[12] X-ray analyses: Cellobioside crystals **I** and **II** were mounted on glass fibres. Diffraction data were collected on a $\kappa$-CCD (ENRAF-NONIUS) diffractometer, $T = 298$ K, $\mathrm{Mo}_{K\alpha}$, $\lambda = 0.71073$ Å (graphite monochromator). The structures were solved by direct methods (SIR-92).[22] Lorentz and polarization corrections were applied, but no correction was made for absorption, given the small crystal dimensions and the wavelength used. Refinement was performed using full-matrix least-squares on $F^2$ (TeXsan program[23]). Crystal data for form **I**: triclinic, $P1$; $a = 4.6726(2)$, $b = 7.5120(7)$, $c = 12.427(1)$ Å, $\alpha = 84.7(5)$, $\beta = 86.0(3)$, $\gamma = 79.7(4)°$, $V = 426.7(5)$ Å$^3$, $Z = 1$, $\rho_{\text{calcd}} = 1.44$ g cm$^{-3}$, $\mu = 1.25$, 10936 reflections measured, 8271 crystallographically independent ($R_{\text{int}} = 0.0345$), and 6419 with $I > 2\sigma(I)$, $2\theta_{\max} = 64°$, $R = 0.055$, $Rw = 0.065$, 223 parameters, H atoms isotropic. Crystal data for form **II**: monoclinic, $P2_1$; $a = 6.617(7)$, $b = 14.117(6)$, $c = 9.344(6)$ Å, $\beta = 108.81(9)°$; $V = 826(1)$ Å$^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.49$ g cm$^{-3}$, $\mu = 1.25$, 2631 reflections measured, 2500 crystallographically independent ($R_{\text{int}} = 0.0218$), and 2053 with $I > 2\sigma(I)$, $2\theta_{\max} = 60°$, 226 parameters: $R = 0.0387$, $Rw = 0.0367$. CCDC-184139 (form **I**) and CCDC-184140 (form **II**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[13] A. L. Spek, *J. Appl. Crystallogr.* **1988**, *21*, 578.

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[19] A. I. Kitaigorodsky, *Molecular Crystals and Molecules*, Academic Press, New York, **1973**.

[20] To evaluate the difference in the energy of interaction in forms **I** and **II**, energy calculations were performed using the Tripos force field[24] present in Sybyl software.[25] Gasteiger–Marsili charges were assigned to the molecules, and the lengths of C–H···O and O–H···O hydrogen bonds were corrected to the theoretical lengths (1.050 and 0.950 Å, respectively). The interaction energy was defined as the difference between the energy of a minicrystal composed of a reference molecule surrounded by the nearest neighbors (i.e., by 11 molecules for form **I** and by 15 molecules for form **II**) and the energy of the same minicrystal but with the reference molecule pulled 100 Å away from its central position (i.e., noninteracting).

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[26] G. A. Jeffrey, *J. Mol. Struct.* **1999**, *485*–486, 293.

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# The Role of Nucleation Inhibition in Optical Resolutions with Families of Resolving Agents**

José W. Nieuwenhuijzen, Reinier F. P. Grimbergen,
Carla Koopman, Richard M. Kellogg,*
Ton R. Vries,* Kees Pouwer, Erik van Echten,
Bernard Kaptein, Lumbertus A. Hulshof, and
Quirinius B. Broxterman*

The separation of enantiomers by diastereomeric salt formation, essentially unchanged in technique since the original description by Pasteur,[1] remains the most widely used method in industry for obtainment of enantiomerically pure organic compounds.[2] In 1998 a significant modification of this classic technique was reported by some of us.[3] Upon simultaneous addition of structurally related resolving agents, high diastereomeric excesses (*de* values) of the first salts were obtained in a large number of resolutions. The success rate was 90–95 % compared to the usual 20–30 % estimated in one of the few studies published.[4] Structurally related resolving agents were denoted as family members and the method itself has become known as "Dutch Resolution".

