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Dutch resolution of racemic 4-hydroxy- and 4-fluorophenylglycine with mixtures of phenylglycine and (+)-10-camphorsulfonic acid

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Abstract

4-Hydroxyphenylglycine and 4-fluorophenylglycine can be resolved with (+)-10-camphorsulfonic acid only if DL- or D-(–)-phenylglycine is added. When using DL-phenylglycine this is co-resolved in this process. In this resolution process mixed crystals are formed of the (+)-10-camphorsulfonic acid salts of the D-(–)-enantiomers of phenylglycine and the *para* substituted phenylglycines. In the crystal lattice of the mixed salts approximately 25–30% of the D-(–)-phenylglycine molecules can be randomly replaced by D-(–)-*para* substituted phenylglycines, resulting in the desired resolution. The overall non-stoichiometric composition of the mixed crystals reflects to some extent the composition in solution. This behaviour is typical for solid solutions. The solid solution behaviour in this so called 'Dutch resolution' is proven by differential scanning calorimetry (DSC), X-ray crystal structure determination and powder diffraction.

1. Introduction

Classical resolution is an important technology for the preparation of enantiopure compounds on an industrial scale. However, finding a suitable resolution method is still a method of trial and error,[1] and very often hampered by the formation of (end) solid solution behaviour of the diastereomeric salts.[2–5] If so, an effective resolution can only be accomplished by subsequent recrystallisations resulting in a substantial loss of product and resolving agent. In extreme cases, in which the diastereomeric salts show solid solution behaviour over the entire range of various

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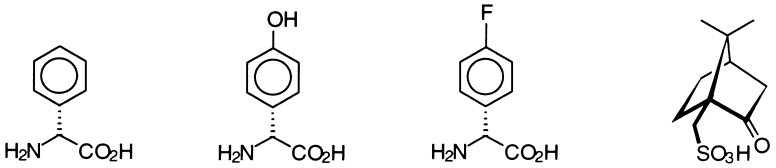
diastereomeric compositions, only by repetitive and time consuming fractional crystallisation can enantiopure product be obtained.[6,7]

Recently we have described the use of mixtures (family) of resolving agents in classical resolutions.[8,9] We have coined the name 'Dutch resolution' for this technology. Use of this classical resolution technology improves the success rate of finding a suitable resolution for most racemates tested.

In this paper we describe the use of this alternative Dutch resolution method for the preparation of enantiopure D-(–)-4-hydroxyphenylglycine (D-Hpg) and D-(–)-4-fluorophenylglycine (D-Fpg) using (+)-10-camphorsulfonic acid ((+)-CSA) as a resolving agent. Racemic Hpg is resolved on an industrial scale with (+)-3-bromocamphor-8-sulfonic acid. However, this resolving agent is expensive and difficult to recycle. On the other hand, racemic phenylglycine (DL-Phg) is resolved with the much cheaper (+)-CSA on a multi-ton scale.[10] The D-enantiomers of both amino acids are widely used for the production of semi-synthetic antibiotics.[11]

4-Fluorophenylglycine (Fpg), especially the L-(+)-enantiomer, has recently received attention as intermediate for substance P analogues.[12] The resolution of DL-Fpg with various resolving agents results only in racemic salt mixtures. Only after esterification could the methyl ester be resolved using 0.25 equiv. of (+)-dibenzoyl tartaric acid.[13]



D-Phg D-Hpg D-Fpg (+)-CSA

The resolution of DL-Hpg is hampered by the formation of mixed crystals with a full solid solution behaviour of both diastereomers. In fact, as can be seen in Fig. 1, the diastereomeric salts form a Roozenboom II type of solid solution[14] in which an approximately 1:1 mixture of the diastereomers has the lowest solubility. In this case even fractional crystallisation is unsuccessful since the racemate of Hpg tends to crystallise. In fact, the solubilities of both diastereomerically pure Hpg·(+)-CSA salts are so high that they could not be determined.

