The presence of mucopolysaccharide sulfates in renal calculi has led to their implication as centers of nucleation for stone growth (4, 8). It is possible that several of the agents that have been employed clinically for halting stone growth, such as the salicylates and 5-nitrofurantoin, may be effective because of their ability to inhibit the formation of mucopolysaccharide sulfates.

It does appear from the data here, however, that this reaction is inhibited because of the metal-binding properties of molecules for the metalloenzymes involved in mucopolysaccharide sulfation. The enzymes that are known to be involved in this reaction include ATP-sulfurylase, ADP-sulfurylase, APS-kinase, and sulfokinase. Magnesium has been identified as a cofactor, but other metal ions may be involved.

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Intermolecular Association of Stereoisomers as Examined by Infrared Spectra

By N. H. CHOULIS

Studies of acid–base association of asymmetric molecules in the solid state involving the determination of infrared spectra of diastereoisomeric salts are examined. Although infrared spectra measurements could not be used to indicate configuration of the components, definite differences in the spectra of salts formed from stereoisomers of like configuration from those of unlike configuration could be determined.

DIFFERENCES in the infrared spectra of various diastereoisomeric salts may be interpreted in terms of the difference in association of the components of these salts. Previously, Eliel and Kofron (1) found that differences in infrared spectra were significant enough to distinguish between an active and a racemic form of a substance.

Rosenberg and Shotte (2) examining the infrared spectra of quasi-racemic compounds found also differences in the infrared spectra of (+)-α,α-dimethylglutaric acid/(−)-α-methylglutaric acid and (+)-α,α-dimethylglutaric acid/(+)-α-methylglutaric acid.

Gronowitz (3) showed a difference in the infrared spectra of (+)-2-thienylsuccinic acid/(+)-3-thienylsuccinic acid and (−)-2-thienylsuccinic acid/(+)-3-thienylsuccinic acid. However, no attempt was made to examine the infrared spectra and the differences occurring between diastereoisomeric salts.

EXPERIMENTAL

Materials.—D-Amphetamine, L-amphetamine, D-α-phenethylamine, L-α-phenethylamine, D-mandelic acid, L-mandelic acid, D-tartaric acid, L-tartaric acid, and *meso*-tartaric acid were used.

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

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

Nujol mulls of the salts were prepared and placed between rock-salt plates, and the spectra were obtained.

Instrument.—The Unicam S.P. 200 was used.

RESULTS

The results showed that the salts formed from optically active acids and optically active bases of similar configuration had different spectra from those of the corresponding salts formed from acids and bases possessing opposite configuration (Tables I–III). Furthermore, as expected, the spectrum of a D-acid/D-base was superimposable to the spectrum of the corresponding L-acid/L-base diastereoisomeric salt. Also the D-acid/L-base and the L-acid/D-base salts had the same infrared spectra but dissimilar to the spectra of D-acid/D-base or L-acid/L-base diastereoisomeric salts.

The spectrum of a salt formed from a racemic or optically inactive acid with one stereoisomer of an optically active base was superimposable with that of the same racemic or inactive acid and the other stereoisomer of the base (Table IV).

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TABLE I.—INFRARED ABSORPTION BANDS OF THE DIASTEREOISOMERIC SALTS D-AMPHETAMINE-D-MANDELATE (AND L/L) AND D-AMPHETAMINE-L-MANDELATE (AND L/D)

