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RACEMIC COMPOUND FORMATION–CONGLOMERATE FORMATION
Part 4. Optical resolution and determination of the melting phase diagrams of 2′,6′-pipecoloxylidide and four 1-alkyl-2′,6′-pipecoloxylidides[1]

Katalin Nemák[a], *Mária Ács*, *D. Kozma*[2,3] *and E. Fogassy*

Department of Organic Chemical Technology, Technical University of Budapest
Budapest POB 91, H-1521
[a]EGIS Pharmaceuticals Ltd., Budapest, Hungary

Abstract

The phenomena of conglomerate formation-racemic compound formation were investigated in a series of five (N-alkyl)-2′,6′-pipecoloxylidides. The optically active enantiomers were prepared by optical resolution of the racemates using 2R,3R-tartaric acid and 0,0′-dibenzoyl-2R,3R-tartaric acid as resolving agent. By DSC measurement of the racemates and the enantiomer the binary phase diagrams were determined.

Among the four racemic molecular compounds the N-methyl derivative is the more stable. By increasing the length of the alkyl chain the stability of the racemic compound decreased, and in case of the longest –butyl– chain conglomerate formation was observed.

Keywords: conglomerate, DSC, melting phase diagram, recemic compound

Introduction

There is a growing interest in the pharmaceutical industry for the separation of optical isomers, since usually there is substantial differences between the biological activity of the two mirror image isomers of a chiral molecule [1]. By crystallization there are two main methods applied for the separation of the racemates into their optical isomers: the optical resolution via diastereoisomeric salt formation and the optical resolution by preferential crystallization [2].

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1 Part 3. D. Kozma, Zs. Böcskei, Cs. Kassai, K. Simon and E. Fogassy: Racemic Compound Formation-Conglomerate Formation. Part 3. Investigation of the Acidic Salts of α-phenylethylamine by Achiral Dicarboxylic Acids. Optical Resolution by Preferential Crystallization and a Structural Study of R-α-phenylethylammonium hydrogen ithaconate, J. Chem. Soc. Perkin Trans. 2 (1996) 1511.

2 Author to whom all correspondence should be addressed.

3 Present address: F. Hoffmann da Roche Ltd., Basel Switzerland, CH-4070.

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The optical resolution by diastereoisomeric salt formation [3] consists at least of four main steps: formation of diastereoisomeric salts by a suitable resolving agent, separation of the diastereoisomers by crystallization, recovery of the optical isomers from the salts and recovery of the resolving agent. Meanwhile, the optical resolution by preferential crystallization is much simpler [4], it does not require any auxiliary reagent, the resolution can be performed simply by seeding the supersaturated solution of the racemate with one antipode. Unfortunately optical resolution by preferential crystallization can be accomplished in the case of conglomerate formation of the racemate. Statistical analyses demonstrated that only about 10% of the racemates forms conglomerate [5], while the majority of them forms racemic compound. In spite of the low frequency of the conglomerates, working on a resolution project as a preliminary experiment it is always worth checking whether the racemate forms conglomerate, since it can result in a very simple resolution.

As a part of a series of articles on conglomerate formation – racemic compound formation [6–8] we study in this paper the behaviour of five 2,'6'-pipecoloxylidides by determination of their melting phase diagrams.

Experimental

The DSC curves were recorded and integrated with the aid of a Perkin-Elmer DSC-2C. Samples of about 2 mg were run in hermetically sealed steal pans with the heating rate of 2.5 °C min^{-1}.

Optical resolution of the bases **1–5** *(General procedure)*

The hot solution of the racemic base (1 or 2 mol) was added dropwise to the hot alcoholic solution of the resolving acid (1 mol) [2R,3R-tartaric acid (TA) and the 0,0'-dibenzoyl-2R,3R-tartaric acid (DBTA)]. The clear solution was left to cool under effective stirring. Under 70 °C the crystals started to precipitate. These were filtered, washed with the solvent and dried. The yields are listed in Table 1.

The base was liberated from the salt by aqueous ammonium-hydroxide and extracted three times by dichloroethane. The combined organic phases were dried and the solvent was evaporated. The specific rotation was measured on a Perkin-Elmer 241 polarimeter. The optical purities were calculated as the ratio of the measured

Table 1 Summary of the resolution experiments

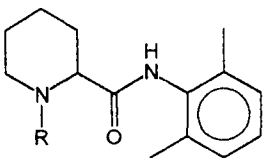
	Resolving agent	Molar ratio base: acid	Solvent	Yield/ %	Optical purity/ %	$[\alpha]_D^{20}$ of the base	Recryst. solvent
1	DBTA	2:1	*i*-PrOH	75.4	94	+43.2[a]	EtOAc
2	DBTA	1:1	EtOH	93.3	99	–63.0[b]	*i*-PrOH
3	DBTA	2:1	*i*-PrOH	63.4	73	+51.2[c]	EtOAc
4	TA	1:1	96% EtOH	93.9	95	+77.0[a]	toluene
5	TA	2:1	*i*-PrOH	68.4	100	+84.0[a]	*i*-PrOH

$[\alpha]_D^{20}$ measured in [a](c:2.3; 1NHCl); [b](c:1; MeOH); [c](c:2; EtOH)

specific rotation and the specific rotation of the pure substance. The specific rotations and the corresponding optical purities are listed in Table 1. None of the bases was completely optically pure, to increase the optical purity above 99 % the bases were recrystallized from solvents listed in the last column of Table 1.