Since neither DL-Hpg nor DL-Fpg can be directly resolved with (+)-CSA we decided to test the principle of Dutch resolution using mixtures of racemates for these two compounds in combination with the DL-Phg resolution with (+)-CSA.

2. Results and discussion

2.1. Dutch resolution of DL-4-hydroxyphenylglycine

Initially, mixtures of DL-Hpg and DL-Phg were crystallised in various ratios with 0.75 equiv. of (+)-CSA in 1N hydrochloric acid (according to the method of Pope and Peachey[15]). The results of this crystallisation study are shown in Table 1. In all (Dutch) resolution experiments crystalline 1:1 salts are formed consisting of a mixture of enantiomerically enriched D-(–)-Phg and D-(–)-Hpg with (+)-CSA.[16] The e.e. of both phenylglycines can be improved to above 99% by recrystallisation.

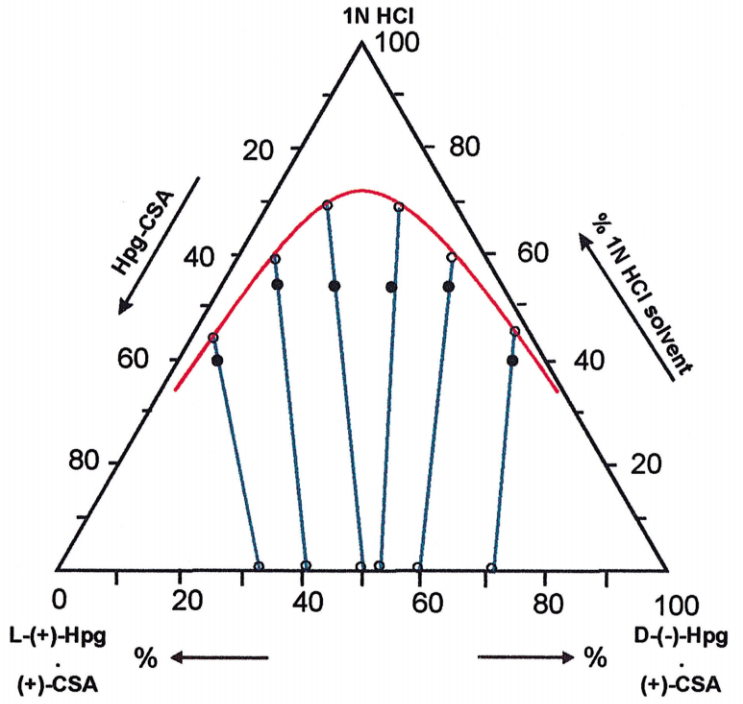


Figure 1. Solubility phase diagram of salts of DL-Hpg and (+)-CSA (solubility curve in red; tie lines in blue; ● starting composition; ○ end composition of saturated solution and solid)

Table 1
Resolution of DL-Hpg with DL-Phg and (+)-CSA

starting ratio Hpg : Phg	crystall. yield	ratio Hpg : Phg	e.e.%** Phg	e.e.%** Hpg
0 : 100	44%	--	87 (>99)	--
25 : 75	35%	13 : 87	94 (>99)	94 (100)
50 : 50	17%	25 : 75	95 (>99)	89 (>95)
75 : 25	5%	31 : 69	94	58
100 : 0*	41%*	--	--	< 5

All resolutions are performed on 10 - 100 mmol scale starting with 40 wt% solutions in 1N HCl and with 0.75 eq. of (+)-CSA, except: * starting concentration is 46 wt%, ** in parenthesis e.e.% after recrystallisation from 1N HCl solution.

There is a strong preference for the incorporation of D-(–)-Phg over D-(–)-Hpg in all crystallisations. Actually, on repeated crystallisation D-(–)-Hpg is slowly lost and diastereomerically pure D-(–)-Phg·(+)-CSA remains.

