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Controlled design of resolutions. Prediction of the efficiency of resolutions based on samples of arbitrary composition

Eelco Ebbers,[a] Gerry J. A. Ariaans,[a] Binne Zwanenburg [a] and Alle Bruggink [a,b,*]

[a]*Department of Organic Chemistry, NSR-Center for Molecular Structure, Design and Synthesis, University of Nymegen, Toernooiveld 1, 6525 ED Nymegen, The Netherlands*

[b]*Chemferm,† De Bijster 18, 4800 DX Breda, The Netherlands*

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Abstract

The rational design of resolution processes is a topic of common interest for the industrial synthesis of enantiopure compounds. However, no efficient method for selecting suitable resolving agents for classical resolution using diastereomeric salts is available yet[1] and the selection of an appropriate resolving agent usually is a matter of trial and error. This article describes an approach using single differential scanning calorimetry (DSC) measurements on mixtures of diastereomers with arbitrary (non-racemic) compositions, with the aim of allowing a more systematic identification of efficient resolving agents and to minimize the possible errors due to uncontrolled experimental factors in the search for resolving agents. It is shown that in many cases a single DSC thermogram can provide valuable information about the maximal possible efficiency of an enantiomer resolution *via* diastereomeric salts.

1. Introduction

Ternary phase diagrams are valuable tools for the identification, selection and determination of the efficiency of resolutions based on differences of solubilities of diastereomeric salt pairs (classical resolution).[2] The formation or existence and composition of a eutectic conglomerate, a primary condition for a resolution, can be determined from the corresponding binary phase diagram. In fact, the eutectic composition represents the most important parameter governing a resolution. A more efficient resolution can be expected if the diagram shows an eccentric eutectic composition (a very high or very low x_{eu}). The maximum yield (R_{max}) and efficiency (S)[3] can be calculated from the eutectic composition using the following equations where x is the molar fraction of the least soluble diastereomer, x_{eu} the eutectic

* Corresponding author. E-mail: zwanenb@sci.kun.nl

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position, k the diastereomer or enantiomer yield (k=1 for 50% chemical yield) and t the optical purity (t=1 for 100% ee).

$$R_{max} = \frac{0.5 - x_{eu}}{1 - x_{eu}} \cdot 100\% \quad (R_{max} = 0 - 50\%,\ x_{eu} < 0.5) \tag{1}$$

$$S = k \cdot t = k = \frac{1 - 2x_{eu}}{1 - x_{eu}} \quad (S = 0 - 1,\ x_{eu} < 0.5) \tag{2}$$

The determination of a ternary phase diagram is a tedious and time consuming procedure requiring the availability of both pure diastereomers. This approach is therefore unsuited for a quick screening of potential resolving agents. However, it is well known that the eutectic composition determined from a binary (melting) phase diagram usually is a good approximation of the eutectic composition in solution.[4] Furthermore, Kozma et al.[5] have shown that such a binary phase diagram and the eutectic composition can be approximated using a single DSC thermogram of a mixture of equal amounts of the diastereomeric salts (x=0.5, obtained from the racemate), provided the mixture of diastereomers behaves ideally (no solid solution or solvent inclusion).

Preparation of mixtures of exactly equal amounts of diastereomeric salts (*i.e.* x_y=0.50) by adding a calculated amount of enantiopure base (or acid) to the racemic acid (or base) can be experimentally troublesome. The two components of the salt have to be combined in exactly equivalent amounts, which may easily lead to impure samples and less accurate results. The alternative of mixing separately prepared pure diastereomers requires the availability of the pure enantiomers. Furthermore, diastereomeric mixtures derived from a racemate with x_y=0.50 will not always give suitable thermograms, showing separate peaks for the eutectic and the pure diastereomer. We have therefore investigated the scope of this method using a modification allowing the construction of a phase diagram from a single DSC measurement of a mixture of arbitrary composition ($x_y \neq 0.5$). This is especially useful if a non-racemic sample with known composition is available from a first resolution attempt.