In practice, three structurally related resolving agents are used in a 1:1:1 ratio. A mixture of these resolving agents was usually found in the first salt, but in nonstoichiometric ratios. In general, the families of resolving agents show solid-solution behavior. However, in the 46 examples of resolutions of single racemates reported in ref. [3], in ten cases no detectable amount of one (or more) of the three resolving agents was present in the salt. In three other cases, one of the resolving agents was present in $<10$ mol %. The resolving agents that are regularly not incorporated, or which are incorporated only to a small extent, in the salt are shown in italics in Scheme 1 for the families used in the current work.[5]

Although direct comparisons are difficult owing to differences in solubilities and the almost certain involvement of

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[*] Prof. Dr. R. M. Kellogg, Dr. T. R. Vries, J. W. Nieuwenhuijzen,
Dr. K. Pouwer, E. van Echten
Syncom B.V.
Kadijk 3, 9747 AT Groningen (The Netherlands)
Fax: (+31) 50-575-7399
E-mail: r.m.kellogg@syncom.nl

Dr. Q. B. Broxterman, Dr. B. Kaptein
DSM Research
DSM Fine Chemicals – Advanced Synthesis & Catalysis
PO Box 18, 6160 MD Geleen (The Netherlands)
Fax: (+31) 046-4767604
E-mail: rinus.broxterman@dsm.com

Dr. R. F. P. Grimbergen, Dr. Ir. C. Koopman
DSM Research
Centre for Particle Technology
PO Box 18, 6160 MD Geleen (The Netherlands)

Dr. L. A. Hulshof
DSM Fine Chemicals
PO Box 81, 5900 AB Venlo (The Netherlands)

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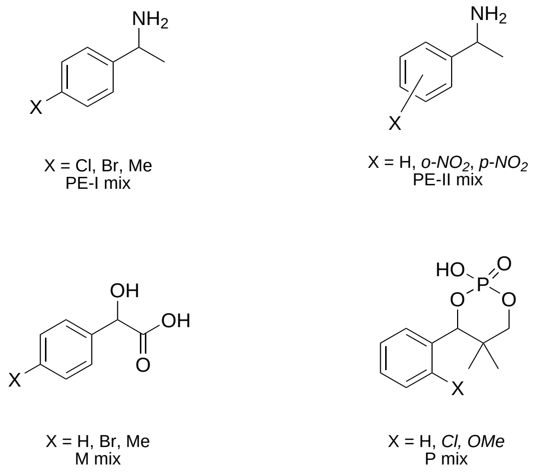
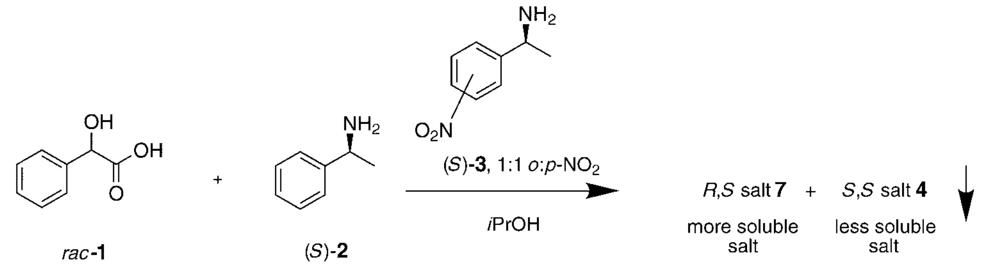


Scheme 1. Families of structurally related resolving agents and the abbreviations from ref. [3].

kinetic effects, we had the strong feeling that resolutions proceeded less well in the absence of these unincorporated (or poorly incorporated) resolving agents. The suspicion arose that they might be "the dog that didn't bark".[6]