Results and discussions

The Mepivacaine (**2**) hydrochloride and the Bupivacaine (**5**) hydrochloride are local anaesthetic agents [9]. More then twenty years ago Tullar found that the optical isomers have different pharmacological activity [10], but in spite of this recognition they are still marketed in racemic form. Working on the development of the industrial scale production of the optically active form of a related compound, we decided to investigate the conglomerate formation-racemic compound formation ability of five analogue compounds of this series (**1–5**) by determining their melting phase diagram.



where R=**1** hydrogen, R=**2** methyl, R=**3** ethyl, R=**4** *n*-propyl, R=**5** *n*-butyl

The shape of the liquidus curve of the binary phase diagram clearly indicates the type of crystallization. For the determination of the melting phase diagram it is enough to measure the sample of the racemates and one of the optical isomers by DSC, since the optically active branch of the liquidus curve can be calculated from the melting point and the heat of fusion value of the optically active enantiomer by the simplified SchroderVan Laar equation [11] Eq. (1):

$$\ln x = \frac{\Delta H_a^f}{R}\left(\frac{1}{T_a^f} - \frac{1}{T^f}\right) \tag{1}$$

where x: the molar fraction of the enantiomer; T_a^f: melting point of the optically active enantiomer (K); ΔH_a^f: heat of fusion of the optically active enantiomer (kJ mol^{-1}); T^f: the melting point, i.e. end of fusion of a mixture with a molar fraction of x (K); R: the ideal gas constant (kJ mol^{-1} K^{-1}).

When the calculated melting point at x=0.5 differ from the melting point measured for the racemate racemic compound formation can be assumed. The racemate branch of the liquidus curve can be calculated by the Prigogine-Defay-Mauser equation [12] (Eq. 2):

$$\ln 4x(1-x) = \frac{2\Delta H_r^f}{R}\left(\frac{1}{T_r^f} - \frac{1}{T^f}\right) \tag{2}$$

where T_r^f: melting point of the racemic compound (K); ΔH_r^f: heat of fusion of the racemic compound (kJ mol^{-1} K^{-1}).