2. Results and discussion

From a DSC thermogram[6] of a mixture of two components consisting of a mechanical, eutectic forming mixture and with an observable separation of the eutectic and the mixture peak, the following parameters can be determined (see Fig. 1): the melting points of the eutectic (T_{eu}) and the remaining component (T_y), the absolute heats of melting (J) of the eutectic (Q_{eu}) and the remaining component (Q_p or Q_n). The melting of the eutectic will usually give a sharp peak in the thermogram, but the onset of melting of the remaining component will coincide with the melting of the eutectic and therefore both peaks will always overlap to some extent (Fig. 1). Peak fitting[7] must be applied to obtain sufficiently accurate values of the peak areas. This new approach was applied to several known and new resolutions and the results were compared with experimentally determined binary phase diagrams to evaluate its merit.

For a sample with known composition x_y (x is defined as the molar fraction of component p), the following equations can be derived starting from the Schröder–van Laar equation[8] (vide infra) (n_{tot} is the total amount (mol) of the sample):

$$\frac{x_y - x_{eu}}{1 - x_{eu}} \cdot \ln\frac{x_{eu}}{x_y} = \frac{Q_p}{n_{tot} \cdot R} \cdot \left(\frac{1}{T_y} - \frac{1}{T_{eu}}\right) \quad (x_y > x_{eu}) \tag{3a}$$

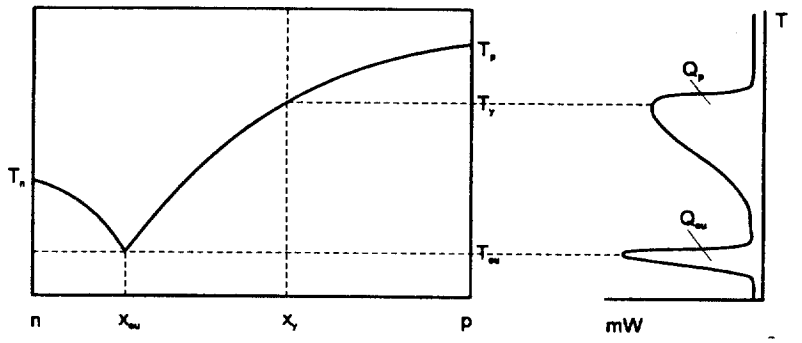

Fig. 1. Calculation of a binary phase diagram based upon a single DSC thermogram of a eutectic mixture of diastereomers with $x_y > x_{eu}$

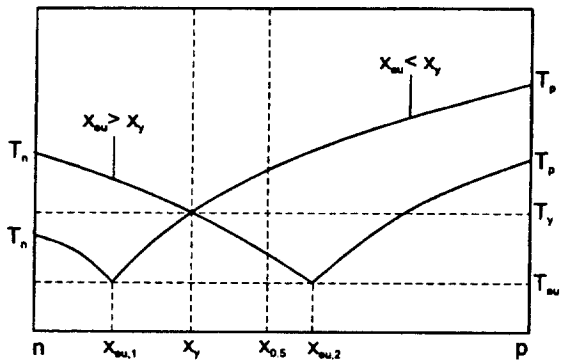

Fig. 2. Two possible binary phase diagrams based on a single DSC thermogram at x_y

$$\frac{x_{eu} - x_y}{x_{eu}} \cdot \ln\frac{1 - x_{eu}}{1 - x_y} = \frac{Q_n}{n_{tot} \cdot R} \cdot \left(\frac{1}{T_y} - \frac{1}{T_{eu}}\right) \quad (x_y < x_{eu}) \tag{3b}$$

From these equations x_{eu} can be determined numerically.[9] However, initially it is unknown whether $x_{eu} > x_y$ or $x_{eu} < x_y$, and two different values of x_{eu} will be obtained from Eq. 3a and Eq. 3b (see Fig. 2).