To test this idea, a model resolution was designed with two resolving agents: one the "parent" resolving agent and the other the "additive" that was poorly or not at all incorporated. The solubility differences between the pure "parent" and "parent/additive" system are assumed to be minimal. The model system chosen was the resolution of *rac*-mandelic acid (**1**) with (*S*)-phenylethylamine ((*S*)-**2**) (Scheme 2). A 1:1 *ortho:para* mixture of nitro-substituted (*S*)-phenylethylamines (**3**; this material is readily available and is used commercially) was chosen as the additive; this mixture together with **2** forms the family "PE-II"[3] and shows little or no incorporation in "family" resolutions. One resolution was done with one equiv of **2** and the other with 0.9 equiv of **2** and 0.1 equiv of **3**.



Scheme 2. Resolution of (*rac*)-mandelic acid (**1**) with (*S*)-phenylethylamine (**2**), with or without 10% (*S*)-nitrophenylethylamines (**3**).

In an early experiment we observed that at the non-optimum concentrations chosen, the resolution of **1** with **2** (Scheme 2) delivered the first salt with a *de* value of 14% and an S factor[7] of 0.19. In the presence of 0.1 equiv of **3** and 0.9 equiv of **2** the *de* value of the first salt increased from 14% to 55% and the S factor to 0.41.[8] No detectable amount of *ortho*- or *para*-(*S*)-**3** was incorporated into the salt.[9]

Crystallization in the presence of (*S*)-**3** as the additive to (*S*)-**2** was qualitatively observed to begin at a lower temperature than with (*S*)-**2** alone. To quantify this observation, turbidity measurements were carried out. For the less soluble diastereomer (*S*)-**2**/(*S*)-mandelic acid (**4**) the dissolution temperature is 70.2 °C and the nucleation temperature is 64.2 °C (Figure 1). Replacement of 10 mol% of (*S*)-**2** with (*S*)-*o*-nitrophenylethylamine (**5**)[10] led to a shift in nucleation temperature to 61.6 °C. The metastable zone is enlarged from 6.0 to 7.1 °C, which change is significantly beyond the experimental error.[11] For comparison, the effect of 10% (*R*)-*o*-nitrophenylethylamine (**6**) is also shown in Figure 1. The *R* additive has no statistically significant effect on nucleation or dissolution temperature.

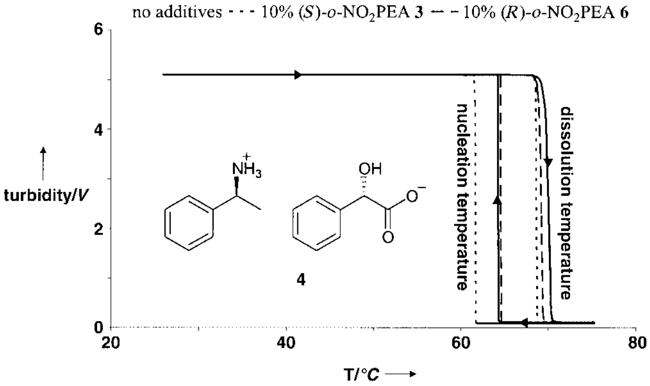


Figure 1. Turbidity measurements on the less soluble diastereomer **4**; 10 mol% (*S*)-*o*-NO$_2$PEA (**5**; PEA = phenylethylamine) or (*R*)-*o*-NO$_2$PEA (**6**) used as inhibitors.

