−7.62 ± 0.03	−7.69 ± 0.03	−7.47 ± 0.03	−6.68 ± 0.03	−6.90 ± 0.03
ΔH^2_{rxn}	−9.04 ± 0.04	−9.49 ± 0.05	−9.17 ± 0.05	−8.78 ± 0.04	−8.09 ± 0.03	−8.44 ± 0.03
ΔH^1_{dissoc}	3.95 ± 0.07	4.49 ± 0.09	3.72 ± 0.05	3.36 ± 0.03	3.44 ± 0.06	3.73 ± 0.05
ΔH^2_{dissoc}	4.55	5.20	4.50	4.05	3.98	4.38
ΔH_{pt}	−10.47	−11.13	−10.48	−9.96	−9.59	−10.09
ΔH_{soln}	7.20 ± 0.09	8.80 ± 0.08	9.51 ± 0.06	9.51 ± 0.05	5.83 ± 0.07	7.22 ± 0.15
ΔH_{fus}	6.22 ± 0.26	11.27 ± 0.41	12.36 ± 0.43	6.61 ± 0.20	5.82 ± 0.12	3.79 ± 0.48

[a] Parameters: ΔH^1_{rxn}, overall molar heat of reaction from the dual titration of equimolar acid and base into pure DMSO; ΔH^2_{rxn}, overall molar heat of reaction from the dual titration of equimolar acid and base into salt solution; ΔH^1_{dissoc}, heat required to separate a mole of ion pairs to free ions from the titration of salt solutions into pure DMSO; ΔH^2_{dissoc}, heat required to separate a mole of ion pairs to free ions calculated from ΔH^1_{rxn} and ΔH^2_{rxn}; ΔH_{pt}, molar heat of proton transfer from acid to base calculated from ΔH^1_{rxn} and ΔH^2_{rxn}; ΔH_{soln}, molar heat of solution of the solid salts to free ions in DMSO; ΔH_{fus}, from DSC.

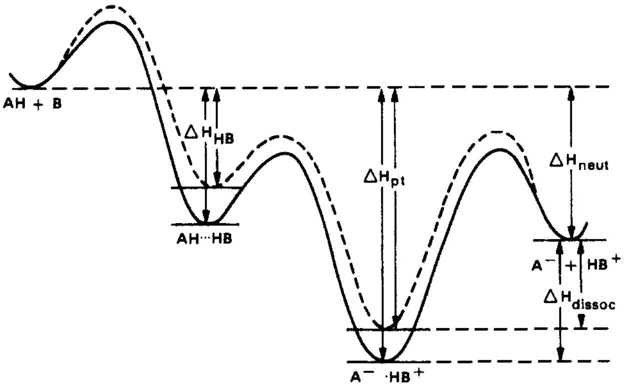

Figure 6. Typical energy–reaction coordinate diagram for the interaction of an acid (AH) and a base (B). The species AH···B and A$^-$···HB$^+$ may exist separately, or a single species with a double-minimum hydrogen bond may also be representative. The relationship of a diastereomeric acid–base pair is represented by a dashed line. Key: ΔH_{HB}, heat of hydrogen-bond formation between the acid and base; ΔH_{pt}, heat of proton transfer between the acid and base; ΔH_{neut}, heat of formation of free ions from the acid and base; ΔH_{dissoc}, heat of dissociation of the ion pair to free ions.

of hydrogen-bond formation (ΔH_{HB}) and proton transfer (ΔH_{pt}) are exothermic, while the enthalpy of dissociation (ΔH_{dissoc}) is endothermic. The overall heat of neutralization of the acid and base to form free ions is exothermic in this particular example.

The dashed line represents the behavior of a system that is diastereomeric to that for the solid line. It is especially important to note that the energies for the two initial states, the enantiomers of the free acid and base, are the same and likewise for the energies of the final states, the free enantiomeric ions. Thus, diastereomeric energy differences only arise for the intermediate complexes due to the interaction between the two chiral species. The observed heats of interaction between chiral acids and bases in solution will differ for diastereomeric acid–base pairs only if there is significant interaction between the acid and base either as the nonionic hydrogen-bonded complex or as the ion pair.

Three solvents were utilized in this investigation, water, DMSO, and dioxane. In aqueous media one would expect the heats of neutralization for diastereomeric acid–base pairs to be identical since the initial states (solvated acid and base) and the final states (solvated ions) are the same. The differences in the pK_a's of mandelic acid[52] (3.4) and the conjugate acids of ephedrine[53,54] (9.5), pseudoephedrine[53,54] (9.7), and α-phenethylamine[55] (9.2) are large enough to ensure complete neutralization of the acid and bases to give the free ions in aqueous media. For aprotic solvents such as dioxane and DMSO, the basicity of the solvent as well as its polarizability are important factors in determining the degree of solvation of the various species in solution. DMSO is more "basic" than dioxane both in the sense of conversion to an oxonium ion by proton transfer and as a hydrogen bond acceptor.[56] Ion pairing has been shown to be significant for a variety of anions and cations in DMSO,[39-41] which proved to be the more suitable solvent for investigating the energetics of ion-pair association. Conductance and calorimetric measurements were utilized to dissect the observed heats of reaction into the heat of proton transfer and the heat of ion-pair dissociation.

A detailed analysis of the structural and energetic relationships in dioxane was not possible because of solubility problems. Thermometric titrations of α-phenethylamine with mandelic acid (Table VI) show dramatic dependence on stoichiometry, but stereochemical effects are small.

The summarized thermochemical data in Table XV show that in all cases where enantiomers have been compared, the results agree well within a rather small experimental error, while in every case where diastereomers are compared they differ well outside of the experimental error. A schematic representation of the results for the α-phenethylammonium mandelates is shown in Figure 7. The most important measurements for considering association in solution are the heats of proton transfer and ion-pair dissociation as well as the heats of reaction from acid–base titrations. Most of these measurements have a standard deviation of less than 50 cal/mol. Heats of fusion are less clearly defined both because of less precise instrumentation and because some DSC thermograms did not give sharp melting peaks due to complicated premelting transitions. Since the largest diastereomeric differences were seen in the heats of fusion, their larger experimental errors are not a source of confusion in making comparisons.

Heats of Fusion and Heats of Solution. Maximum interactions between cations and anions are to be expected in the crystalline state and should be revealed when the crystal structure is destroyed. Accordingly, large differences were observed both in the heats of fusion and heats of solution for diastereomeric salts (Table XV). The most striking numerical differences are in the heats of fusion between the two diastereomeric α-phenethylammonium mandelates or between the two ephedrinium mandelates. The idea that diastereomeric salts should have different crystallization properties is familiar since it is the basis of one of the three classical methods of resolution.[19] Nonetheless, the variation of 5–6 kcal/mol between diastereomers is large and interesting with few published precedents.[23] Differences in the heats of solution for diastereomeric salts are in the same direction as those differences in the heats of fusion. As we shall see, there are significant differences in the structures and packing of the crystals of those diastereomeric salts that display the largest differences in ΔH_{fus}

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[52] Petrov, S. M.; Umanski, Y. I.; Mullin, I. F.; Tertichniyi, A. N. *Russ. J. Phys. Chem.* (*Engl. Transl.*) **1973**, *47*, 363.