Additional information is therefore necessary to determine whether $x_{eu} > x_y$ or $x_{eu} < x_y$. In most cases this information is available because mixtures with $x_y \neq 0.5$ usually originate from initial resolution experiments starting from the racemic composition $x_y = 0.5$. When a mixture with composition x_y is obtained from a resolution starting from racemic material, there is an enrichment in one of the diastereomers to the side of the phase diagram opposite from x_{eu}. As a consequence, the inequalities Eq. 4a and Eq. 4b can be applied when the sample with composition x_y results from a resolution experiment starting from a racemic mixture (x=0.5).

$$x_y < 0.5 \Rightarrow x_{eu} > 0.5 \Rightarrow x_y < x_{eu} \tag{4a}$$

$$x_y > 0.5 \Rightarrow x_{eu} < 0.5 \Rightarrow x_y > x_{eu} \tag{4b}$$

For the example given in Fig. 2 this would lead to the conclusion that $x_{eu,2}$ is the correct eutectic composition. If the mixture is not obtained from a resolution procedure a second sample with a different composition will be required to distinguish between these two possibilities.

In the case that, due to overlap, no separate peaks can be determined in the DSC of the first batch of crystalline material from a resolution, a second crop of crystalline material with a different composition may be obtained by (complete) evaporation of the mother liquor.

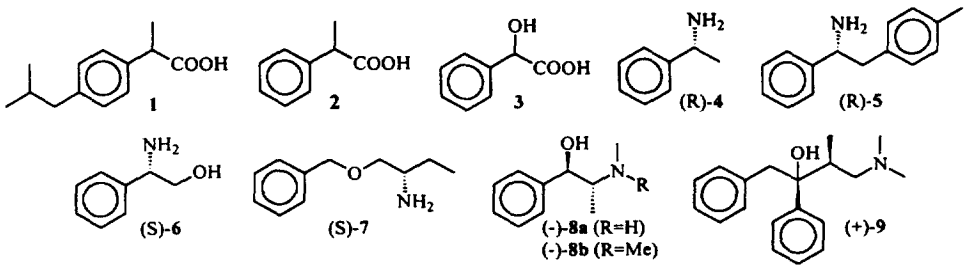

Fig. 3. Substrates and resolving agents

The heat of fusion (ΔH_p or ΔH_n) and the melting point (T_p or T_n) of the remaining diastereomer (not completely included in the eutectic) can be calculated using Eq. 5a and Eq. 5b, and Eq. 6a and Eq. 6b:

$$\Delta H_p = R \cdot T_y \cdot T_{eu} \cdot \frac{\ln(x_{eu}) - \ln(x_y)}{(T_{eu} - T_y)} \quad (x_y > x_{eu}) \tag{5a}$$

$$\Delta H_n = R \cdot T_y \cdot T_{eu} \cdot \frac{\ln(1 - x_{eu}) - \ln(1 - x_y)}{(T_{eu} - T_y)} \quad (x_y < x_{eu}) \tag{5b}$$

$$T_p = \frac{\Delta H_p}{R \cdot \ln(x_{eu}) + \frac{\Delta H_p}{T_{eu}}} \quad (x_y > x_{eu}) \tag{6a}$$

$$T_n = \frac{\Delta H_n}{R \cdot \ln(1 - x_{eu}) + \frac{\Delta H_n}{T_{eu}}} \quad (x_y < x_{eu}) \tag{6b}$$

The heat of melting of the eutectic (ΔH_{eu}) is determined by the heats of melting of the two components and the heat of mixing as shown in Eq. 7. It is therefore possible to calculate the heat of melting of the other diastereomer and the other section of the binary phase using Eq. 7 and Eq. 8a and Eq. 8b, provided that ΔH_{mix} can be neglected.

$$\Delta H_{tot} = \Delta H_{eu} + \Delta H_y = (1 - x_y) \cdot \Delta H_n + x_y \cdot \Delta H_p + \Delta H_{mix} \tag{7}$$

$$\Delta H_{eu} = \frac{Q_{eu}}{n_{tot}} \cdot \left(\frac{1 - x_{eu}}{1 - x_y}\right) \quad (x_y > x_{eu}) \tag{8a}$$

$$\Delta H_{eu} = \frac{Q_{eu}}{n_{tot}} \cdot \left(\frac{x_{eu}}{x_y}\right) \quad (x_y < x_{eu}) \tag{8b}$$