In the case of the more soluble diastereomer (*S*)-**2**/(*R*)-mandelic acid (**7**; at a much higher concentration) a clear effect on nucleation temperature is also observed (Figure 2). The metastable zone width increases from 11.4 to 28.0 °C on substitution of 0.1 equiv of (*S*)-**2** with (*S*)-**5**.[12]

For both diastereomers, nucleation inhibition is observed, whereas the dissolution temperatures remain more or less identical. These results can be better understood in terms of a qualitative ternary phase diagram (at constant temperature).[4] In Figure 3, the area that would lead to 100% *de* value in the less soluble salt, without

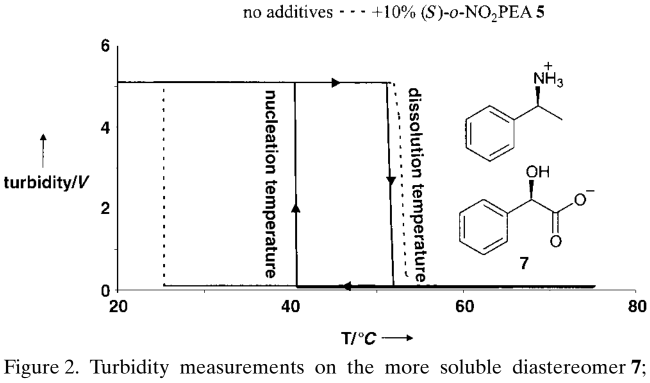


Figure 2. Turbidity measurements on the more soluble diastereomer **7**; 10 mol% (*S*)-*o*-NO$_2$PEA (**5**).

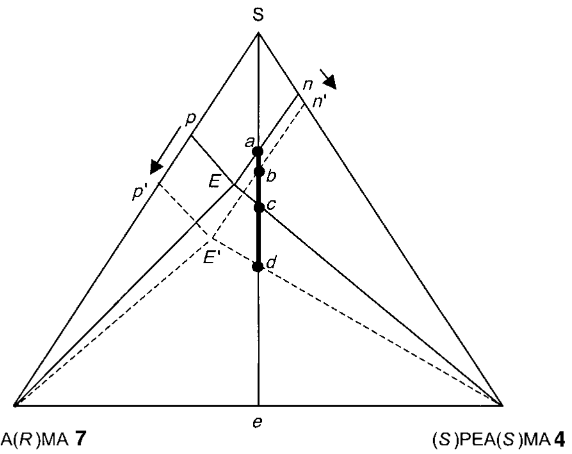


Figure 3. Ternary phase diagram with representation of the metastable zone width. MA = mandelic acid

additives, is represented by the triangle *nE***4**. Starting from the 1:1 mixture (the line S*e*), the line *ac* shows the concentration range in which diastereomerically pure salt will be obtained, without the use of additives. The turbidity measurements (Figures 1 and 2) indicate that the nucleation lines without additive fall in between the solubility lines and the nucleation lines with additive. For clarity of illustration these former lines have been omitted. The dashed lines *p'E'* and *n'E'* represent the metastable nucleation lines that come into play on use of the additive. The intersection points of triangle *n'E'***4** with line S*e* define the line *bd*, which is longer than the line *ac*, which implies that the operating window for a successful resolution is larger. Also, it can be seen that high *de* values should be obtainable at higher concentrations than in the situation without additive.

To verify this latter conclusion, the resolution of **1** with (*S*)-**2** was performed at different concentrations using in this case an even smaller amount, 5 mol %, of (*S*)-**3**. The resolution in the presence of the additive is still successful at 0.50 M in 2-propanol, whereas the resolution efficiency without additive drops dramatically to between 0.25 and 0.33 M, as shown in Figure 4.[8]

To establish generality, additional resolutions were carried out, all based on the same principle: the use of 10 % of an unincorporated family member of the resolving agent as the suspected nucleation inhibitor together with the resolving agent. The additives were initially chosen from the pool of known families of resolving agents.[3] The 2-nitrosubstituted phosphoric acid (entry 8b, see Table 1) was not reported in ref. [3], but was investigated on the basis of the present developments. In nine out of the ten systems given in Table 1, there were significant improvements in the *de* value of the first salt. The S factors were in the same range or in some cases even higher in the presence of an additive. Improvements were sometimes dramatic, for example, entries 8 a/b. Only for the resolution of *p*-chloromandelic acid, as shown in entries 4 a/b, was no significant improvement observed. The resolutions were deliberately performed in such a way that the *de* value without additive was not high because of simultaneous crystallization of both diastereomeric salts, so that improvements could be easily detected. Concentrations and conditions for the experiments with additives were analogous to those without additives. The resolutions given in entries 9 and 10 were performed in a reverse manner, that is, an enantiomerically pure family member of the racemate was added instead of a compound structurally related to the resolving agent.[13]