Wavelengths	Wavenumbers	Band Characteristic[a]
D-Amphetamine-D-mandelate or L-Amphetamine-L-mandelate		
14.18	705	v.s.
13.89	720	v.s.
13.42	745	s.
13.25	755	s.
13.07	765	w.
12.58	795	m.
11.11	900	w.
10.87	920	m.
9.90	1010	w.
9.70	1030	s.
9.31	1065	v.s.
9.09	1100	v.s.
8.77	1140	m.
8.54	1170	m.
8.40	1190	s.
8.19	1220	v.s.
8.00	1250	w.
7.84	1265	w.
7.81	1280	m.
7.69	1300	w.
7.54	1320	s.
7.14	1400	v.s.
6.69	1465	v.s.
6.66	1500	m.
6.49	1540	w.
6.32	1580	b.
6.23	1595	b.
6.11	1625	s.
4.65	2150	s.
3.90	2560	w.
3.77	2650	w.
3.63	2750	w.
3.39	2950	b.
3.24	3080	w.
D-Amphetamine-L-mandelate or L-Amphetamine-D-mandelate		
14.39	695	v.s.
14.29	700	m.
13.51	740	v.s.
12.83	780	w.
10.87	920	w.
10.64	940	s.
9.90	1010	m.
9.80	1020	w.
9.43	1060	v.s.
9.25	1080	v.s.
8.81	1135	s.
8.47	1180	s.
8.23	1205	s.
8.09	1226	w.
8.06	1240	w.
7.81	1280	s.
7.40	1350	m.
7.21	1375	m.
7.19	1390	m.
7.14	1400	s.
6.82	1455	v.s.
6.71	1490	w.
6.62	1510	m.
6.41	1560	v.s.
6.11	1625	s.
6.06	1650	m.
4.54	2200	m.
4.00	2500	m.
3.77	2650	w.
3.16	3160	w.

[a] v.s., very strong; b., broad; s., strong; m., medium; w., weak.

TABLE II.—INFRARED ABSORPTION BANDS OF THE DIASTEREOISOMERIC SALTS D-α-PHENETHYLAMINE-D-MANDELATE (AND L/L) AND D-α-PHENETHYLAMINE-L-MANDELATE (AND L/D)

Wavelengths	Wavenumbers	Band Characteristic[a]
D-α-Phenethylamine-D-mandelate or L-α-Phenethylamine-L-mandelate		
14.93	670	s.
14.29	700	v.s.
14.25	702	w.
13.70	730	v.s.
13.16	760	s.
12.82	780	m.
11.56	865	w.
10.93	915	m.
10.70	935	w.
10.20	980	w.
10.00	1000	w.
9.90	1020	m.
9.43	1060	v.s.
9.25	1080	v.s.
9.09	1100	w.
8.81	1135	w.
8.71	1145	w.
8.62	1160	w.
8.47	1180	s.
8.19	1220	m.
7.81	1280	m.
7.51	1330	m.
7.24	1380	v.s.
7.14	1400	w.
6.87	1455	s.
6.53	1530	s.
6.36	1570	s.
6.22	1608	s.
4.00	2500	w.
3.77	2650	w.
3.70	2700	w.
3.39	2950	b.
3.03	3230	s.
D-α-Phenethylamine-L-mandelate or L-α-Phenethylamine-D-mandelate		
14.39	695	v.s.
13.79	725	v.s.
13.42	745	m.
13.25	755	w.
12.90	775	m.
12.74	785	w.
10.99	910	w.
10.87	920	w.
9.95	1005	w.
9.70	1030	m.
9.43	1060	s.
9.21	1085	m.
8.43	1185	m.
8.19	1230	s.
7.93	1260	w.
7.69	1300	w.
7.57	1320	w.
7.38	1355	s.
7.24	1380	s.
7.04	1420	v.s.
6.83	1462	v.s.
6.66	1500	m.
6.36	1570	v.s.
6.17	1620	w.
6.11	1635	w.
4.54	2200	m.
3.93	2540	w.
3.72	2685	w.
3.39	2950	b.
2.94	3400	s.

[a] v.s., very strong; b., broad; s., strong; m., medium; w., weak.