The resolution of racemic Hpg can be improved by gradual replacement of DL-Phg in the simultaneous resolution with half of the amount of enantiomerically pure D-(–)-Phg. As can be seen from Table 2 the (inert) fraction of L-(+)-Phg can be omitted without a considerable influence on the Hpg resolution performance (for example, compare entry 3 in Table 1 with entry 1 in Table 2).

Table 2
Resolution of DL-Hpg with D-(–)-Phg and (+)-CSA

starting ratio DL-Hpg : D-(-)-Phg	crystall. yield	ratio Hpg : Phg	e.e.% Hpg
67 : 33	26%	26 : 74	87%
50 : 50	53%	19 : 81	67%

Starting concentration 40 wt% in 1N HCl solution and 0.70 eq. of (+)-CSA.

In a typical multi-gram scale experiment the resolution of a 1:1 mixture of DL-Hpg (8.4 g, 50 mmol) and D-(–)-Phg (3.8 g, 25 mmol) with 0.67 equiv. (11.6 g, 50 mmol) of (+)-CSA (40 wt% in 1N HCl solution) produced 7.4 g of mixed crystalline salt (Hpg:Phg 26:74, $e.e._{Hpg}$ 84%). After this first crystallisation step a second crop of mixed salt can be obtained from the mother liquor upon addition of a second portion of D-(–)-Phg (3.8 g). Thus, another 7.1 g of mixed salt are obtained with a somewhat lower Hpg content (Hpg:Phg 15:85) but with an even higher e.e. of 88%.

2.2. DSC measurements and X-ray diffraction of the mixed crystals

To get more insight into the nature of the simultaneous resolution, diastereomerically pure mixed crystals of D-(–)-Hpg and D-(–)-Phg with (+)-CSA were prepared for differential scanning calometry (DSC) and X-ray analysis (ratio Hpg:Phg 26:74). DSC measurements reveal that the mixed crystals have a congruent melting point which is only slightly lower than that of the pure D-(–)-Phg·(+)-CSA salt (see Table 3). On the other hand, the heat of fusion (ΔH_f) of the mixed crystals is considerably lower than that of the pure D-(–)-Phg salt, indicating that the pure D-(–)-Phg·(+)-CSA salt is more stable than the mixed salt. This is in agreement with the observation that D-(–)-Hpg is lost after repetitive crystallisations. The fact that the mixed crystals show one (sharp) melting point is typical for solid solution behaviour of quasi-racemates with a homogeneous composition of the solid state.[17–19] This is confirmed by single crystal X-ray analysis (vide supra). Also the single melting point of DL-Hpg·(+)-CSA confirms the solid solution behaviour observed earlier (Fig. 1).

The X-ray crystal structures of D-(–)-Phg·(+)-CSA and of a D-(–)-Hpg/D-(–)-Phg·(+)-CSA mixed crystal (ratio 26:74) are determined and shown in Figs. 2 and 3. The crystallographic data can be found in Table 4. Comparisons of the two unit cells are shown both in Table 4 and Fig. 4.

Table 3
DSC data of D-(–)-Hpg/D-(–)-Phg·(+)-CSA mixed crystals (ratio 26:74) compared with D-(–)-Phg·(+)-CSA and DL-Hpg·(+)-CSA crystals

	melting point	ΔH_f
D-(-)-Hpg/D-(-)-Phg.(+)-CSA	204.1 °C	96 J/g
D-(-)-Phg.(+)-CSA	205.1 °C	116 J/g
DL-Hpg.(+)-CSA	129.6 °C	80 J/g