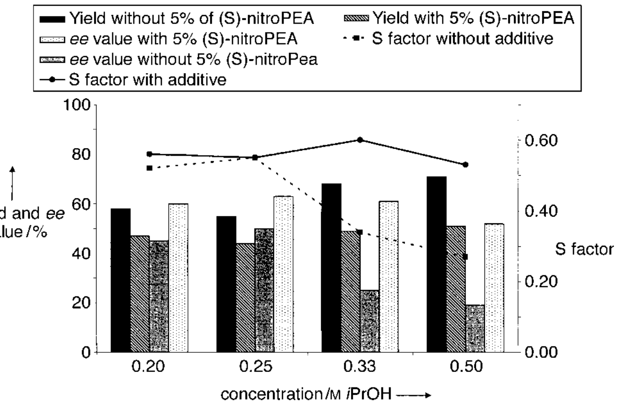


Figure 4. Concentration dependent resolutions with and without 5 % additive (*S*)-**3**.

The salts that were obtained in the presence of additives were sometimes difficult to filter or sticky. On examination under a microscope, it was found that, in general, the crystals were smaller and/or the crystal habit less well-defined. These observations indicate the involvement of a kinetic effect of the additive as a habit modifier.

The Dutch Resolution approach, with families of resolving agents, provides a high chance of finding a successful resolution in which nucleation inhibition can be involved. Some characteristics of potential nucleation inhibitors are clear, although at this stage we obviously cannot predict with certainty all the structural aspects. Substitution in an aromatic ring can be especially effective, particularly with nitro as well as methoxy groups and sometimes haloatoms. The position of the substituent must also be a contributing factor.[14] Dutch Resolution provides a simple search procedure for discovery of potential nucleation inhibitors. If a component of a Dutch Resolution process is not, or only poorly, incorporated, one may then turn to a single resolving agent approach aided by the "missing component" as a potential nucleation inhibitor.

The use of an additive in a resolution by using crystallization is related to the work of Lahav and co-workers, who used enantiopure "tailor-made additives" in the resolution of conglomerates by preferential crystallization.[15] By addition of small amounts of certain structurally related compounds, the crystallization rate of one of the enantiomers was retarded dramatically, which thereby leads to efficient resolution. Modification of the habit of the crystals was observed, caused by the selective adsorption of the additive on a crystal face. We deal here with diastereomers rather than enantiomers that form conglomerates. To our knowledge, this approach has not been described before. Habit modification of a diastereomeric salt has been reported by Saigo and co-workers,[16] but resolutions in the presence of a habit modifier have not been reported.

We have shown here that nucleation inhibition and associated kinetic effects can play a role in Dutch Resolution.

Table 1. Resolutions in the presence of 10% of a family member of the resolving agent.