TABLE III.—INFRARED ABSORPTION BANDS OF THE DIASTEREOISOMERIC SALTS D-AMPHETAMINE-D-TARTRATE (AND L/L) AND D-AMPHETAMINE-L-TARTRATE (AND L/D)

Wavelengths	Wavenumbers	Band Characteristic[a]
	D-Amphetamine-D-tartrate or L-Amphetamine-L-tartrate	
14.93	670	v.s.
14.29	700	v.s.
13.99	715	w.
13.33	750	v.s.
12.99	770	m.
11.90	840	m.
11.11	900	v.s.
10.10	990	m.
9.90	1010	m.
9.17	1090	v.s.
8.85	1130	v.s.
8.33	1200	m.
8.23	1215	m.
8.13	1230	m.
7.87	1275	s.
7.35	1360	m.
7.24	1380	m.
7.14	1400	w.
7.04	1420	m.
6.84	1460	v.s.
6.71	1490	w.
6.41	1560	w.
6.25	1610	b.
6.15	1710	v.s.
3.92	2550	w.
3.77	2650	w.
3.39	2940	v.s.
2.89	2450	v.s.
	D-Amphetamine-L-tartrate or L-Amphetamine-D-tartrate	
14.71	680	m.
14.29	700	v.s.
13.89	720	w.
13.42	745	s.
12.66	790	w.
11.90	840	w.
11.11	900	v.s.
10.10	990	m.
9.42	1065	s.
9.25	1080	s.
8.92	1120	v.s.
8.33	1200	m.
8.05	1240	w.
7.63	1310	w.
7.40	1350	w.
7.24	1380	v.s.
6.84	1460	v.s.
6.62	1510	w.
6.25	1610	w.
5.98	1670	b.
3.39	2950	v.s.
2.89	3450	w.

[a] v.s., very strong; b., broad; s., strong; m., medium; w., weak.

TABLE IV.—INFRARED ABSORPTION BANDS OF THE DIASTEREOISOMERIC SALTS D-AMPHETAMINE-*meso*-TARTRATE AND L-AMPHETAMINE-*meso*-TARTRATE

Wavelengths	Wavenumbers	Band Characteristic[a]
	D-Amphetamine-*meso*-tartrate or L-Amphetamine-*meso*-tartrate	
14.39	695	v.s.
13.51	740	v.s.
12.82	780	s.
11.90	840	w.
11.24	890	w.
10.87	920	v.s.
9.90	1010	s.
9.70	1030	w.
9.31	1075	v.s.
9.12	1095	m.
8.31	1205	v.s.
8.19	1220	w.
8.06	1240	m.
7.24	1380	b.
7.16	1395	b.
6.82	1465	v.s.
6.66	1500	w.
6.53	1530	w.
6.34	1575	s.
6.09	1640	v.s.
4.54	2200	s.
3.92	2550	m.
3.77	2650	m.
3.39	2950	v.s.
2.89	3450	v.s.

[a] v.s., very strong; b., broad; s., strong; m., medium; w., weak.

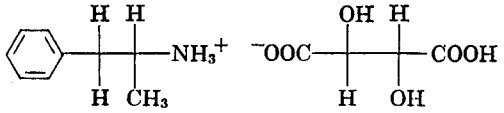
DISCUSSION

Although differences in the infrared spectra of amphetamine mandelates (D/D and L/D diastereoisomeric salts) were observed (Table I), it was difficult to reach a conclusion about the factors influencing these differences since differences appeared over most of the spectrum examined. Similarly, this was the case for α-phenethylamine mandelate diastereoisomeric salts. (See Table II.)

The association of amphetamine stereoisomers with tartaric acid stereoisomers in molecular proportions, in the solid state, gives differences in the infrared spectra of the diastereoisomeric salts which are indicative of molecular interactions between the constituted molecules.

It is assumed that the cationic head of the amine associates closely with the carboxyl ion from one of the carboxyl groups of the tartaric acid molecule and that the second carboxyl group is free to interact with a portion of the amine molecule other than the cationic head. The ionized carboxyl group in all the various diastereoisomeric salts appeared at 1610 cm.$^{-1}$, *i.e.*, the known position (1610–1550 cm.$^{-1}$) for an ionized carboxyl group. However, the carbonyl absorption band of the free carboxyl group in the various diastereoisomeric salts varies greatly with the configuration of the constituent molecules of the salts, *i.e.*, for D- or L-amphetamine with *meso*-tartaric acid it was 1640 cm.$^{-1}$ while for D-amphetamine-L-tartrate 1670 cm.$^{-1}$, and for D-amphetamine-D-tartrate 1710 cm.$^{-1}$ (Tables III, IV, and Figs. 1–3).