[53] Raffa, R. J.; Stern, M. J.; Malspeis, L. *Anal. Chem.* **1968**, *40*, 70.

[54] Everett, D. H.; Hyne, J. B. *J. Chem. Soc.* **1958**, 1636.

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[56] Arnett, E. M.; Mitchell, E. J.; Murty, T. S. S. R. *J. Am. Chem. Soc.* **1974**, *96*, 3875.

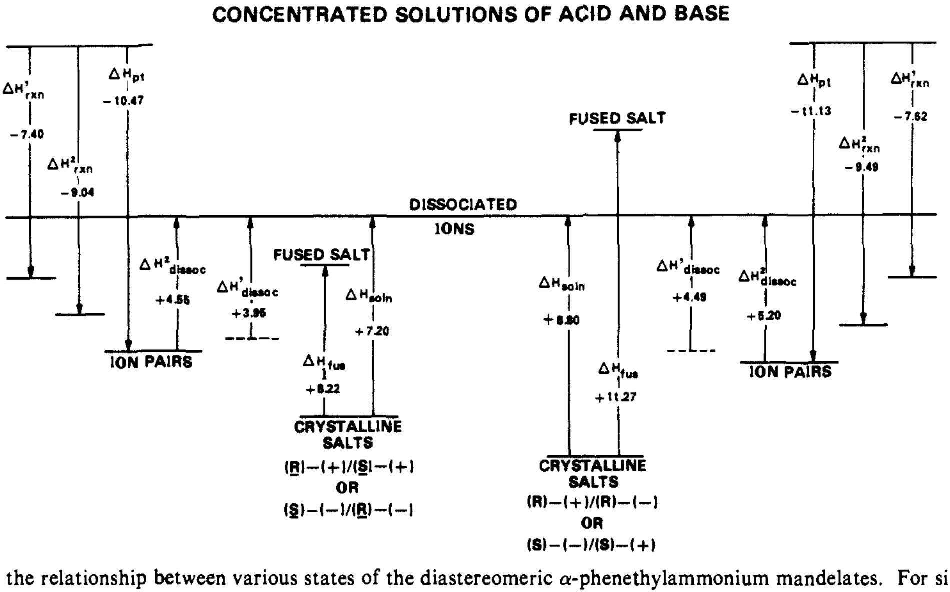

Figure 7. Diagram of the relationship between various states of the diastereomeric α-phenethylammonium mandelates. For simplicity only average values of the various enthalpies for enantiomers are given. The enthalpy terms are defined in Table XV.

and ΔH_{soln}. Thus, many of the differences in the ionic forces that produced the diastereomeric effect in the crystals are carried over to differentiate the melts. The possible use of chiral fused salts as media for stereospecific reactions or the resolution of enantiomers is unprecedented to our knowledge and worth looking into.

Heats of Reaction and Proton Transfer. The terms referred to as the heats of reaction (ΔH_{rxn}) were obtained by adding equally concentrated solutions of acid and base from separate syringe pumps at the same rate into a calorimeter full of pure, dry solvent (ΔH^1_{rxn}) or into a solution of the corresponding salt (ΔH^2_{rxn}). Thus, the stoichiometric equivalency of the two reactants is maintained throughout the titration. The heat of reaction applies to the equilibria shown in eq 9, which can be dissected into the

$$AH + B \overset{\Delta H_{pt}}{\rightleftharpoons} A^-{\cdots}HB^+ \overset{\Delta H_{dissoc}}{\rightleftharpoons} A^- + HB^+ \qquad (9)$$

following terms: the heats of dilution of mandelic acid and the base from their initial concentrations in their syringe pumps to the various concentrations covered by the titration; the heat of proton transfer (ΔH_{pt}) represented by the first equilibrium; the heats of dilution of the ions and ion pairs; the heats of dissociation of the ion pairs represented by the second equilibrium.

Heats of dilution of the acid and base were measured easily and are small in all cases (<0.10 kcal/mol). However, there is no direct way to determine experimentally the heats of dilution of the ions and ion pairs separately. At dilutions that are high enough to produce complete ionization, the heat change for diluting the ions further is ipso facto too small to measure. At high concentrations where association is nearly complete, dilution of the ion pair results in dissociation so that the heat of dilution of the ion pairs themselves cannot be found. These terms are also probably small and should be identical for enantiomeric ions. The heats of dilution of diastereomeric ion pairs should also be quite similar. Thus, our inability to correct the observed heats of reaction for these dilution terms should not affect discrimination of differential diastereomeric interactions whatever might be the errors in the absolute values of the heats of proton transfer and the heats of dissociation.

The heats of dissociation (ΔH^2_{dissoc}) and the heats of proton transfer (ΔH_{pt}) are obtained from the heats of reaction by utilizing two simultaneous equations (eq 10 and 11). The heats of proton

$$\Delta H^1_{rxn} = \Delta H_{pt} + \alpha_1 \Delta H^2_{dissoc} \qquad (10)$$

$$\Delta H^2_{rxn} = \Delta H_{pt} + \alpha_2 \Delta H^2_{dissoc} \qquad (11)$$

transfer derived in this manner were all exothermic and on the order of 10–11 kcal/mol. These heats are consistent with the average range of hydrogen-bonding and proton-transfer enthalpies.[57] The heats of dissociation of the ion pairs are all endothermic and on the order of 3–5 kcal/mol. Further discussion of the heats of dissociation is given in the next section.

Table XVI. Diastereomeric Discrimination (kcal mol^{-1}) in the Thermometric Parameters for the Ammonium Mandelate Salts in DMSO at 25 °C

parameters[a]	α-phenethylammonium mandelate	ephedrinium mandelate	pseudoephedrinium mandelate
$\delta\Delta H^1_{rxn}$	0.22	0.22	0.22
$\delta\Delta H^2_{rxn}$	0.45	0.39	0.35
$\delta\Delta H^1_{dissoc}$	0.50	0.41	0.31
$\delta\Delta H^2_{dissoc}$	0.70	0.54	0.41
$\delta\Delta H_{pt}$	0.69	0.44	0.53
$\delta\Delta H_{soln}$	1.60	3.03	1.39
$\delta\Delta H_{fus}$	5.05	5.75	2.03

[a] The thermometric parameters are defined in Table XV.

Table XVI summarizes the diastereomeric discrimination factors for the various processes in solution. All of them lie between 0.20 and 0.70 kcal/mol, which is enough to affect product distributions for stereoselective reactions going through ion-pair intermediates.

All of our evidence points to a simple equilibrium between ion pairs and free ions for the mandelate salts in DMSO. However, results from pumping different ratios of α-phenethylamine and mandelic acid into dioxane suggest strongly that a variety of homoconjugate ion pairs (AHA^-HB^+ or BHB^+A^-) may also be formed in that solvent under stoichiometrically nonequivalent conditions. The results may be taken as due to the superior ability of DMSO to accept hydrogen bonds as well as its higher dielectric constant.