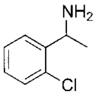
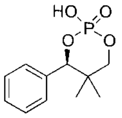
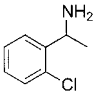
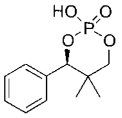
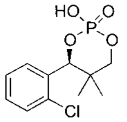
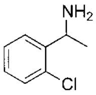
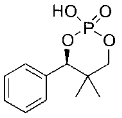
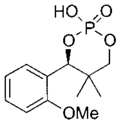
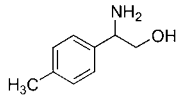
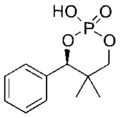
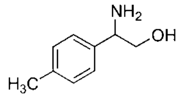
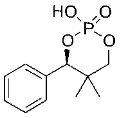
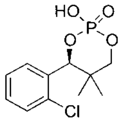
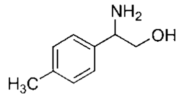
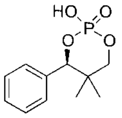
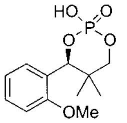
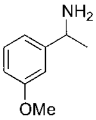
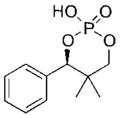
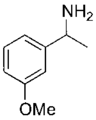
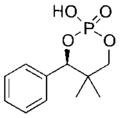
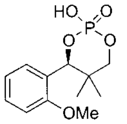
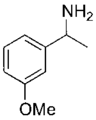
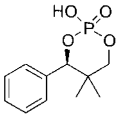
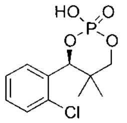
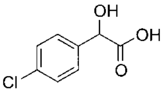
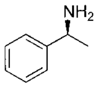
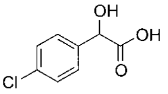
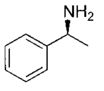
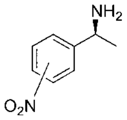
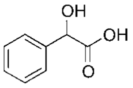
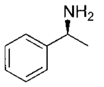
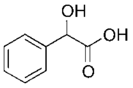
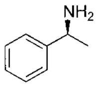
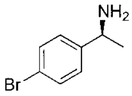
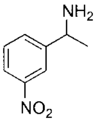
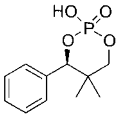
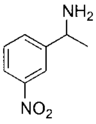
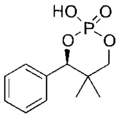
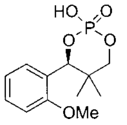
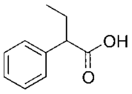
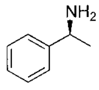
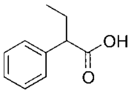
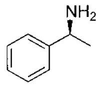
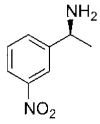
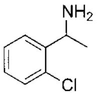
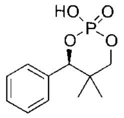
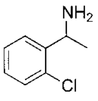
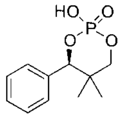
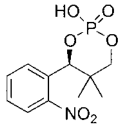
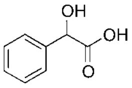
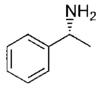
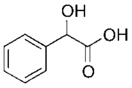
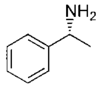
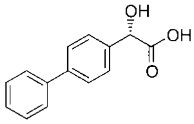
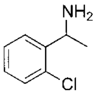
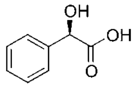
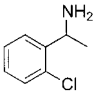
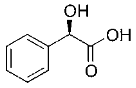
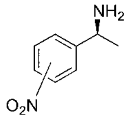
| Entry | Substrate | Resolving agent | Additive | Concentration | Yield [%] | *ee* value [%] | S factor | HPLC[b] |
|---|---|---|---|---|---|---|---|---|
| 1a |  |  | – | 0.20 M EtOH | 23 | 68 | 0.31 | 2 |
| 1b[a] |  |  |  | 0.20 M EtOH | 29 | 86 | 0.50 | 2 |
| 1c |  |  |  | 0.20 M EtOH | 30 | 88 | 0.53 | 2 |
| 2a |  |  | – | 0.10 M *i*PrOH | 40 | 74 | 0.59 | 2 |
| 2b[a] |  |  |  | 0.10 M *i*PrOH | 39 | 93 | 0.73 | 2 |
| 2c |  |  |  | 0.10 M *i*PrOH | 36 | 89 | 0.64 | 2 |
| 3a |  |  | – | 0.25 M *i*PrOH | 41 | 14 | 0.11 | 1 |
| 3b |  |  |  | 0.25 M *i*PrOH | 33 | 28 | 0.18 | 1 |
| 3c[a] |  |  |  | 0.25 M *i*PrOH | 29 | 53 | 0.31 | 1 |
| 4a |  |  | – | 0.10 M *i*PrOH | 39 | 73 | 0.57 | 3 |
| 4b |  |  |  | 0.10 M *i*PrOH | 34 | 76 | 0.52 | 3 |
| 5a |  |  | – | 0.25 M *i*PrOH | 58 | 49 | 0.57 | 1 |
| 5b[a] |  |  |  | 0.25 M *i*PrOH | 45 | 63 | 0.57 | 1 |
| 6a |  |  | – | 0.20 M *i*PrOH/$H_2O$ 4:1 | 61 | 12 | 0.15 | 4 |
| 6b |  |  |  | 0.20 M *i*PrOH/$H_2O$ 4:1 | 39 | 38 | 0.30 | 4 |