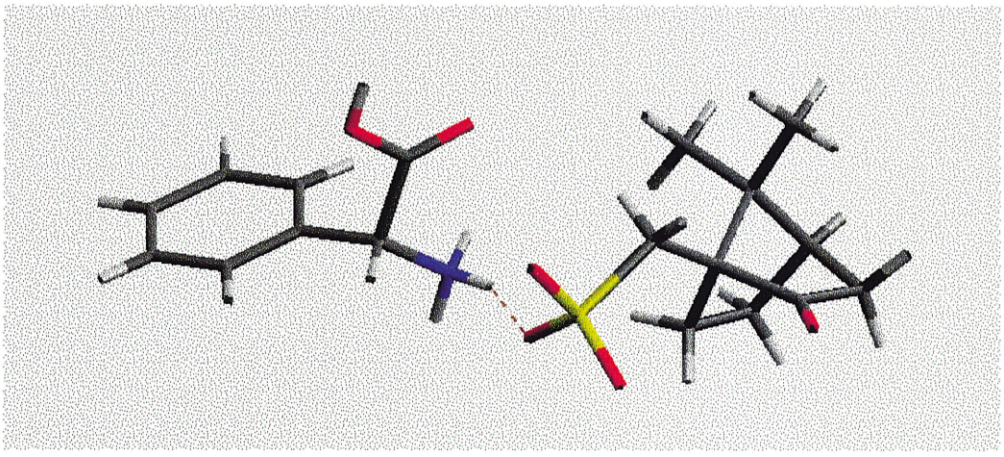


Figure 2. X-Ray crystal structure of D-(–)-Phg·(+)-CSA

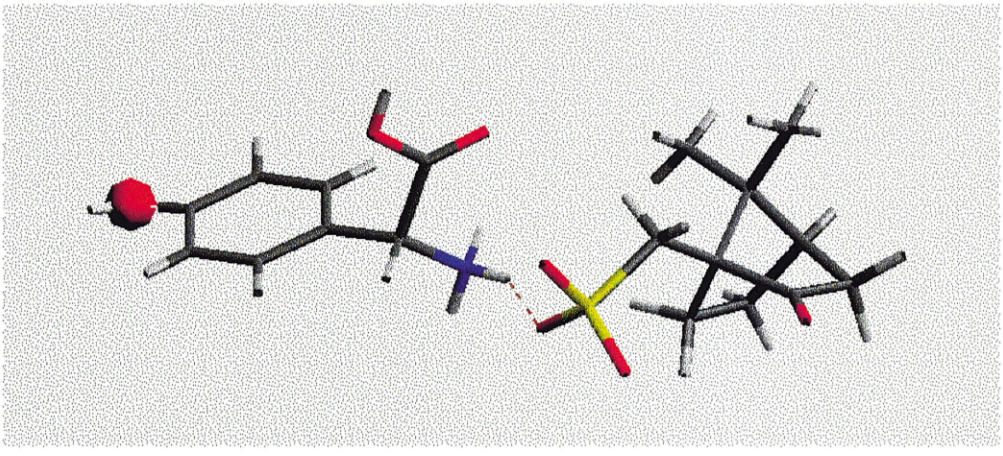


Figure 3. X-Ray crystal structure of D-(–)-Hpg/D-(–)-Phg·(+)-CSA mixed crystals

Table 4
Crystal data and details of the structure determination of D-(–)Phg·(+)-CSA and D-(–)Hpg/D-(–)Phg·(+)-CSA mixed crystals

	D-(-)Phg.(+)-CSA	**D-(-)Hpg/D-(-)Phg.(+)-CSA**
Moiety formula	$[C_{10}H_{15}O_4S]^-.[C_8H_{10}NO_2]^+$	$[C_{10}H_{15}O_4S]^-.[C_8H_{10}NO_2]^+_{0.776}\,[C_8H_{10}NO_3]^+_{0.224}$
Formula Weight, g.mol^{-1}	383.47	387.06
Crystal system	Orthorhombic	Orthorhombic
Space Group, no.	$P\,2_12_12_1$, 19	$P\,2_12_12_1$, 19
a, Å	6.847(1)	6.857(2)
b, Å	15.285(1)	15.348(4)
c, Å	17.092(1)	17.144(6)
V, Å^3	1788.8(3)	1804.3(9)
Formula Z	4	4
Space Group Z	4	4
Z (=Formula Z / Space Group Z)	1	1
ρ_{calc}, g.cm^{-3}	1.424	1.425
F (000), electrons	816	823.2
μ (MoKα), cm^{-1}	2.2	2.2
colour, habit	colourless, prism	colourless, prism
Crystal size, mm^3	0.25 x 0.28 x 0.5	0.13 x 0.36 x 0.38