Heats of Dissociation. All 12 of the ammonium mandelate salts in this study have similar endothermic heats of dissociation—between 4.16 and 5.67 kcal/mol, which suggests that similar forces—probably a simple hydrogen bond—are holding all of the ion pairs together and that probably no major changes in conformation or structure occur in any of them on going from the ion pairs to dissociated ions (see X-ray and NMR data below). The driving force of dissociation is thus entropic.

Conductance and Thermodynamics of Ion Pairing. The concentration dependence of conductance and spectral data in DMSO is fitted well by a simple two-state equilibrium between ion pairs

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(57) Pimentel, G. C.; McClellan, A. L. *The Hydrogen Bond*; W. H. Freeman: San Francisco, CA, 1960. Joesten, M. D.; Schaad, L. J. *Hydrogen Bonding*; Marcel Dekker: New York, NY, 1974. Vinogradov, S. N.; Linnel, R. W. *Hydrogen Bonding*; Van Nostrand Rheinhold: New York, NY, 1971. Caldin, E. F.; Gold, V. *Proton-Transfer Reactions*; Chapman and Hall: London, England, 1975.

Table XVII. Thermodynamic Parameters for Ion-Pair Association of Ammonium Mandelate Salts in DMSO at 25 °C

	thermodynamic parameters[a]			
	K_a, mol^{-1}	$-\Delta G_a^0$, kcal mol^{-1}	$-\Delta H_a^0$, kcal mol^{-1}	$-\Delta S_a^0$, cal·deg^{-1} mol^{-1}
α-Phenethylammonium Mandelates				
(+)B(+)A and (−)B(−)A	73.5	2.56	4.97	8.09
(+)B(−)A and (−)B(+)A	75.0	2.56	5.67	10.44
Ephedrinium Mandelates				
(+)B(+)A and (−)B(−)A	88.6	2.66	4.70	6.85
(+)B(−)A and (−)B(+)A	89.2	2.66	4.16	5.03
Psuedoephedrinium Mandelates				
(+)B(+)A and (−)B(−)A	51.2	2.33	4.48	7.21
(+)B(−)A and (−)B(+)A	50.9	2.33	4.89	8.59

[a] K_a = equilibrium constant for ion-pair formation; $\Delta G_a^0 = -1.364 \log K_a$, free energy of ion-pair formation; $\Delta H_a^0 = \Delta H^2{}_{\mathrm{dissoc}}$, enthalpy of association of free ions to the ion pair. $\Delta S_a^0 = (\Delta H_a^0 - \Delta G_a^0)/T$, entropy of ion-pair association where T is 298 K.

and dissociated ions. In Table XVII the association constants are presented along with the standard free energies ΔG_a°, enthalpies ΔH_a°, and entropies ΔS_a° for ion-pair formation.

Diastereomeric salts derived from enantiomeric bases in each case have exactly the same association constants and free energies of association. Accordingly, the observed diastereomeric differences in heats of ion pairing may be considered rather simply in terms of differences in the strengths of bonding between ions and directly compensating entropy losses with possible contributions from solvation enthalpies and entropies. Insofar as the present study is a prototype for considering the energetics of chiral discrimination, the enthalpy/entropy compensation to minimize free energy changes is important.

Crystal Structures of the Diastereomeric Ion Pairs. Single-crystal X-ray analyses were performed on (1*S*,2*R*)-(+)-ephedrinium (*S*)-(+)-mandelate (**1**), (1*S*,2*R*)-(+)-ephedrinium (*R*)-(−)-mandelate (**2**), (1*R*,2*R*)-(−)-pseudoephedrinium (*R*)-(−)-mandelate (**3**), and (1*S*,2*S*)-(+)-pseudoephedrinium (*R*)-(−)-mandelate (**4**). Packing diagrams and Newman projections with torsion angles are available.[15] The crystal structures of the α-phenethylammonium mandelates were determined previously by Brianso.[14]

The conformations of the ephedrinium cations of **1** and **2** are very similar with respect to interatomic distances, bond angles, and torsion angles. The bond lengths of the ephedrinium cations in these two salts are also very similar to those that have been found for the ephedrinium cations in other salts.[58] The only significant difference between the mandelate salts and other ephedrinium salts is in the torsion angle Ψ (defined as C(8′)–C(7′)–O(12′)–H(12′)). This seems reasonable since Ψ would depend largely upon hydrogen bonding to or from the hydroxyl group. Thus, one would expect the particular anion involved to impose some constraints on the direction of the O–H bond. The conformations of the pseudoephedrinium cations in **3** and **4** are likewise very similar not only to each other but also to the conformation adopted by the free base and the salt pseudoephedrine hydrochloride.[59]

Corresponding bond lengths and angles of the ephedrinium and pseudoephedrinium cations in **1**–**4** are similar, but the torsion angles differ significantly. The similarities between the ephedrinium and pseudoephedrinium cations are noteworthy if one considers the differences found in the hydrogen bonding of the four salts. It can, therefore, be said that, as in the case of other ephedrine[58] and pseudoephedrine[59] salts, hydrogen bonding from the amine to the counterion seems to have little effect upon the solid-state conformations of ephedrine or pseudoephedrine.

The only significant difference in the bond lengths of the four mandelate anions involves the C–O bonds of the carboxyl group. The C(sp^2)–OH and C(sp^2)=O bond lengths for mandelic acid[60] are 1.314 and 1.211 Å, respectively. One would expect to find two nearly equivalent C(sp^2)–O bonds in the mandelate ion. In **1**, **2**, and **4**, however, the C(sp^2)–O bond lengths are significantly different, whereas in **3** the carboxyl oxygens come the closest to complete hybridization. Apparently the differences in the local environments of the oxygen atoms, resulting from variation in hydrogen bonding, significantly influence the C(sp^2)–O bond lengths. A similar situation has been found for α-phenethylammonium mandelate, where the C(sp^2)–O bond lengths are 1.23 and 1.27 Å.[14]

Another factor besides hydrogen bonding that controls the crystal packing of ephedrinium and pseudoephedrinium mandelates is the interaction between the phenyl rings of the anion and cation. This type of interaction may also be implicated in determining the solution-state conformations of the ion pairs.

Nuclear Magnetic Resonance. Both the NMR spectral data and the conductance results imply that a simple equilibrium lies predominantly between the ion pair and the free ions for all of the mandelate salts in DMSO. The observed chemical shifts and the concentration effects are similar for all of the mandelate salts in DMSO-d_6. The methine resonance of the mandelate anion is shifted upfield relative to the un-ionized acid due to the shielding effect of the negative charge. As the concentration of the salt is increased the methine resonance shifts downfield toward that observed for the un-ionized acid. This may in part be due to intramolecular hydrogen bonding of the hydroxyl to the carboxylate, which would result in a partial negative charge density on the hydroxyl oxygen adjacent to the methine.