The applicability of the method described above was checked by comparing the results from experimentally determined complete binary phase diagrams with data calculated from single point measurements. Salts of the carboxylic acids ibuprofen **1**, hydratropic acid **2** and mandelic acid **3**, with the resolving agents, α-methylbenzylamine (MBA) (R)-**4**, (R)-1-phenyl-2-*p*-tolylethylamine (PTEA) (R)-**5**, (S)-phenylglycinol (S)-**6**, (S)-1-(benzyloxymethyl)-propylamine (BOP) (S)-**7**, (−)-ephedrine (−)-**8a**, (−)-*N*-methylephedrine (−)-**8b** and (+)-(2S,3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (DMDB) (+)-**9** were prepared and analyzed (Fig. 3).

The composition of the eutectic mixture (x_{eu}) and the section of the phase diagram to which the mixture belongs, could be reproduced with sufficient accuracy, *i.e.* starting from a mixture x_y (Fig. 1) the eutectic composition (x_{eu}), melting point (T_p) and section of the diagram between x_{eu} and remaining pure diastereomer could be calculated with sufficient accuracy, even though in several cases the calculated heat of fusion (ΔH_p or ΔH_n) deviated considerably from the experimentally determined value (Table 1).

Calculation of the other section of the diagram using Eq. 7, Eq. 8a and Eq. 8b resulted in incorrect values for ΔH and T_{melt} of the other diastereomer, in the cases studied. Obviously the enthalpy of mixing (ΔH_{mix}) for these diastereomeric salts cannot be neglected, as is the case for the mixing of pure enantiomers.[10] As experimental values for ΔH_p and ΔH_n are available it is possible to determine ΔH_{mix} for the examples given (Table 1). However, the inability to obtain the ΔH values with high accuracy from single DSC measurements forms no obstruction for application of this method, as the eutectic point (x_{eu}), which is the essential parameter for qualification of resolutions, is determined with sufficient accuracy.

The results of the calculations and the comparison with experimental data are collected in Table 1. These data reveal that calculation of the eutectic composition from arbitrary mixtures gives reliable results. In all cases a sufficiently accurate eutectic point (x_{eu}) was calculated (± 0.05). Therefore, this method can be applied in the selection and qualification of a resolving agent for a given substrate with a minimal amount of experimental work according to the following protocol.

- Initial resolution experiment to give a mixture of diastereomeric salts with composition x_y.
- Determination of the yield and the diastereomeric (enantiomeric) excess, which gives an impression of the experimental aspects of the resolution.
- Analyzing the mixture x_y by a single calorimetric (DSC) measurement and calculation of the eutectic composition (x_{eu}).
- Calculation of the theoretical maximal possible efficiency.
- Go/no go decision for further development of the resolution procedure.

This approach offers the advantage that a potentially useful resolving agent is not discarded because of an incorrect experimental set-up for the first resolution attempt (i.e. bad choice of solvent, temperature or concentration). Measurement of a DSC thermogram will also quickly reveal deviations from ideal behavior, such as solid solution.

Comparison of the resolving bases **4**–**8a** for ibuprofen **1** revealed that phenylglycinol **6** is the best resolving base for this compound.[16] The single point DSC calculations collected in Table 1 would have led to the same conclusion. The salt formed from ibuprofen **1** and (−)-ephedrine (−)-**8a** behaves as a solid solution, as is apparent from the DSC thermogram (only one broad peak). This observation is in line with poor resolution processes. A not frequently encountered observation was made for the salt of PTEA (R)-**5** and ibuprofen **1**, which shows partial formation of a solid solution between conglomerates. Such a case can only be identified by construction of the entire diagram. Calculation of this diagram by the present method would have led to wrong conclusions. MBA **4** was identified as the best resolving base for mandelic acid **3**, after evaluation of the bases **4**, **8** and **9**. Also in this case the same conclusion would have been obtained from the single point calculations shown in Table 1.

3. Conclusions

A method for the calculation of efficiencies of resolution starting from arbitrary conglomerate mixtures was tested. The method proved to be useful for the selection and qualification of resolution processes with a minimal amount of experimental work using the described protocol. Peak fitting software for separating DSC peaks is indispensable for obtaining reliable results.