It is obvious that the environment of the carboxyl group varies in the above salts; *head to tail* association between amine and acid as in I is unlikely.



I

It is therefore assumed that the association between the amine and the acid stereoisomeric molecules allows a potential interaction of the free carboxyl group with the aromatic ring as indicated in II.

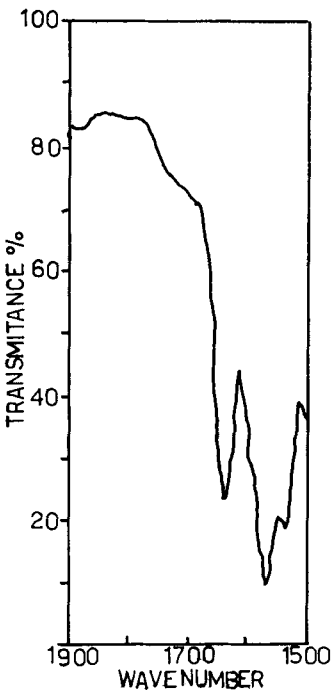


Fig. 1.—Partial infrared spectrum of D-amphetamine-*meso*-tartrate (or L-amphetamine-*meso*-tartrate).

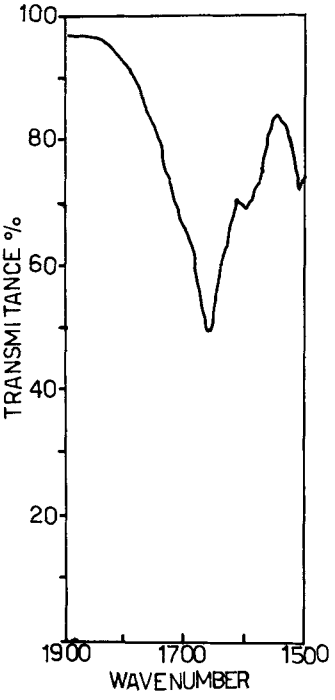


Fig. 2.—Partial infrared spectrum of D-amphetamine-L-tartrate (or L-amphetamine-D-tartrate).

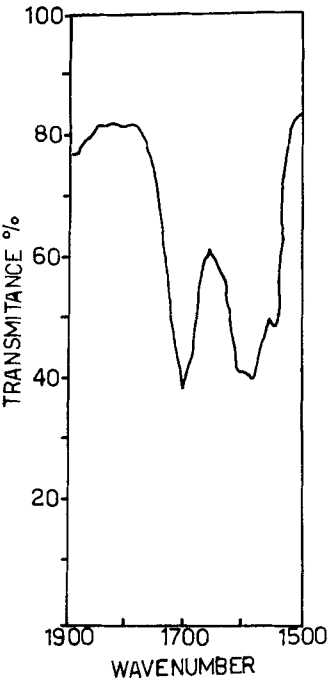
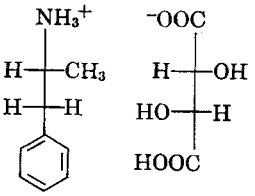
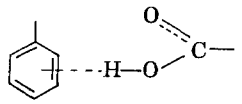


Fig. 3.—Partial infrared spectrum of D-amphetamine-D-tartrate (or L-amphetamine-L-tartrate).



II

It seems reasonable to assume that interaction between the carboxyl group and the π-orbital of the aromatic structure is III.



III

The extent of the interaction will be influenced by the configuration of the interactive molecules because one region of the interactive molecules is fixed by the ionic/cationic head association. The firmer the association of the hydrogen from the carboxyl with the aromatic ring, the longer the distance between C and O of the C·····O group would be expected.

At present, the shift of the carbonyl frequency of the free carboxyl group of these various diastereoisomeric salts can only be used to indicate the difference in molecular interaction which can occur between different stereoisomers in diastereoisomeric salts; and although infrared spectra may be used to distinguish between salts formed from compounds of opposite configuration, they cannot be used to allocate the configuration of the compounds.

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