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Predictions of which Diastereoisomeric Salt Precipitates during an Optical Resolution via Diastereoisomeric Salt Formation

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Abstract: The DSC data of sixteen conglomerate forming diastereoisomeric salt pairs were analysed. It was demonstrated that during optical resolution via fractional crystallization of diastereoisomeric salt pairs always that diastereoisomeric salt precipitates which has the higher melting point. When one of the salts is amorphous that remains in the mother liquor. If one of the diastereoisomeric salt crystallizes with solvate that will precipitate during optical resolutions.

INTRODUCTION

A common way for the preparation of optical isomers is the optical resolution of racemates via diastereoisomeric salt formation¹. During the resolution, the racemate (containing the two mirror image enantiomers with the same physical properties) forms diastereoisomeric salt pair with a chiral resolving agent. As the diastereoisomers have different physical properties, they can be separated by physical methods², usually by fractional crystallization. Efficient resolution can be expected only in the case of conglomerate forming salt pairs, when both diastereoisomeric salts crystallise separately and there are substantial differences in physico-chemical properties between the two diastereoisomeric salts³. In a recent paper we demonstrated that not only the conglomerate formation, but the efficiency of the resolution is also can be calculated from the melting phase diagrams of diastereoisomeric salt pairs⁴. The use of binary phase diagrams has already extended application in the investigation of resolution processes. Unfortunately the melting phase diagram cannot be determined when thermal decomposition takes places, one of the diastereomeric salt is solvated or not crystalline. In the present paper, we investigate whether we can recognise any rule among thermal data of pure diastereoisomeric salts what can be applied for prediction of results of optical resolutions even when the determination of the binary phase diagram is hindered.

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RESULTS AND DISCUSSION

In Table 1. the thermal data of sixteen conglomerate forming diastereoisomeric salt pairs⁵ are listed, all of them belong to successful resolutions⁷⁻²². The 1-8. salt pairs have no thermal decomposition before or during the melting. Analysing them, we can see that it is always the salt with the higher melting point that precipitates during optical resolutions of a racemate by fractional crystallization. The differences between the melting point of the precipitating salt and the salt remaining in the mother liquor are between 24-68 K (which is corresponds 6-16%, calculated in K, based on higher melting point). These substantial differences in melting points usually accompanied by large difference in heat of fusion data too, the differences can go up to 30 kJ/mol (50%, calculated on the higher ΔH). The usual heat of fusion value of such diastereoisomeric salts with a molar weight around 250-350 are between 20-60 kJ/mol. When the heat of fusion is higher than 60 kJ/mol we can suspect thermal decomposition^{23,24}.

Table 1. Thermal data of diastereoisomeric salt pairs of successful resolutions

		p salt		n salt		Refs.
		<i>T</i> K	ΔH kJ/mol	<i>T</i> K	ΔH kJ/mol	
1.	III-R-R-XIII	387	35.88	437	49.04	7
2.	IV-R,R-XIII	358	34.98	426	34.98	8
3.	XX-D-VIII	393	30.40	431	61.63	9
4.	XVI-L-VI	381	32.14	357	28.80	10
5.	XVI-R-IX	382	30.30	450	48.87	11
6.	XVI-R-XI	391	51.5	352	30.60	12
7.	IX-R-XXI	413	52.7	380	33.50	13
8.	XIX-R-IX	429	25.39	484	51.51	14
9.	I-R,R-XIV	amorphous		390	38.43	15
10.	II-R,R-XV	423	decomposition	amorphous		16
11.	X-treo-XVIII	462	decomposition	amorphous		17
12.	V-R,R-XIV	422	decomposition	405	decomposition	18
13.	XVII-R-IX	393	40.70	410	decomposition	19
14.	XX-R-IX	411	decomposition	427	decomposition	20
15.	XVI-(+)-VII	Hydrate		464	decomposition	21
16.	XII-R-XVI	Hydrate		395	32.08	22

