

Molecular Interaction of Stereoisomers When in Solid State

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Studies of acid-base association of asymmetric molecules in the solid state, involving the determination of melting points of the formed diastereoisomeric salts, their infrared spectra, and for a number of examples, X-ray diffraction powder photography, have been carried out. In these examples, in which crystalline salts were obtained using optically active acids and bases, the diastereoisomeric salts prepared from components of the same configuration had higher melting points than those of different configuration. Although infrared measurements could not be used to indicate configuration of the components, definite differences in the spectrum of salts formed from isomers of like configuration from those of unlike configuration have been observed; likewise, the X-ray diffraction pattern was different.

JAROWSKI AND Hartung (2), working with the mandelates of ephedrine-type molecules, showed some correlation between chemical structure and physiological properties; they also reported the melting points of the salts formed. However, no attempt was made to interpret the differences in melting points in terms of differences in the geometry of the components of these diastereoisomeric salts.

Ricci (3) discussed the principles of the quasi-racemic method of configurational assignment and concluded that molecular interactions in a system of two substances of opposite configuration cause negative deviation from ideality as compared to the phase equilibrium in the corresponding system between related configurations.

Differences observed in infrared spectra of diastereoisomeric salts have already been the subject of another paper (1).

The X-ray method has been used by Bijvoet *et al.* (4) to deduce configurations and also by examining X-ray photographs (5-7), the degree of association of the molecules within the diastereoisomeric salts.

In the present investigation, melting point measurements, infrared spectra evaluations, and X-ray diffraction powder photographs of a number of different diastereoisomeric compounds have been examined.

EXPERIMENTAL

Materials.—The optically active acids and bases used are those recorded in Table I.

The signs *D*- and *L*- refer to the absolute configuration of the compounds used.

Preparation of the Salts.—Equimolar quantities (about 0.5 Gm.) of the appropriate acid and base were dissolved in an appropriate solvent (*e.g.*, methyl or ethyl alcohol, ether, etc.) under reflux. The solution was cooled and placed in the refrigerator until crystals separated. These crystals were filtered off, dried under vacuum, and melting points were taken; these salts were recrystallized to constant melting points.

The substance (small quantity in a melting point tube) was placed in the melting point apparatus when the temperature was about 10° below the melting point. Heating at a rate of about 2°/min. was then carried out.

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For the infrared spectra Nujol mulls of the salts were prepared (1). The same salts were sent for X-ray diffraction powder photographs.¹

Instruments.—The following instruments were used: (a) the Townson and Mercer melting point apparatus and (b) the Unicam S.P. 200 spectrophotometer.

RESULTS

Melting Point Measurements.—The results (Table I) indicate that salts formed from optically active acids and optically active bases, and possessing the same configuration, had a higher melting point than those formed from the corresponding acids and bases of opposite configuration. The latter salts in some cases could only be obtained in the form of oils.

As expected, the melting points of *D*-acid/*D*-base salts were similar to those of the corresponding *L*-acid/*L*-base salts; *L*-acid/*D*-base salts also had the same melting points as *D*-acid/*L*-base salts.

X-Ray Diffraction Powder Photography.—The results (Table II) indicate that *d*-values, calculated from the application of Bragg's law (Eq. 1), were not the same for both diastereoisomers (*i.e.*, between *D/D* and *D/L* or between *L/L* and *L/D*).

$$n\lambda = 2d \sin \vartheta^\circ \quad (\text{Eq. 1})$$

where

n = order of reflection

λ = wavelength

d = interplanar spacing

ϑ° = angle of deviation from the direct X-ray beam.

DISCUSSION

The results indicated that in the series studied, diastereoisomeric salts, formed from compounds of the same configuration (*e.g.*, *D*-amphetamine-*D*-mandelate or *L*-amphetamine-*L*-mandelate) have a different arrangement of the molecules, and consequently a difference in association between the isomers, from that of diastereoisomeric salts from compounds of unlike configuration (*e.g.*, *D*-amphetamine-*L*-mandelate or *L*-amphetamine-*D*-mandelate).

This dissimilarity between the *D/D* (or *L/L*) and *D/L* (or *L/D*) diastereoisomeric salts was observed in differences in melting points (*e.g.*, *D*-amphetamine-*D*-mandelate, m.p. 166°, *D*-amphetamine-*L*-mandelate, m.p. 162°), differences in their spectra, and also

¹ The X-ray diffraction powder photographs were carried out by Mr. G. H. Hunt, Overseas Geological Surveys, London, England.