The proton resonances of the α-phenethylammonium cation are shifted downfield with respect to the un-ionized base due to the deshielding effect of protonation. Increasing the salt concentration shifted the methine resonance upfield as a result of ion pairing, which decreased the deshielding effect of protonation of the nitrogen (i.e., decreased charge density on the nitrogen).

Diastereomeric discrimination was observed in the chemical shifts for all of the side-chain resonances of the α-phenethylammonium mandelates as well as the aromatic protons, with the largest discrimination being for the methine of the α-phenethylammonium cation. Discrimination in the aromatic region of the spectra suggested some interaction between the phenyl rings of the anion and cation.

The proton resonances of the ephedrinium and pseudoephedrinium cations are also shifted downfield with respect to the corresponding un-ionized bases, and both the C–CH_3 and N–CH_3 resonances of the ephedrinium and pseudoephedrinium cations shift back upfield as the concentration increases. In contrast, the methine resonances move even further downfield for both the ephedrinium and pseudoephedrinium cations. Other factors besides the charge density on the ammonio group must, therefore, control the concentration dependence of these methine resonances. This may be due to conformational restrictions imposed upon the ephedrinium and pseudoephedrinium ions by association with the mandelate anions.

The largest concentration dependence for the side-chain resonances was found for the methine resonances of the mandelate anions and for those adjacent to the hydroxyl groups in both the ephedrinium and pseudoephedrinium cations. Both of these methines are adjacent to hydroxyl groups that are involved in intramolecular hydrogen bonding with either the carboxylate or the ammonio group.

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(58) Phillips, D. C. *Acta Crystallogr.* **1954**, *7*, 159. Dergin, R. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1971**, *B27*, 381. Hearn, R. A.; Bugg, C. E. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1972**, *B28*, 3662. Hearn, R. A.; Freeman, G. R.; Bugg, C. E. *J. Am. Chem. Soc.* **1973**, *95*, 7150.

(59) Matthew, M.; Palenik, G. J. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1977**, *B33*, 1016.

(60) Cameron, T. S.; Duffin, M. *Cryst. Struct. Commun.* **1974**, *3*, 539. Wei, K.-T.; Ward, D. L. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1976**, *B33*, 797.

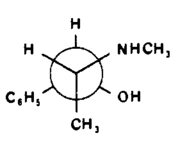
Table XVIII. Vicinal Coupling Constants for Ephedrine Bases, Their Salts, and Related Morpholines in DMSO[a]

	J_{vic},[b] Hz	
	ephedrine	pseudoephedrine
free base	4.14 (4.26)	7.54 (7.89)
hydrochloride	2.32 (2.43)	(9.42)
tetraphenylborate	2.55	9.18
mandelate	2.48	9.20
morpholine	(2.95)	(8.70)
morpholine hydrochloride	(2.47)	(10.02)

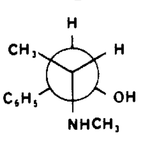
[a] The values in parentheses are from ref 165. [b] The error in the data from ref 165 is ±0.1 Hz. The other values are ±0.18 Hz.

Chiral discrimination was observed for several of the side-chain resonances of both the ephedrinium and pseudoephedrinium mandelates, but there are significant differences between the discrimination observed for the ephedrine and pseudoephedrine salts.

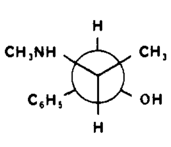
As with the α-phenethylammonium mandelates, the aromatic regions of the ephedrinium and pseudoephedrinium mandelates displayed chiral discrimination. The differences in the para protons of phenyl rings of the diastereomers of ephedrinium and pseudoephedrinium mandelate salts are especially suggestive of an interaction between the phenyl groups. The vicinal spin–spin coupling constants (J_{vic}) may be used to determine the preferred solution conformations of ephedrine and pseudoephedrine if they are compared with closely related compounds of known conformational preference.[61,62] Portoghese[63] conducted a very thorough study of the preferred conformations of ephedrine and pseudoephedrine and closely related model compounds *cis*- and *trans*-3-methyl-2-phenylmorpholine and their hydrochloride salts. Ephedrine (I) and pseudoephedrine (II) each can exist in three possible staggered conformations. The vicinal coupling constant J_{ab} represents a weighted average of all conformations.



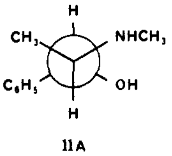
IA



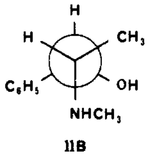
IB



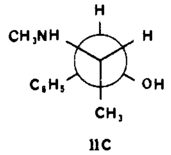
IC



IIA



IIB



IIC

The values of J_{ab} for ephedrine and pseudoephedrine determined by Portoghese[63] in solvents of widely differing polarity suggest that ephedrine exists chiefly in conformations (IA, IB) that possess a gauche OH to NHCH$_3$ relationship and that IIA is the most populated rotamer for pseudoephedrine. The fact that DMSO, a solvent known to form strong hydrogen bonds, produces very little effect on J_{ab} suggests that $\Delta G°$ for intramolecular hydrogen bonding compensates for the greater steric interactions present in IA and IB when compared with IC. For pseudoephedrine, steric factors actually favor intramolecular hydrogen bonding, since rotamer IIA possesses the fewest nonbonding interactions.

The vicinal coupling constants in DMSO for ephedrine and pseudoephedrine and their hydrochloride, tetraphenylborate, and mandelate salts as well as the related morpholines are given in Table XVIII. The coupling constants determined for both the ephedrinium and pseudoephedrinium mandelates were independent of concentration. This indicates that there are no significant differences between the conformations of the free ions and the ion pairs for either the ephedrine or pseudoephedrine salts. Portoghese's results also showed no profound change in the rotamer distribution of ephedrine and pseudoephedrine in various nonpolar solvents. However, in DMSO there is a disruption in a small fraction of the intramolecularly hydrogen-bonded rotamers. The coupling constants for the salts of ephedrine and pseudoephedrine suggest that the predominant protonated rotamers are identical with those of the free base (IA, IIA). These rotamers are stabilized by intramolecular hydrogen bonding. The decrease in J_{ab} for the protonated ephedrines compared with the free base actually indicates an increase in rotamer A. Similarly, the increase in J_{ab} for the pseudoephedrinium salts compared with the corresponding free bases also suggests an increase in rotamer A. The solid-state structures for the ephedrinium and pseudoephedrinium mandelates were shown to resemble IA and IIA, respectively.

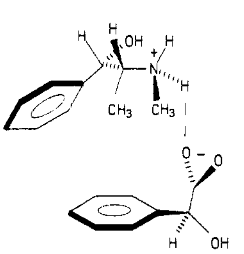


Figure 8. Proposed structure for the (1*S*,2*R*)-(+)-ephedrinium (*S*)-(+)-mandelate ion pair.