Table 1 (Continued)

| Entry | Substrate | Resolving agent | Additive | Concentration | Yield [%] | *ee* value [%] | S factor | HPLC[b] |
|---|---|---|---|---|---|---|---|---|
| 7a |  |  | – | 0.50 M *i*PrOH | 56 | 40 | 0.45 | 1 |
| 7b |  |  |  | 0.50 M *i*PrOH | 43 | 55 | 0.47 | 1 |
| 8a |  |  | – | 0.25 M *i*PrOH | 58 | 22 | 0.26 | 2 |
| 8b |  |  |  | 0.25 M *i*PrOH | 36 | 86 | 0.62 | 2 |
| Reverse resolutions with a family member of the racemate as the additive. | | | | | | | | |
| 9a[c] |  |  | – | 0.50 M *i*PrOH | 61 | 43 | 0.52 | 1 |
| 9b |  |  |  | 0.50 M *i*PrOH | 38 | 65[d] | 0.49 | 1 |
| 10a |  |  | – | 0.25 M *i*PrOH | 39 | 44 | 0.34 | 2 |
| 10b |  |  |  | 0.25 M *i*PrOH | 10 | 87[e] | 0.17 | 2 |

[a] In this case some of the additive is incorporated in the crystal, but always less than 10%. [b] HPLC columns: 1: Chiralpak AD; 2: Crownpak Cr; 3: Ultron ES OVM; 4: Chiralpak AS. [c] The resolution of mandelic acid (**1**) with (*S*)-phenylethylamine (**2**) in this experiment was performed at a different concentration than the one described in the text, hence the difference in results. [d] The *R*,*R* salt precipitates selectively in this case. [e] The *R*,*R* salt is presumed to precipitate selectively; however, the absolute configuration of 2-chlorophenylethylamine has not been determined unambiguously.

This leads to a second generation of Dutch Resolution, namely the use of small amounts of a certain family member of the resolving agent as an additive. This procedure seems to be reasonably general among several available families of resolving agents and may well have industrial applications. A two-component resolution system, especially one in which the minor component is not incorporated, is potentially more interesting for industrial applications than the (typically) three-component Dutch Resolution approach. In addition, the use of higher concentrations is beneficial, because more material can be resolved in one batch.

## *Experimental Section*

General procedure for the resolutions described in Table 1: The resolving agent (2 mmol), suspended or dissolved in the appropriate solvent, was added to the substrate (2 mmol). In cases where an additive (0.2 mmol) was used, 1.8 mmol of the racemate or the resolving agent was added, so that the ratio racemate: resolving agent was always 1:1. The mixture was heated until a clear solution was obtained. The Kimble test tube (diameter 25 mm and height 150 mm) was covered and placed in a Reactivate, an apparatus that can hold ten tubes. A stirring speed of 900 rpm was chosen, using standard 1 cm magnetic stirring bars. The temperature program started at 65 °C, cooling to 20 °C at 0.1 °C $\text{min}^{-1}$. After reaching 20 °C, the mixture was stirred overnight at that temperature. The salt present in the Kimble test tube was collected and analyzed by $^1$H NMR spectroscopy and LC–MS to check if additive was present. HPLC analysis was used to determine the *ee* value of the substrate.