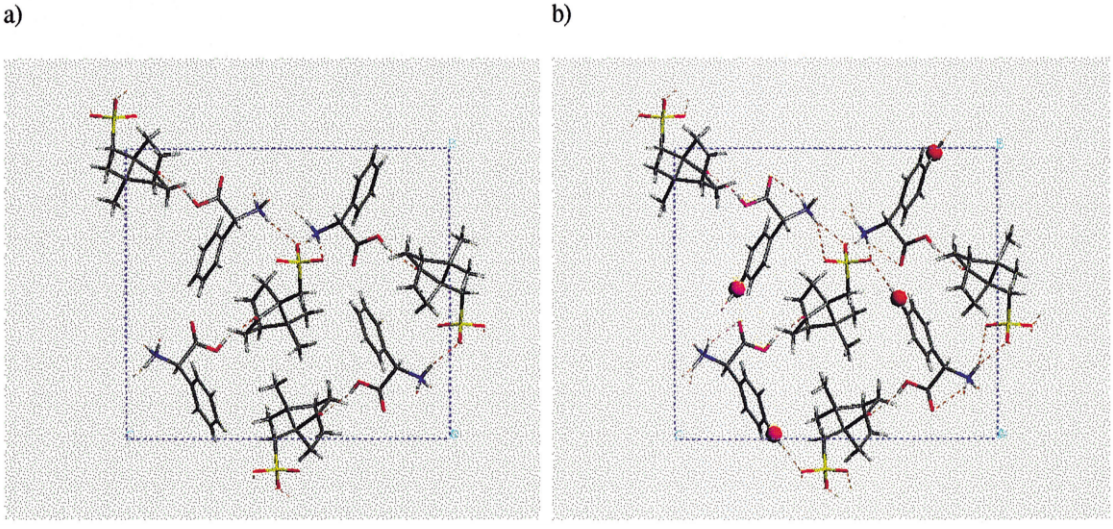


Figure 4. Unit cells of (a) D-(–)-Phg·(+)-CSA and (b) D-(–)-Hpg/D-(–)-Phg·(+)-CSA mixed crystals

In the mixed crystal D-(–)-Phg and D-(–)-Hpg are randomly distributed in the crystal lattice, which is typical for solid solution behaviour. From the X-ray crystal structures it can be seen that the Phg and Hpg units appear superimposed and occupy positions with orientations also observed for Phg in the D-(–)-Phg·(+)-CSA crystal structure. In addition to all of the Phg–CSA interactions in the crystal lattice, the Hpg units form an additional hydrogen bond to the CSA sulfonate group. Due to the incorporation of Hpg the unit cell parameters of the mixed salt slightly differ from the D-(–)-Phg·(+)-CSA salt. The random incorporation of Hpg is also

translated into a slightly higher (apparent) thermal movement and refraction index (R(F) = 0.0253 and 0.0584, respectively).

2.3. Dutch resolution of DL-4-fluorophenylglycine

Identical to the Dutch resolution of DL-Hpg described above, the resolution of racemic Fpg was performed with (+)-CSA and various amounts of DL-Phg (see Table 5). Also in these experiments the D-(–)-Fpg/D-(–)-Phg·(+)-CSA mixed salt preferentially crystallises. However, the e.e.s of D-(–)-Fpg are somewhat lower compared to the Hpg experiments and there is a stronger preference for inclusion of D-(–)-Phg.

Table 5
Resolution of DL-Fpg with DL-Phg and (+)-CSA

starting ratio Fpg : Phg	crystall. yield	ratio Fpg : Phg	e.e.% Phg	e.e.% Fpg
25 : 75	25%	9 : 91	92	83
50 : 50	28%	24 : 76	85	52
75 : 25	4%	38 : 62	85	40
100 : 0	n.d.*	--	--	< 5

All resolutions are performed on 10 mmol scale starting with 40 wt% solutions in water and with 1.0 eq. of (+)-CSA. * n.d. is not determined.