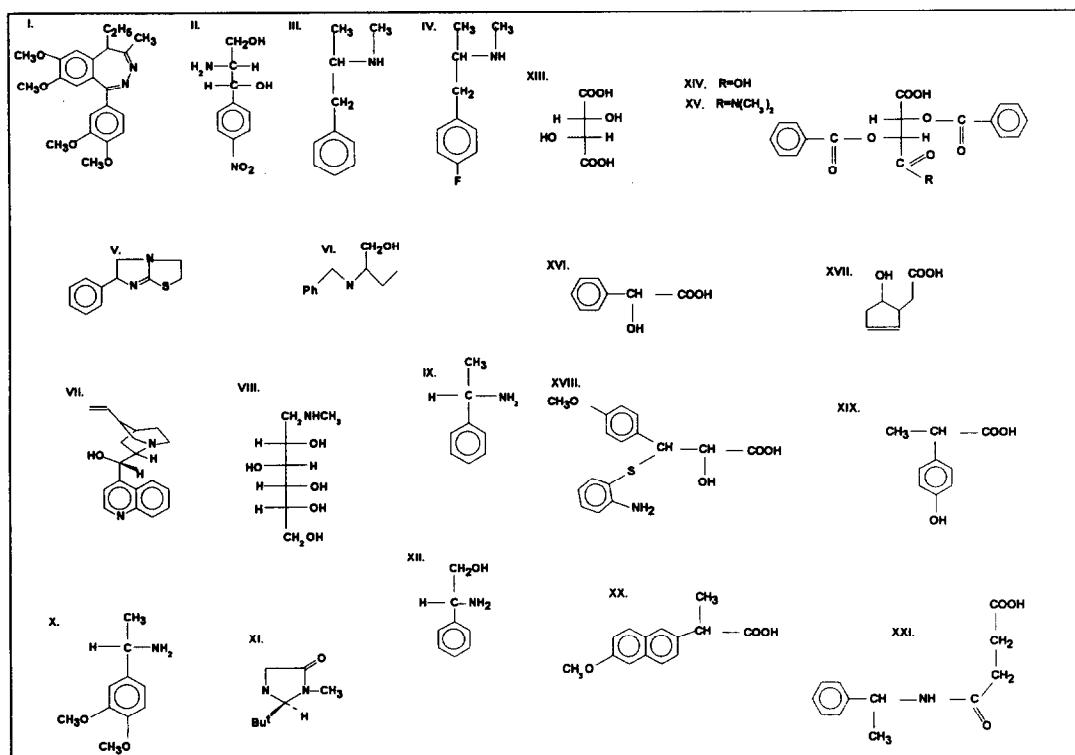
bold precipitating salt

In the cases of I-XIV,II-XV and X-XVIII one of the diastereomeric salts are not crystalline, they are amorphous. The melting phase diagram of such salt pair is meaningless. In those instances the DSC curves do not reveal any traces of melting. Always the amorphous salt remains in the mother liquor and the crystalline salt precipitates during the optical resolution. The large difference in crystallization properties of these salt pairs result the efficient resolutions.

The 1-14. cases in Table 1. are in accordance with our observation that always the higher melting salt precipitates, considering the amorphous salts as the salts with lower melting point.

At the XVI-VII and XVI-XII salt pairs one of the diastereoisomeric salt is solvated. To get a stable crystal in these two cases one molecule of water has been incorporated in the crystal structure. The solvation can easily be detected by TG. The DSC curves of solvated salts do not represent the salt taking part in the resolution process. It seems always that the solvated salt is the more stable, and that this precipitates during the resolution process.

Figure 1. The model compounds



CONCLUSIONS

Our investigations show that we can get useful information from optical resolution via diastereoisomeric salt formation by DSC and TG measurements, even if the determination of the melting phase diagram of the diastereoisomeric salt pair is hindered.