Proposed Structures for the α-Phenethylammonium, Ephedrinium, and Pseudoephedrinium Mandelate Ion Pairs. The X-ray crystal structures for the ephedrinium and pseudoephedrinium mandelates show that two factors control the solid-state structures of the diastereomeric mandelate salts of ephedrine and pseudoephedrine. First, there is extensive hydrogen bonding. For a given neighboring cation and anion pair at least one intermolecular $-^{+}NH\cdots{}^{-}O-$ bond is formed between the carboxylate and ammonio groups. In addition, the hydroxyl groups of both the mandelate anion and the ephedrinium or pseudoephedrinium cation act as either hydrogen bond donors or acceptors. Although intramolecular hydrogen bonding of the type $-^{+}NH\cdots O-$ between the hydroxyl and ammonio groups was not indicated in the crystal structures, all of the ephedrinium and pseudoephedrinium mandelates are in conformations in which the OH and $^{+}NH_2CH_3$ are gauche to one another. The vicinal coupling constants indicate that ephedrinium and pseudoephedrinium cations prefer this gauche conformation in solution in DMSO for both the free ions and the ion pairs. In solution intramolecular hydrogen bonding is preferred, and indeed the NMR data suggest that this plays an important role in determining the solution conformations of ephedrine and pseudoephedrine as well as the corresponding protonated forms. The NMR and thermodynamic data also suggest that ion pairing produces no significant change in the solution conformations of the ephedrinium and pseudoephedrinium cations.

Although intramolecular hydrogen bonding of the type $-OH\cdots{}^{-}O-$ between the hydroxyl and carboxyl groups of the mandelate anion was only observed in the solid-state structures of the pseudoephedrine salts, even in the ephedrine salts the torsion angle between the OH and COO$^-$ was less than 40°. In solution one would expect the intramolecular hydrogen bond to be favored entropically, and in fact this has been shown to be the case for mandelic acid and sodium mandelate.[64]

The second factor that determines the solid-state structures of the mandelate salts is interaction between the phenyl moieties. This appears to be a van der Waals type attraction since the planes of the two rings are not parallel to each other. Brianso's crystal

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[61] Laszlo, P.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1963**, *85*, 2709. Williamson, K. L.; Lanford, C. A.; Nicholson, C. R. *J. Am. Chem. Soc.* **1964**, *86*, 762.

[62] Williams, D. H.; Bhacca, N. S. *J. Am. Chem. Soc.* **1964**, *86*, 2742. Booth, H. *Tetrahedron Lett.* **1965**, 411. Booth, H.; Gidley, G. C. *Tetrahedron* **1965**, *21*, 3429.

[63] Portoghese, P. S. *J. Med. Chem.* **1967**, *10*, 1057.

[64] Mori, N.; Asano, Y.; Irie, T.; Tsuzuki, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 482. Mori, N.; Tanaka, Y.; Tsuzuki, Y. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1490. Abramovich, M. A.; Ginzburg, I. M.; Ioffe, D. V. *Teor. Eksp. Khim.* **1971**, *7*, 225.

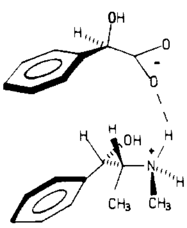


Figure 9. Proposed structure for the (1*S*,2*R*)-(+)-ephedrinium (*R*)-(−)-mandelate ion pair.

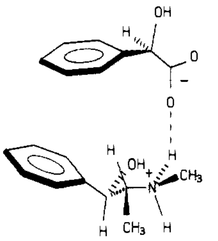
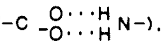


Figure 10. Proposed structure for the (1*R*,2*R*)-(−)-pseudoephedrinium (*R*)-(−)-mandelate ion pair.

structures of the α-phenethylammonium mandelates[14] show that the same factors, i.e., hydrogen bonding and van der Waals interactions, also control the solid-state conformations of these salts.

a. Ephedrinium Mandelates. The proposed structures for the diastereomeric ephedrinium mandelate ion pairs are shown in Figures 8 and 9. It is assumed that there is an intramolecular hydrogen bond between the hydroxyl and carboxyl groups of the anions and another between the hydroxyl and ammonio groups of the cations. The remaining carboxyl oxygen and ammonio proton are hydrogen bonded to one another. The intramolecular interactions should make formation of the bidentate-type hydrogen bond



$$(-\mathrm{C}\begin{smallmatrix}\mathrm{O}\cdots\mathrm{H}\\ -\mathrm{O}\cdots\mathrm{H}\end{smallmatrix}\mathrm{N}-).$$

which generally occurs for primary and secondary amines, unlikely.

The chiral discrimination in the PMR spectra of the ephedrinium mandelates in DMSO (see Table XIII) may be rationalized on the basis of the proposed structures for the diastereomeric ion pairs. Both the N–CH_3 and C–CH_3 groups are above the plane of the phenyl ring of the mandelate anion in the (+)-ephedrinium (+)-mandelate ion pair (Figure 8), which would account for the upfield shift in the proton resonances for these groups relative to the diastereomeric salt. On the other hand, H(7′) is over the mandelate phenyl ring in the (+)-ephedrinium (−)-mandelate ion pair (Figure 9). The ^{1}H NMR chemical shift for H(7′) is shifted upfield for the (+)-ephedrinium (−)-mandelate salt relative to the diastereomer. In both of the diastereomeric pairs of ephedrinium mandelates, H(8′) is directed away from the mandelate phenyl group and, as one would expect, no difference was observed for the H(8′) resonances in the ^{1}H NMR spectra of the diastereomeric ephedrinium mandelate salts in DMSO. The acid methine also exhibited no chiral discrimination.

The observed differences in the thermodynamic parameters (see Table XVI) show that the (+)-ephedrinium (+)-mandelate and (−)-ephedrinium (−)-mandelate salts have the more exothermic heats of ion-pair association and should thus form the more stable ion pairs. The proposed structures for the ion pairs do not, however, suggest a good reason for their superior stability.

b. Pseudoephedrinium Mandelates. The proposed structures for the diastereomeric pseudoephedrinium mandelate ion pairs are shown in Figures 10 and 11 and should be dominated by the same interactions that were assumed to control the structures of the ephedrinium mandelate ion pairs, i.e., intramolecular hydrogen bond between the ammonio and carboxylate groups and overlap of the phenyl rings of the cation and anion.

The chiral discrimination observed in the ^{1}H NMR spectra of the pseudoephedrinium mandelate salts in DMSO (See Table XIII) was, however, quite different from that observed for the ephedrinium mandelates. In the proposed structures for the pseudoephedrinium mandelate ion pairs, the C–CH_3 and H(7′) are above the plane of the mandelate phenyl ring in the (−)-pseudoephedrinium (+)-mandelate ion pair (Figure 11), which would account for the upfield shift in the proton resonances of these groups relative to the diastereomeric (−)-pseudoephedrinium (−)-mandelate ion pair (Figure 10). On the other hand, H(8′) is over the mandelate phenyl ring in the (−)-pseudoephedrinium (−)-mandelate ion pair. The ^{1}H NMR chemical shift for H(8′) would, therefore, be shifted upfield for the (−)-pseudoephedrinium (−)-mandelate ion pair relative to the diastereomer, as was observed. Unlike the ephedrinium mandelates, chiral discrimination was also observed for the mandelate methine group in the pseudoephedrine salts.