The method is restricted to diastereomeric mixtures forming a eutectic or enantiomers forming a conglomerate (majority of crystalline diastereomeric salts, minority of crystalline enantiomers). Solid solutions can be identified by a single broad peak in the DSC thermogram. However, partial formation of solid solutions cannot be identified properly and may lead to false conclusions. Also, the inclusion of solvates or (pseudo)-polymorphism cannot be established by this method.

Table 1
Calculation of the physico-chemical data of conglomerates from DSC experiments and comparison with experimental data[11–15]

Salt	Experimental values from DSC				Calculated					Ref.
	x_y	Q_p/n_{tot} (kJ/mol)	Q_{eu}/n_{tot} (kJ/mol)	T_y (K)	T_{eu} (K)	x_{eu}	S_{max}	ΔH_p (kJ/mol)	ΔH_n (kJ/mol)	T_p (K)	T_n (K)	ΔH_{mix} (kJ/mol)	
(R/S)-**1**•(S)-**4**	0.16	52.2	2.8	445	421	0.71	0.59		67.6		450	-6.3	
	0.38	36.1	12.7	438	422	0.72	0.61		76.9		448	-11.9	
	0.46	28.6	20.9	435	423	0.71	0.59		80.5		447	-10.9	
	0.50	23.5	25.7	432	423	0.70	0.57		81.7		446	-11.1	
	0.71	19.8	27.1	424	422	0.65	0.46	104.8		429		-12.8	
Obtained from complete binary phase diagram:					*422*	*0.66*	*0.48*	*58.8*	*61.8*	*433*	*450*		*11*
(R/S)-**1**•(S)-**6**	0.67	15.9	13.4	389	369	0.89	0.88		64.5		412	+1.4	
	0.73	11.3	11.8	382	368	0.88	0.86		66.1		408	-3.4	
	0.78	5.1	13.1	376	364	0.87	0.85		49.1		417	-7.2	
	0.88	1.7	17.2	372	367	0.85	0.82	8.6		390		-4.2	
Obtained from complete binary phase diagram:					*370*	*0.83*	*0.80*	*20.4*	*43.1*	*374*	*419*		*11*
(R/S)-**1**•(S)-**7**	0.25	7.8	11.8	342	339	0.33	0.51		34.5		351	-9.9	
	0.40	4.9	14.8	343	338	0.32	0.53	42.2		365		-10.8	
	0.50	7.8	20.5	351	343	0.37	0.41	37.8		371		-2.8	
Obtained from complete binary phase diagram:					*339*	*0.33*	*0.51*	*34.3*	*27.9*	*363*	*349*		*11*
(R/S)-**2**•(S)-**4**	0.10	13.3	20.5	416	406	0.24	0.68		22.7		423	-9.3	
	0.70	31.0	10.8	427	406	0.31	0.55	54.9		437		-5.8	
	0.75	32.1	6.1	429	402	0.30	0.67	49.9		437		-9.7	
	0.80	35.8	1.9	432	402	0.36	0.37	49.8		439		-10.6	
Obtained from literature data:					*406*	*0.33*	*0.51*	*51.6*	*41.9*	*437*	*420*		*12, 13*
(R/S)-**3**•(S)-**4**	0.50	36.2	0.3	430	382	0.97	0.97		75.1		445	+2.6	
	0.50	31.3	0.9	430	378	0.96	0.96		65.3		447	-1.8	
	0.80	25.1	6.4	403	381	0.98	0.98		135.3		421	+1.8	
Obtained from complete binary phase diagram:					*381*	*0.91*	*0.90*	*26.9*	*41.0*	*386*	*449*		*12, 14, 15*
(R/S)-**3**•(-)-**8b**	0.20	7.3	13.4	352	346	0.12	0.86	82.4		373		-10.9	
	0.30	3.3	14.8	361	346	0.20	0.75	27.3		416		-14.6	
	0.40	12.4	13.6	369	347	0.16	0.81	43.8		394		-7.7	
	0.50	16.4	14.8	378	353	0.19	0.77	42.7		399		-3.6	
Obtained from complete binary phase diagram:					*348*	*0.18*	*0.78*	*40.1*	*29.5*	*405*	*365*		*14*
(R/S)-**3**•(+)-**9**	0.12	58.9	0.2	439	416	0.69	0.55		71.0		441	+0.7	
	0.40	16.4	36.3	426	417	0.57	0.25		53.2		441	-5.3	
	0.50	7.9	48.4	424	418	0.59	0.31		52.7		444	-1.6	
	0.80	32.4	37.6	421	416	0.63	0.41	70.3		426		+12.5	
Obtained from complete binary phase diagram:					*415*	*0.65*	*0.46*	*57.2*	*58.6*	*427*	*440*		*14*