TABLE I.—MELTING POINTS OF VARIOUS SALTS FORMED FROM OPTICALLY ACTIVE ACIDS AND OPTICALLY ACTIVE BASES OF KNOWN CONFIGURATION

Acids	Bases			
	D-Isomers	Salts, M.p.	L-Isomers	Salts, M.p.
D-Mandelic	Amphetamine	166.2	Amphetamine	162.0
L-Mandelic	Amphetamine	162.0	Amphetamine	166.2
D-Mandelic	Adrenaline	139.0	Adrenaline	oil
L-Mandelic	Adrenaline	oil	Adrenaline	139.0
D-Mandelic	α -Phenethylamine	177.4	α -Phenethylamine	104.7
L-Mandelic	α -Phenethylamine	104.7	α -Phenethylamine	177.4
D-Tartaric	Amphetamine	169.7	Amphetamine	145.2
L-Tartaric	Amphetamine	145.2	Amphetamine	169.7
<i>m</i> -Tartaric	Amphetamine	199.1	Amphetamine	199.1
L-Tartaric	Adrenaline	144.0	Adrenaline	150.5
D-4-CH ₃ -POP ^a	Amphetamine	187.2	Amphetamine	156.0
L-4-CH ₃ -POP ^a	Amphetamine	156.0	Amphetamine	187.2
D-NOP ^b	Amphetamine	104.5	Amphetamine	oil
L-NOP ^b	Amphetamine	oil	Amphetamine	104.5
D-4-Cl-POP ^a	Amphetamine	178.5	Amphetamine	147.5
L-4-Cl-POP ^a	Amphetamine	147.5	Amphetamine	178.5
D-POB ^c	Amphetamine	153.0	Amphetamine	148.1
L-POB ^c	Amphetamine	148.1	Amphetamine	153.0
D-POP ^a	Amphetamine	150.5	Amphetamine	146.7
L-POP ^a	Amphetamine	146.7	Amphetamine	150.5
D-2-OCH ₃ -POP ^a	α -Phenethylamine	120.5	α -Phenethylamine	oil
L-2-OCH ₃ -POP ^a	α -Phenethylamine	oil	α -Phenethylamine	120.5
D-4-Br-POP ^a	α -Phenethylamine	155.2	α -Phenethylamine	124.7
L-4-Br-POP ^a	α -Phenethylamine	124.7	α -Phenethylamine	155.2

^a Phenoxy- α -propionic. ^b Naphthoxy- α -propionic. ^c α -Phenoxybutyric.

TABLE II.—*d*-VALUES OF SOME DIASTEREOMERS AS DETERMINED BY USING THE X-RAY DIFFRACTION POWDER PHOTOGRAPHIC TECHNIQUE

D-Amphet-amine-D-Mandelate	D-Amphet-amine-L-Mandelate	D- α -Phenethylamine-D-Mandelate	D- α -Phenethylamine-L-Mandelate
14.5 Å.	14.5 Å.	12.8 Å.	12.8 Å.
5.1	5.15	6.35	6.35
4.65	4.9	5.2	5.2
4.35	4.57	4.51	4.60
3.86	4.2	4.09	4.4
3.59	3.70	3.54	3.60
2.75	2.93	3.31	...

differences in *d*-values in X-ray diffraction powder photographs.

Because of the observed influence of the geometry of the components of diastereoisomeric salts on the melting points of the latter, the use of melting point differences of salts to assign configuration to acids and bases may become possible. For example, the configuration of a base isomer may be determined if an isomer pair of acids of known configuration are available and crystalline salts can be prepared from the base and these two isomeric acids; the higher melting point diastereoisomeric salt will have components of the same configuration (*i.e.*, if a mandelic acid isomer forms a salt, m.p. 166°, with D-amphetamine and one, m.p. 162°, with L-amphetamine, the mandelic acid isomer used would have the D-configuration).

The infrared spectra also showed significant differences between the diastereoisomeric salts formed from stereoisomers of unlike and of like configuration.

However, infrared spectra cannot be used to allocate the configuration of the components (1).

X-Ray diffraction powder photography also showed differences between diastereoisomeric salts, formed from stereoisomers of unlike and of like configuration (*e.g.*, D-amphetamine-D-mandelate and D-amphetamine-L-mandelate) (Table II).

Since these differences were observed between the interplanar spacing (*d*) of the diastereoisomeric salts, it is suggested that there is a difference of packing between the stereoisomers in the crystals.

Smaller *d*-values for the diastereoisomeric salt formed from stereoisomers of like configuration as compared with the diastereoisomeric salt with stereoisomers of unlike configuration, suggested closer packing of the crystals and, therefore, better association. However, the number of examples studied for the X-ray method was not enough to show that this method could be used for configurational assignment and further work is needed.

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