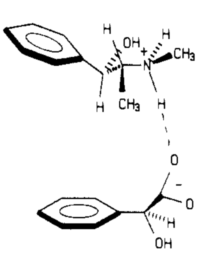


Figure 11. Proposed structure for the (1*R*,2*R*)-(−)-pseudoephedrinium (*S*)-(+)-mandelate ion pair.

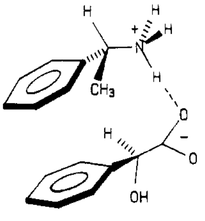


Figure 12. Proposed structure for the (*R*)-(+)-α-phenethylammonium (*S*)-(+)-mandelate ion pair.

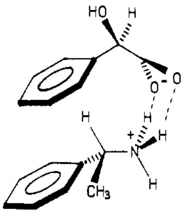


Figure 13. Proposed structure for the (*R*)-(+)-α-phenethylammonium (*R*)-(−)-mandelate ion pair.

As with the ephedrinium mandelates, the differences in the thermodynamic parameters for the pseudoephedrinium mandelates in DMSO (see Table XVI) are difficult to interpret in terms of the proposed ion-pair structures.

c. α-Phenethylammonium Mandelates. The proposed structures for the diastereomeric α-phenethylammonium mandelate ion pairs are shown in Figures 12 and 13. The primary interaction between the anion and cation is assumed to be a bidentate-type, intermolecular hydrogen bond between the carboxyl oxygens and the ammonio protons. The hydroxyl group of the mandelate anion is also hydrogen bonded to the carboxyl group.

The observed chiral discrimination in the ^{1}H NMR spectra of the α-phenethylammonium mandelates in DMSO (see Table XIII) may be rationalized on the basis of the proposed structures of the ion pairs. In the (+)-α-phenethylammonium (−)-mandelate (Figure 13) a bidentate-type, intermolecular hydrogen bond is proposed between the carboxyl and ammonio groups. While in the (+)-α-phenethylammonium (+)-mandelate (Figure 12) only a single hydrogen bond is suggested. Bidentate hydrogen bonding would result in less negative charge on the hydroxyl oxygen; therefore, the acid methine of the (+)/(−) salt should be deshielded and the resonance shifted upfield with respect to the diastereomeric salt, as was observed. The base methine lies over the phenyl ring in the (+)/(−) salt, while the methyl group is positioned over the ring in the (+)/(+) salt. The chemical shift for the base methine in the (+)/(−) salt lies upfield of the diastereomeric salt, while the methyl resonance is shifted upfield for the (+)/(+) salt relative to the diastereomer.

The observed differences in the thermodynamic parameters for the interaction of mandelic acid and α-phenethylamine are given in Table XVI. The (+)-α-phenethylammonium (−)-mandelate and (−)-α-phenethylammonium (+)-mandelate salts have the more exothermic heats of ion-pair association. The proposed (+)-α-phenethylammonium (−)-mandelate ion pair, in addition to bidentate hydrogen bonding, has better overlap between the phenyl rings and less steric interactions (i.e., the base methyl group does not lie over the ring) than the diastereomeric (−)-α-phenethylammonium (−)-mandelate ion pair. Thus, ion pairing is favored for the (+)/(−) salt.

Conclusion

This is the most extensive stereochemical study to date of the effects of structural change on energy for a clearly defined intermolecular interaction (hydrogen bonding) in solution and the crystalline state. Proton transfer from the enantiomers of mandelic acid to the enantiomers of ephedrine and pseudoephedrine generate eight diastereomerically related salts. A simpler pair of salts from the mandelic acid enantiomers and those of α-phenethylamine were also compared. In all cases cross-chiral checks of the thermodynamic results were obtained by using all combinations of the chiral bases with enantiomers of the acid.

The results provide quantitative details for the reasonable notion that stereochemical differences in the hydrogen-bonded ion pairs are related directly to their stabilities. The facts in summary are as follows:

(a) Extensive and complex hydrogen-bonding interactions were found in all crystal structures. Interactions between the phenyl rings of the cations and anions played a secondary role.

(b) The densities of the unit cells were related closely to the melting points and heats of fusion of the crystals—a large (5.79 kcal/mol) difference between the heats of fusion of the diastereomeric ephedrinium mandelates being noteworthy.

(c) Proton NMR spectra (at 300 and 600 MHz) and conductance for all of the mandelate salts were determined as a function of concentration in DMSO and confirm that a simple equilibrium between ion pairs and free ions holds over the range studied in this solvent.

(d) Treatment of the conductance data by the Fuoss–Justice (F–J), Fuoss-1977 (F-77), and the Onsager limiting law (OLL) equations showed distinct differences between the ion-paired systems and the method of treatment. In all cases OLL gave considerably lower estimates of Λ_0, K_a, and ΔG_a than F–J, which in turn were slightly lower than F-77. Structural effects on the association constants were very small.

(e) NMR coupling constants indicate that all of the ephedrinium and pseudoephedrinium mandelates are in conformations with OH and NH_2CH_3 gauche to each other. Conformations of the cations and their ion pairs are essentially the same and are determined primarily by intramolecular hydrogen bonding. There is chiral discrimination between the NMR spectra of DMSO solutions of the various salts and their ion pairs, but no simple interpretation is obvious.

(f) Heats of fusion show large differences between the diastereomeric mandelates of α-phenethylamine. Large differences are also found between ephedrinium mandelates. Differences between the pseudoephedrinium mandelates are small.

(g) Heats of solution of the crystalline salts in DMSO differ significantly between each diastereomeric pair.

(h) Heats of reaction for enantiomers of the three bases with the enantiomers of the acid show small stereospecific differences in DMSO. Comparable heats of reaction for α-phenethylamine in dioxane depend strongly on the acid/base ratio.

(i) No diastereomeric differences are observed in aqueous solutions where the salts are completely dissociated.

(j) We are unable to provide a complete structural interpretation of the ion-pairing behavior, even for this carefully chosen system.

Experimental Section

Methods. Details of methods and compound purification are provided in the thesis of S.P.Z., University of Pittsburgh, 1982.

Solution Calorimetry. The calorimeters used in this study were a Tronac Model 450 titration calorimeter, which was modified by the addition of a second micrometer syringe,[36] and a Tronac Model 1250 calorimeter with an ampule breaker. The precision and accuracy of the 1250 calorimeter was checked by measuring the heat of solution of KCl in deionized water at 25 °C. The KCl was purified by recrystallization from deionized water. The observed heat of solution was 4.156 ± 0.022 kcal/mol (lit. 4.13,[36] 4.115[65] kcal/mol). Heats of neutralization and heats of dilution were measured with the Tronac 450.

The validity of the two-buret method using the Tronac 450 was checked by measuring the heat of protonation of tris(hydroxymethyl)aminomethane (THAM) with aqueous hydrochloric acid.[36] Enthalpies obtained by the single- and double-buret techniques were −11.34 ± 0.03 and −11.30 ± 0.05 kcal/mol, respectively (lit.[35] −11.33 kcal/mol).