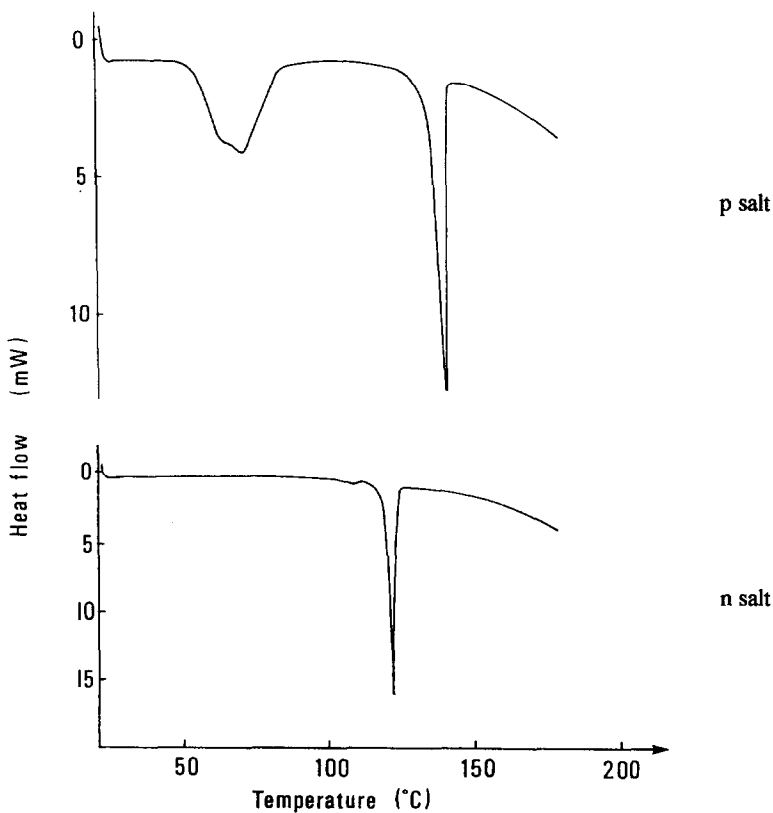
When thermal decomposition occurs usually the melting point is still observable. From the melting point of a diastereoisomeric salt pair without preparative experiments we can give some prediction for the resolution process.

Efficient resolution can be expected if there are at least 20 K differences between the melting point of the diastereoisomeric salt pair.

- Always the salt with the higher melting point will precipitate during the resolution.
- When one of the diastereoisomeric salt is amorphous we can expect successful resolution. The amorphous salt will remain in the mother liquor.
- When one of the diastereoisomeric salt is solvated that will precipitate during the resolution.

These observations can be used for selecting of resolving agent, even in case of thermal decomposition, making diastereoisomeric salt pairs of a racemate by different resolving agents, and measuring them by DSC. In lack of other thermal instrument a simple melting point device may be used.

Figure 2. The DSC curves of the R-phenyl-glycinol-R-mandelate monohydrate (XVI-XII) p salt and S-phenyl-glycinol-R-mandelate n salt



EXPERIMENTAL

The diastereoisomeric salts for DSC measurements were prepared from equimolar amounts of optically pure isomers in 96% ethanol.

The DSC curves were recorded and integrated with the aid of a DuPont 1090B Thermal Analysis System. Samples of 1-3 mg were run both in hermetically sealed and open aluminium pans with a heating rate of 5 K/min. The temperature range of thermal decomposition and loss of solvent was determined by thermogravimetric measurements (TG) (carried out on the same system).

The salts were considered having no thermal decomposition, when the loss of weight measured by TG was less than 2% at the temperature of the end of the DSC melting curve of the sample. Always the temperature of the maximum of the peak was taken as melting point. When the loss of weight was higher, but less than 2% at the temperature of the DSC melting curve maximum, we recorded an approximate melting point, but have not integrated the peak for heat of fusion value, because of the thermal decomposition. The amorphous salts can easily be recognised from the nearly horizontal DSC curves and from the reflection free X-ray powder diffractograms.