After recrystallisation of a primarily obtained mixed salt, the diastereomerically pure D-(–)-Fpg/D-(–)-Phg·(+)-CSA mixed salt could be obtained, although with only low contents of D-(–)-Fpg. Consequently, the resolution efficiency is rather low, but resolution is not possible without addition of racemic Phg.[13] No further resolution experiments with addition of enantiomerically pure D-(–)-Phg were performed.

3. Conclusions

From all of the results above it can be concluded that D-(–)-Hpg and D-(–)-Fpg show solid solution behaviour with D-(–)-Phg in the crystalline salts with (+)-CSA, with a preference for the incorporation of D-(–)-Phg. The ratio between D-(–)-Hpg/D-(–)-Phg or D-(–)-Fpg/D-(–)-Phg is always non-stoichiometric and no preferred/stable composition is found. Repeated crystallisation results in pure D-(–)-Phg·(+)-CSA crystals with loss of D-(–)-Hpg and D-(–)-Fpg. The latter can be isolated from the mother liquor.

In addition to the presented Dutch resolution of DL-Hpg and DL-Fpg other derivatives of phenylglycine also show the same behaviour. Preliminary experimental results show that the methyl ester of Hpg as well as the amide of Phg can be resolved with (+)-CSA and racemic Phg

also forming mixed crystals. X-Ray powder diffraction confirms the formation of mixed crystals with unit cell parameters identical with the D-(–)-Phg·(+)-CSA salt.

4. Experimental

4.1. Resolution experiments

All resolution experiments were performed on a 10–100 mmol scale by mixing the various phenylglycines and (+)-10-camphorsulfonic acid at room temperature in water or 1N HCl solution with starting concentrations and ratios as described in Tables 1, 2 and 5. The mixture was heated at 70–100°C to dissolve the salts and then slowly cooled under stirring to room temperature. In all experiments spontaneous crystallisation started on cooling. The mixtures were left stirring at room temperature for 5–18 h to reach (thermodynamic) equilibrium. Crystalline salts were filtered off and air-dried to constant weight. The composition and enantiomeric excess were determined by chiral HPLC. Column: C-18 Nucleosil 12.5 cm in series with a Chrompack CR(+), eluent: 0.10 M $HClO_4$ solution, flow: 0.8 ml/min, temp.: 25°C, sample concentration: 30 mg/100 ml, injection volume: 20 μl, detection: UV 254 nm.

Retention times (min):	Phg	Hpg	Fpg
D-(-)	7.02	4.22	8.21
L-(+)	12.91	10.33	15.90

4.2. DSC

DSC thermograms were determined using a Netzsch DSC200 instrument, calibrated with In, Pb, Zn and Sn. Samples (7–10 mg) were weighed with an accuracy of 0.01 mg and encapsulated in reusable high pressure stainless steel pans (40 μl, Perkin–Elmer, sealed under nitrogen). Thermograms were recorded at a scanning rate of 5°C/min, with an empty pan as reference under a nitrogen atmosphere. With broad lines the onset temperature was taken as the start of the melting point (solidus line); the top of the peaks were taken as the end of melting (liquidus line).

4.3. Crystal structure determination

Single crystal X-ray diffraction of a D-(–)-Phg·(+)-CSA crystal (parallelepiped, size $0.25\times0.28\times0.50$ mm) and of a D-(–)-Phg/D-(–)-Hpg·(+)-CSA mixed crystal (parallelepiped, size $0.13\times0.36\times0.38$ mm) was performed on an Enraf–Nonius CAD-4F diffractometer, interfaced to an INDY (Silicon Graphics) UNIX computer (Mo tube, 50 kV, 40 mA, monochromated Mo–Kα radiation, $\Delta\omega = 1.20+0.34$ tg θ). Unit cell parameters can be found in Table 4; additional information is available from Cambridge Crystallographic Data Bank.

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