Despite these limitations this method is useful for a first selection and qualification of resolution processes following the protocol described and offers an improvement of the traditional 'trial and error' method.

4. Derivation of the equations

The starting point is a mixture of two pure isomers (diastereomers or conglomerate forming enantiomers) **n** and **p** which form a mechanical mixture with composition $x_{p,y}$ (Eq. 9). The total amount of this mixture (n_{tot}) is described by Eq. 11, and the total amount of the eutectic contained within this mixture n_{eu} is described by Eq. 12. The following variables can be obtained from a single DSC thermogram: melting point of the eutectic (T_{eu}) and remaining component (T_y) respectively, heat of melting of the eutectic (Q_{eu}) and of the remaining component (Q_p).

$$x_{p,y} = \frac{n_{p,y}}{n_{tot}} \Leftrightarrow n_{p,y} = n_{tot} \cdot x_{p,y} \tag{9}$$

$$x_{n,y} = 1 - x_{p,y} = \frac{n_{n,y}}{n_{tot}} \Leftrightarrow n_{n,y} = n_{tot} \cdot (1 - x_{p,y}) \tag{10}$$

$$n_{tot} = n_{n,y} + n_{p,y} \text{ (n in mol)} \tag{11}$$

$$n_{eu} = n_{n,eu} + n_{p,eu} \tag{12}$$

When the sample is richer in component **p** than the eutectic (*i.e.* $x_{p,y} > x_{p,eu}$) the amount of eutectic (n_{eu}) is determined exclusively by the amount of component **n** present in the mixture, and the sample can be considered to be a mixture of eutectic and excess component **p** (component **n** is completely integrated in the eutectic, Eq. 13). The amount of component **p** not integrated in the eutectic (n_p) is given by Eq. 14.

$$n_{n,eu} = n_{n,y} \tag{13}$$

$$n_p = n_{p,y} - n_{p,eu} \tag{14}$$

The molar fraction of the eutectic is defined as shown in Eqs 15 and 16.

$$x_{p,eu} = \frac{n_{p,eu}}{n_{eu}} \tag{15}$$

$$x_{n,eu} = 1 - x_{p,eu} = \frac{n_{n,eu}}{n_{eu}} \tag{16}$$

Combination of Eqs 13–16 leads to Eq. 17.

$$n_p = n_{p,y} - \left(\frac{x_{p,eu}}{1 - x_{p,eu}}\right) \cdot n_{n,y} \tag{17}$$

Combination of Eq. 17 with Eqs 9 and 10 leads to Eq. 18.

$$n_p = \left(\frac{x_{p,y} - x_{p,eu}}{1 - x_{p,eu}}\right) \cdot n_{tot} \tag{18}$$

The following two relations (Eqs 19 and 20) are given by the simplified Schröder–van Laar equation[8] where ΔH_p is the heat of fusion of component **p**, R is the gas constant, T_p and T_{eu} the melting point of

pure component **p** and the eutectic respectively. Eliminating T_p by combination of Eqs 19 and 20 results in Eq. 21.

$$\ln(x_{p,y}) = \frac{\Delta H_p}{R} \cdot \left(\frac{1}{T_p} - \frac{1}{T_y}\right) \tag{19}$$

$$\ln(x_{p,eu}) = \frac{\Delta H_p}{R} \cdot \left(\frac{1}{T_p} - \frac{1}{T_{eu}}\right) \tag{20}$$

$$\ln\left(\frac{x_{p,eu}}{x_{p,y}}\right) = \frac{\Delta H_p}{R} \cdot \left(\frac{1}{T_y} - \frac{1}{T_{eu}}\right) \tag{21}$$