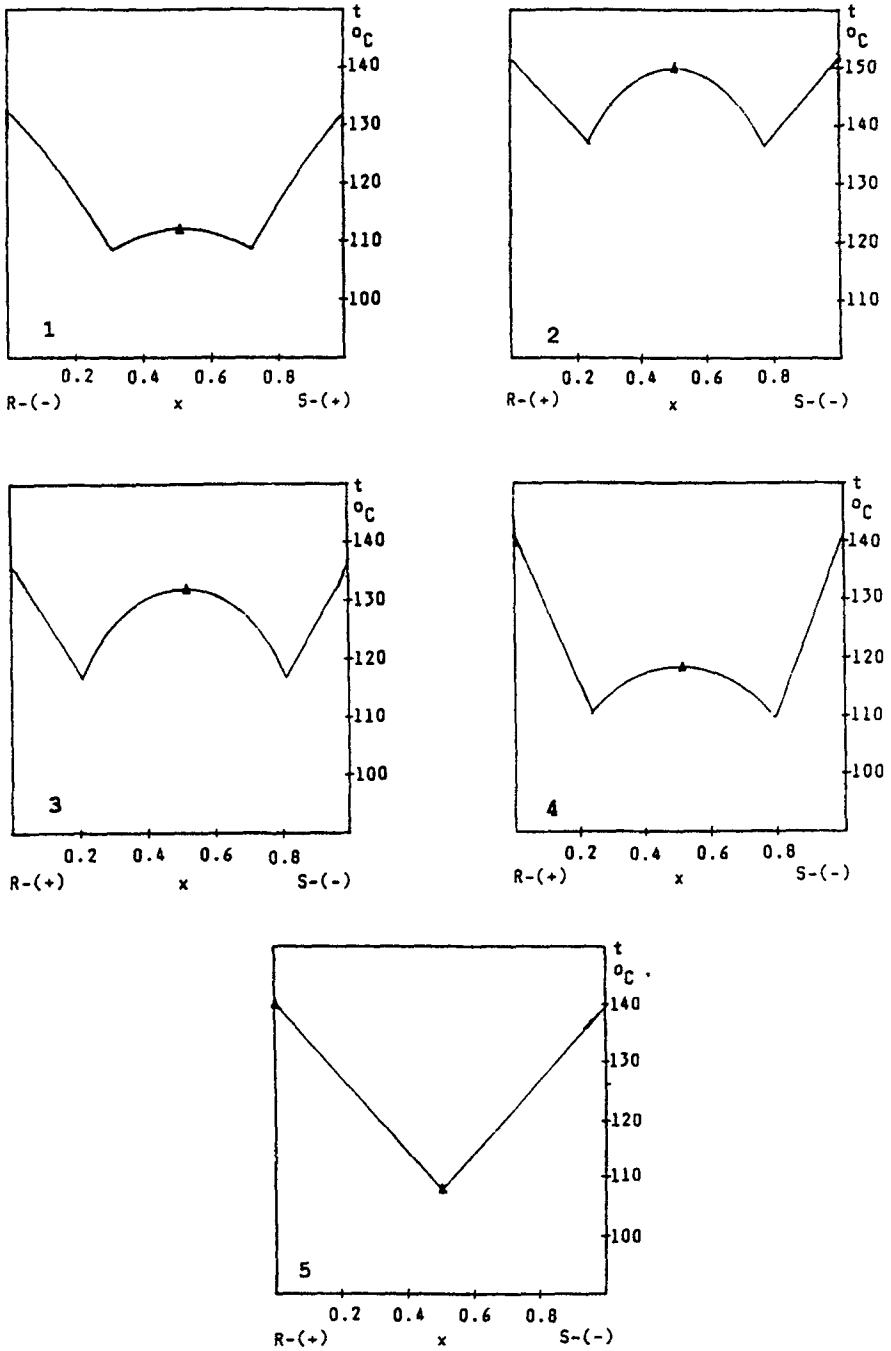


Fig. 1 The binary phase diagrams of the (N-alkyl)-2′,6′-pipecoloxylidides

The racemates of the five compounds were kindly supplied by the EGIS Pharmaceuticals, while the optical isomers was not available. The optical resolution of **1**, **2** and **5** were already published [10, 13, 14], for **3** and **4** there has been no resolution described. We prepared the optically active form of **1**, **2**, **5** by slight modification of their known resolution. For the resolution of **3** and **4** we developed new routes. **3** was resolved by 0,0'-2R,3R-dibenzoyl-tartaric acid in iso-propanol, while **4** by 2R,3R-tartaric acid in 96% ethanol. Table 1 summarizes the resolution experiments. The optical purity of the bases was increased further by recrystallization of the free bases. The optically active and racemic samples were measured by DSC, the results are summarized in Table 2. The calculated binary phase diagrams is displayed on the Fig. 1.

Table 2 The summary of the DSC measurements

	Sample	*m.p.*/ °C	Heat of fusion/ kJ mol^{-1}	$[\alpha]_D^{20}$ of the sample
1	active	130	24.19	+47.6[a]
	racemic measured	112	23.13	
	calculated	95		
2	active	153	17.77	–63.0[b]
	racemic measured	150	16.94	
	calculated	101		
3	active	135	19.90	–68.7[c]
	racemic measured	132	18.10	
	calculated	92		
4	active	141	44.50	+80.0[a]
	racemic measured	118	23.80	
	calculated	104		
5	active	140	26.25	+84.0[a]
	racemic measured	103	19.35	
	calculated	102		

$[\alpha]_D^{20}$ measured in [a](c:2.3; 1NHCl); [b](c:1; MeOH); [c](c:2; EtOH)

Only one compound, the Bupivacaine (**5**) forms conglomerate, while **1–4** form racemic compound. The racemic compounds can be classified into two groups: in the thermodynamically stable racemic compounds the racemic compound has higher melting point than the enantiomer, while the less stable racemic compound melts at lower temperatures than their constituent enantiomers. The melting point of the racemates was lower in all the four racemic compounds than that of the enantiomer, which indicates that thermodynamically they are not very stable. The comparison of the ratio of the melting temperature of the enantiomers and the race-

mates and the comparison of the absolute value of the melting point of the racemates result in the same conclusion: the N-methyl derivative (**2**) is the more stable. The stability order of the racemic compounds is the following: N-methyl (**2**) > N-ethyl (**3**) > N-propyl (**4**) > non substituted (**1**). By increasing the length of the alkyl chain the stability of the racemic compound decreased, and in case of the longest –butyl– chain conglomerate formed.

Conclusions

From the five investigated model compounds only one, the Bupivacaine forms conglomerate, providing possibility for optical resolution by preferential crystallization.

The determination of the melting phase diagram is useful, not only for the determination of the type of crystallization, but it made possible to measure the optical purity of the bases by a simple melting point measurement.

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