The Figure 2. shows a representative example of the DSC curves of a diastereoisomeric salt pair.

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REFERENCES AND NOTES

- 1.) Newman, P. Optical Resolution Procedures for Chemical Compounds, vols. 1-3, Optical Resolution Information Center, Manhattan College, New York, 1978-84
- 2.) Jacques, J.; Collet, A.; Willen, S.H. Enantiomers, Racemates and Resolutions, Wiley and Sons, New York, 1981
- 3.) Willen, S.H.; Collet, A.; Jacques, J. Tetrahedron, **1977**, 33, 2725
- 4.) Kozma, D.; Pokol, Gy.; Ács, M. J. Chem. Soc. Perkin Trans. 2, **1992**, 435
- 5.) p salt: diastereomeric salt formed from constituents having like sign of optical rotation; n salt diastereomeric salt formed from constituents of unlike sign of optical rotation⁶
- 6.) ref. 2 251. pp.
- 7.) 169845. Hungarian patent (1976)
- 8.) Ács, M.; Fogassy, E.; Faigl, F.; Faigl-Birkás, E.; Török, Z. Presented at the 14th International Conference on the Synthesis of Natural Products, Nancy 1988
- 9.) 2025963. British patent (1980)
- 10.) Stoll, A.; Peyer, J.; Hofmann, A. Helv. Chim. Acta, **1943**, 26, 929
- 11.) Ingersoll, A. W.; Balbock, S.H.; Burns, F.B. J. Am. Chem. Soc., **1933**, 55, 411
- 12.) Ács, M.; Novotny-Berger, E.; Simon, K.; Argay, Gy. J. Chem. Soc. Perkin Trans. 2., **1992**, 2011
- 13.) Kozma, D.; Poszavác, L.; Ács, M.; Pokol, Gy.; Fogassy, E. submitted to J. Therm. Anal.
- 14.) 8683144. Japan patent (1987)

- 15.) Tóth, G.; Fogassy, E.; Ács, M.; Tóke, L.; Láng, T. *J. Heterocyclic Chem.*, **1983**, 20, 709
- 16.) 163526. Hungarian patent (1971)
- 17.) Kozma, D. unpublished results
- 18.) Fogassy, E.; Ács, M.; Felmeri, J.; Aracs, Zs. *Per. Pol.*, 1976, 20, 247
- 19.) 177583. Hungarian patent (1978)
- 20.) Fogassy, E. unpublished results
- 21.) McKenzie, A. *J. Chem. Soc.*, **1899**, 380
- 22.) Larsen, S.; Kozma, D.; Ács, M. *J. Chem. Soc. Perkin Trans. 2*, **1994**, 000
- 23.) The heat of fusion of the p salt of III-XIII was published²⁵ as 70.0 kJ/mol with the note, that thermal decomposition process accompanies the melting. This was measured in an open DSC pan in argon atmosphere. The loss of weight starts at 388 K. The remeasurements of this salt in hermetically sealed DSC pans gives reasonable values, because in a closed system the decomposition is retarded. This is why all the DSC measurements in Table 1. were performed in hermetically sealed DSC pans.
- 24.) Thermal data for diastereoisomeric salt pair XVII-IX were published²⁶, but for the heat of fusion of the n salt an extremely large value was given: 161.5 kJ/mol. The remeasurement of the salt by TG and DSC show that the thermal decomposition starts at 407 K, so this high value involves the heat of decomposition too.
- 25.) Fogassy, E.; Ács, M.; Faigl, F.; Simon, K.; Rohány, J.; Ecsery, Z. *J. Chem. Soc. Perkin Trans. 2*, **1986**, 1881
- 26.) Ács, M.; Faigl, F.; Réti, G.; Fogassy, E.; Pokol, Gy.; Czugler, M.; Simon, K. *Proc. of 41th Int. Meeting on Phys. Chemistry, Elsevier Sci. Publ. B. V. Amsterdam*, 1987

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