Differential Scanning Calorimetry. The transition temperatures and the transition enthalpies for the ephedrinium, pseudoephedrinium, and α-phenethylammonium mandelate salts were studied with a Perkin-Elmer DSC-1B differential scanning calorimeter. The instrument was calibrated with a set of Fisher certified thermometric standards (Catalog No. T-418) consisting of naphthalene, benzoic acid, and adipic acid and hexamethylbenzene purified in this laboratory (mp 165.5 ± 0.2 °C).[66] The method used for determining DSC transition temperatures was that of Chapman et al.[67] and Lundquist.[68] Benzoic acid and naphthalene (Fisher certified primary standards) were used as standards for the calculation of transition enthalpies.[69] Thermograms for the standards were repeated at least three times, both before and after thermograms for the mandelate salts were run.

Conductance. The resistance of the salt solutions was determined with a Beckman Model RC-18A conductance bridge. The conductance cell used was a modified Jones cell devised by Kraus[70] in which an Erlenmeyer flask is connected to the electrode compartment. The platinized[71] electrodes were platinum disks, which were gold soldered onto platinum rods, and the cell was thermostated to 25.00 ± 0.05 °C. Duplicate measurements were made of the conductance of three independently prepared aqueous 0.0100 demal KCl solutions.[72] The cell constant obtained was 0.7907 ± 0.0003 cm^{-1}. This value was checked by measuring the equivalent conductance of a 0.005 00 demal aqueous solution of KCl (lit.[73] 143.55 mho cm^{-1} L $equiv^{-1}$; obsd value 144.38 ± 0.16 mho cm^{-1} L $equiv^{-1}$). The concentrations of the mandelate salts were varied by using the Hawes–Kay cup dispensing device,[74] and the cell was purged with argon during the entire procedure. The limiting equivalent conductances and ion-pairing constants were calculated from the resistance data with both the Justice modification[44,45] of the Fuoss–Hsia 1957 conductance equation[75] (Fuoss–Justice calculation) and the Fuoss 1977 conductance equation[46] (Fuoss 1977 equation). Results obtained with the Onsager limiting law[48] are also included for comparison purposes.

Proton Magnetic Resonance. Proton magnetic resonance spectra at 250 and 600 MHz were run on spectrometers built at Mellon Institute that use Westinghouse superconducting magnets, one operating at 60 kG and the other at 144 kG. ^1H NMR spectra were also obtained at 300 MHz by using a Bruker WH 300 in the FT mode. Both spectrometers were operated in the fast linear frequency sweep mode.[76]

Chemicals. 1,4-Dioxane. 1,4-Dioxane (Baker analyzed reagent or Fisher ACS certified) was purified by the method of Oglukian.[77,78] The

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dioxane was stored in a refluxing still over sodium and was freshly distilled as needed. The purity of each batch of dioxane was checked by ultraviolet spectroscopy[79] and refractometry.[80] The water content by the Karl Fisher method was below 80 μg/mL.

Dimethyl Sulfoxide. Dimethyl sulfoxide (DMSO) was purified by a method developed in this laboratory.[81] The water content checked by the Karl Fischer method was below 80 μg/mL.

Water. The water was purified by passing through a charcoal filter and an ion-exchange column from Continental Water Corp. The filter system was equipped with an indicator that was activated when the conductance increased to greater than 10^5 Ω.

Deuteriated solvents were used as received.

Mandelic Acid. Mandelic acid (Sigma or Aldrich) was recrystallized at least three times from benzene[82] and vacuum dried at 30 °C. Comparisons with published rotations[83,84] established an optical purity of 99.3 ± 0.4%.

α-Phenethylamine. α-Phenethylamine (Norse Laboratories) was purified by vacuum distillation.[85] Comparison with published rotations[86,87] established an optical purity 98.2 ± 0.4%.

Ephedrine. Ephedrine (Sigma) was purified by vacuum distillation,[54] optical purity 99.2 ± 0.5% by comparison with the literature.[88]

Pseudoephedrine. Pseudoephedrine (Sigma) was recrystallized at least three times from deionized water and dried under vacuum at 50 °C,[54] optical purity 99.6 ± 0.5% by comparison with the literature.[89]

α-Phenethylammonium Mandelates. Equivalent amounts of the enantiomers of mandelic acid and α-phenethylamine were combined in the appropriate solvent and refluxed for 1 h.[5,8,90] The solutions were filtered while hot, and the salts were allowed to crystallize slowly. The salts are denoted in the following manner: (*R*)-(+)-α-phenethylammonium (*R*)-(−)-mandelate ≡ (*R*)-(+)/(*R*)-(−); (*R*)-(+)-α-phenethylammonium (*S*)-(+)-mandelate ≡ (*R*)-(+)/(*S*)-(+); (*S*)-(−)-α-phenethylammonium (*R*)-(−)-mandelate ≡ (*S*)-(−)/(*R*)-(−); (*S*)-(−)-α-phenethylammonium (*S*)-(+)-mandelate ≡ (*S*)-(−)/(*S*)-(+). The (*R*)-(+)/(*R*)-(−) and (*S*)-(−)/(*S*)(+) salts were recrystallized from ethanol. The (*R*)-(+)/(*S*)-(+) and (*S*)-(−)/(*R*)-(−) salts were recrystallized from toluene or benzene. Recrystallizations were continued until the melting point and optical rotation were constant. At least three recrystallizations were performed on each salt.

(*S*)-(−)/(*R*)-(−): mp 107.8–109.0 °C cor; $[\alpha_{D}^{25}$ −66.7 ± 0.2° (*c* 1, H_2O) (lit.[22] $[\alpha]^{25}_{D}$ −58.9°). Anal. Found: C, 70.1; H, 6.9; N, 5.0. Calcd: C, 70.3; H, 7.0; N, 5.1. (*R*)-(+)/(*S*)-(+): mp 108.1–109.6 °C lit.[28] mp 109–111 °C; $[\alpha]^{25}_{D}$ +66.0° (lit.[22] $[\alpha]^{25}_{D}$ +65.9°). Anal. Found: C, 70.3; H, 7.1; N, 5.0. (*R*)-(+)/(*R*)-(−): mp 165.8–168.8 °C; $[\alpha]^{25}_{D}$ −61.5° (lit.[22] $[\alpha]^{25}_{D}$ −60.4°). Anal. Found: C, 70.3; H, 7.1; N, 5.0. (*S*)-(−)/(*S*)-(+): mp 166.3–169.5 °C (lit.[28] mp 176–178 °C); $[\alpha]^{25}_{D}$ +62.1°. Anal. Found: C, 70.3; H, 6.9; N, 5.0.