Using Eq. 18 the heat of fusion of component **p** (ΔH_p) can be expressed as shown in Eq. 22.

$$\Delta H_p = \frac{Q_p}{n_p} = \frac{Q_p}{n_{tot}} \cdot \left(\frac{1 - x_{p,eu}}{x_{p,y} - x_{p,eu}}\right) \tag{22}$$

Finally, combination of Eqs 21 and 22 leads to Eq. 3a.
For the case that $x_y < x_{eu}$ replacing x_{eu} with $1-x_{eu}$, x_y with $1-x_y$ and Q_p with Q_n leads to Eq. 3b.

5. Experimental section

Racemic and enantiopure (S)-ibuprofen **1** were a kind gift from DSM Andeno, Venlo, The Netherlands. (R)-Ibuprofen **1** was prepared by resolution with MBA **4** and recrystallization of the obtained optically enriched (R)-ibuprofen, (R)-MBA salt or of the ibuprofen sodium salt. The chiral base 1-(R)-phenyl-2-*p*-tolyl-ethylamine (PTEA) **5** was a kind gift from Sumitomo Chemical Co. Ltd, Japan.

Enantiomeric excesses of ibuprofen **1**, hydratropic acid **2** and mandelic acid **3** were determined using chiral HPLC (Daicel Chiralcel ODH column, UV-detection at 254 nm, flow-rate 0.5 ml/min): ibuprofen **1** (eluent: hexane/2-propanol/trifluoroacetic acid=980/20/2.5, v/v), hydratropic acid **2** (eluent: hexane/2-propanol/trifluoroacetic acid=950/50/2.5, v/v), mandelic acid **3** (eluent: hexane/2-propanol/trifluoroacetic acid=875/125/2.5, v/v).

Calculations were performed using Microsoft Excel© version 5.0 for Windows.

5.1. DSC

DSC thermograms were determined using a Perkin–Elmer DSC7 instrument, calibrated with In and Zn or Sn. Samples (2–10 mg) were weighed with an accuracy of 0.01 mg and encapsulated in stainless steel large volume pans (75 μl). Thermograms were recorded at a scanning rate of 10°C/min, a data rate of 0.4–0.8 sec/point and with an empty pan as a reference under a nitrogen atmosphere. Melting points are given as the top of the peaks because of broad peaks. Fitting of peaks for accurate determination of peak surface areas was performed using PeakFit™© version 4 (Jandel Scientific Software). Pearson IV peaks were used as peak descriptors.

5.2. Preparation of salts

Pure diastereomeric salts were prepared by mixing equimolar amounts of the respective enantiopure bases **4–9** and enantiopure acids **1–3** in ethanol. The salts obtained were allowed to crystallize, filtered and then dried in vacuo.

Diastereomeric salt mixtures were prepared by the method described by Jacques, Collet and Wilen.[17] Accurately weighed amounts of the pure salts were dissolved in ethanol and the solution obtained was evaporated. The residue was dried in vacuo. The composition of mixtures obtained was analyzed by chiral HPLC of the free ibuprofen **1**, hydratropic acid **2** or mandelic acid **3**.

5.3. Hydrolysis of ibuprofen, hydratropic acid or mandelic acid salts (general procedure)

Ibuprofenates or hydratropates were acidified with 1 N aqueous sulfuric acid to pH 1–2, stirred for 0.5 h at room temperature and extracted with dichloromethane (three times). The combined organic layers were extracted with brine, dried over $MgSO_4$ and concentrated in vacuo to give ibuprofen **1** or hydratropic acid **2**.

Mandelates were acidified with 2 N aqueous hydrochloric acid to pH 1–2, stirred for 0.5 h at room temperature and extracted with ethyl acetate (three times). The combined organic layers were extracted with brine, dried over $MgSO_4$ and concentrated in vacuo to give mandelic acid **3**.

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