Ephedrinium Mandelates. The ephedrinium mandelate salts were prepared in the same manner as above.[90,91] The salts are denoted in the following manner: (1*S*,2*R*)-(+)-ephedrinium (*S*)-(+)-mandelate ≡ (1*S*,2*R*)-(+)/(*S*)-(+); (1*R*,2*S*)-(−)-ephedrinium (*R*)-(−)-mandelate ≡ (*R*,2*S*)-(−)/(*R*)-(−); (1*S*,2*R*)-(+)-ephedrinium (*R*)-(−)-mandelate ≡ (*S*,2*R*)-(+)/(*R*)-(−); (1*R*,2*S*)-(−)-ephedrinium (*S*)-(+)-mandelate ≡ (1*R*,2*S*)-(−)/(*S*)-(+). The (1*S*,2*R*)-(+)/(*S*)-(+) and (1*R*,2*S*)-(−)/(*R*)-(−) salts were recrystallized from ethanol. The (1*S*,2*R*)-(+)/(*R*)-(−) and (1*R*,2*S*)-(−)/(*S*)-(+) salts were recrystallized from benzene.

(1*S*,2*R*)-(+)/(*S*)-(+): mp 165.4–167.0 °C cor (lit.[90] mp 168–169 °C); $[\alpha]^{25}_{D}$ +78.7 ± 0.2° (*c* 2, H_2O) (lit.[90] $[\alpha]^{18.5}_{D}$ 79.3° (*c* 4, H_2O). Anal. Found: C, 68.1; H, 7.3; N, 4.5. Calcd: C, 68.1; H, 7.3; N, 4.4. (1*R*,2*S*)-(−)/(*R*)-(−): mp 165.6–167.4 °C (lit.[90] mp 168–169 °C); $[\alpha]^{25}_{D}$ −78.9° (lit.[90] $[\alpha]^{25}_{D}$ −79.3°). Anal. Found: C, 68.2; H, 7.4; N, 4.5. (1*S*,2*R*)-(+)/(*R*)-(−): mp 111.2–111.9 °C; $[\alpha]^{25}_{D}$ −34.0°. Anal. Found: C, 68.2; H, 7.4; N, 4.3. (1*R*,2*S*)-(−)/(*S*)-(+): mp 110.9–111.9 °C (lit.[92] mp 78.91 °C); $[\alpha]^{25}_{D}$ +33.7° (lit.[93] $[\alpha]^{25.5}_{D}$ +21.3° (*c* 2.818, H_2O)). Anal. Found: C, 68.0; H, 7.3; N, 4.5.

Pseudoephedrinium Mandelates. The pseudoephedrinium mandelates were prepared in the same manner as the ephedrine and α-phenethylamine salts. All of the pseudoephedrine salts were recrystallized from benzene. The salts are denoted in the following manner: (1*S*,2*S*)-(+)-pseudoephedrinium (*S*)-(+)-mandelate ≡ (1*S*,2*S*)-(+)/(*S*)-(+); (1*R*,2*R*)-(−)-pseudoephedrinium (*R*)-(−)-mandelate ≡ (1*R*,2*R*)-(−)/(*R*)-(−); (1*S*,2*S*)-(+)-pseudoephedrinium (*R*)-(−)-mandelate ≡ (1*S*,2*S*)-(+)/(*R*)-(−); (1*R*,2*R*)-(−)-pseudoephedrinium (*S*)-(+)-mandelate ≡ (1*R*,2*R*)-(−)/(*S*)-(+). There was no available literature data for the pseudoephedrinium mandelate salts.

(1*S*,2*S*)-(+)/(*S*)-(+): mp 110.5–111.3 °C cor; $[\alpha]^{25}_{D}$ +95.3 ± 0.2° (*c* 2, H_2O). Anal. Found: C, 68.0; H, 7.3; N, 4.3. Calcd: C, 68.1; H, 7.3; N, 4.4. (1*R*,2*R*)-(−)/(*R*)-(−): mp 110.2–111.2 °C; $[\alpha]^{25}_{D}$ −95.0°. Anal. Found: C, 68.3; H, 7.3; N, 4.3. (1*S*,2*S*)-(+)/(*R*)-(−): mp 115.9–116.7 °C; $[\alpha]^{25}_{D}$ −16.9°. Anal. Found: C, 68.3; H, 7.4; N, 4.3. (1*R*,2*R*)-(−)/(*S*)-(+): mp 116.0–116.9 °C; $[\alpha]^{25}_{D}$ +17.0°. Anal. Found: C, 68.1; H, 7.3; N, 4.3.

Amine Tetraphenylborates. Ephedrine and pseudoephedrine tetraphenylborate (TPB) salts were prepared by the addition of 0.1 M aqueous sodium tetraphenylborate (Alfa) to an equal volume of acetate-buffered (pH 4.6) solutions of the amines (0.1 M).[94] After the mixture was stirred for 30 min under a nitrogen atmosphere, the precipitate was filtered and washed with deionized water. The salts were recrystallized from MeOH/H_2O (1:3) and dried under vacuum at 30 °C. Both enantiomers of the ephedrine salts melted at 131.2–133.0 °C (lit. mp 135–136.5,[94] 128–129.5[95] °C). The melting point of both pseudoephedrine salts was 139.7–140.4 °C (no literature value was available).

Sodium Mandelate. The salt was prepared by neutralizing a solution of mandelic acid with an equivalent quantity of sodium carbonate and evaporating the solution to dryness on the rotoevaporator.[96] The salt was recrystallized from ethanol and dried in a vacuum at 50 °C.

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Registry No. (*R*)-(+)-α-Phenethylammonium (*R*)-(−)-mandelate, 4067-93-0; (*R*)-(+)-α-phenethylammonium (*S*)-(+)-mandelate, 4067-91-8; (*S*)-(−)-α-phenethylammonium (*R*)-(−)-mandelate, 4067-90-7; (*S*)-(−)-α-phenethylammonium (*S*)-(+)-mandelate, 4067-92-9; (1*S*,2*R*)-(+)-ephedrinium (*S*)-(+)-mandelate, 112532-00-0; (1*R*,2*S*)-(−)-ephedrinium (*R*)-(−)-mandelate, 112532-01-1; (1*S*,2*R*)-(+)-ephedrinium (*R*)-(−)-mandelate, 93982-06-0; (1*R*,2*S*)-(−)-ephedrinium (*S*)-(+)-mandelate, 112532-02-2; (1*S*,2*S*)-(+)-pseudophedrinium (*S*)-(+)-mandelate, 112532-03-3; (1*R*,2*R*)-(−)-pseudoephedrinium (*R*)-(−)-mandelate, 112532-04-4; (1*S*,2*S*)-(+)-pseudoephedrinium (*R*)-(−)-mandelate, 112532-05-5; (1*R*,2*R*)-(−)-pseudoephedrinium (*S*)-(+)-mandelate, 112532-06-6; (1*R*,2*S*)-ephedrine, 299-42-3; (1*R*,2*S*)-ephedrine hydrochloride, 50-98-6; (1*R*,2*S*)-ephedrine tetraphenylborate, 24533-76-4; (1*R*,2*R*)-pseudoephedrine, 90-82-4; (1*R*,2*R*)-pseudoephedrine tetraphenylborate, 33462-18-9.

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