Turbidity measurements were performed in a double-walled vessel, equipped with a He/Ne laser and a detector. The temperature of the solution was monitored with a Pt (100) temperature sensor. All equipment was connected to a computer that monitored the development of turbidity in the solution as a function of temperature. The vessel was connected to a water bath, the temperature of which could be programmed. The temperature program consisted of consecutive cooling and heating runs, each at 10 °C $\text{h}^{-1}$. Because of the limitations of the equipment used, the cooling rate in the turbidity measurements is not the same as that in the resolution experiments. When the turbidity is close to zero, the solution is clear. An (arbitrary) turbidity value close to 5 corresponds to a fully crystallized solution.

Chemicals: Phencyphos (2-hydroxy-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane), chlocyphos (4-(2-chlorophenyl)-2-hydroxy-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane), and anicyphos (2-hydroxy-4-(2-methoxyphenyl)-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane) were prepared and resolved according to a standard procedure.[5]Compounds **1**, 2-phenylbutyric acid, and **2** were obtained from Aldrich. A standard Suzuki coupling method was used to prepare (*S*)-4-phenylmandelic acid from (*S*)-4-bromomandelic acid. The corresponding (*S*)-4-bromomandelic acid was obtained from 4-bromoacetophenone by standard procedures and was resolved with **2**. The substituted phenylethylamines were prepared from the corresponding acetophenones by a standard Leuckardt procedure. A Strecker reaction was used to prepare 4-methylphenylglycine, which was reduced to 4-methylphenylglycinol.

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[8] Reproducibilities are good; the experimentally determined error limit of the S factor is ±5%.

[9] Analogous experiments with pure (*S*)-*o*-nitrophenylethylamine (**5**) as the inhibitor led to a *de* value of 51% and an S factor of 0.55. With pure (*S*)-*p*-nitrophenylethylamine as the inhibitor the *de* value was 62% and the S factor was 0.56. We conclude that use of the more readily available mixture instead of the pure materials is entirely justified and allows direct comparison with the data given in ref. [3].

[10] In this experiment we used only *o*-nitrophenylethylamine instead of the 1:1 mixture of *o,p* isomers for reasons of simplicity.

[11] The experimentally determined error limit is ±0.3 °C for this experiment.

[12] The dissolution temperatures differ somewhat, owing to the high concentrations in this experiment (1.6 M); the experimentally determined error limit is ±0.7 °C.

[13] A manuscript covering the concept of reverse resolutions is in preparation: Dutch Resolution of Alaninol with (*R*)-Mandelic acid by addition of (*S*)-or (*R*)-2-Amino-1-butanol; the Role of Nucleation Inhibition; B. Kaptein, K. L. Pouwer, T. R. Vries, R. F. P. Grimbergen, H. M. J. Grooten, H. L. M. Elsenberg, J. W. Nieuwenhuijzen, R. M. Kellogg, Q. B. Broxterman, *Chem. Eur. J.*, unpublished work.

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# Shape Control of Thermodynamically Stable Cobalt Nanorods through Organometallic Chemistry **

Frédéric Dumestre, Bruno Chaudret,* Catherine Amiens, Marie-Claire Fromen, Marie-José Casanove, Philippe Renaud, and Peter Zurcher

The synthesis of nanoparticles is of fundamental importance for the development of novel technologies based on nanomaterials. This is particularly true for magnetic nanomaterials which could be used, amongst other things, for high-density information storage.[1] These materials would ideally consist of spatially separated particles in the nanometer range that would function as a single magnetic domain that exhibits ferromagnetic behavior at room temperature, and could be electronically isolated. In addition, the organization of the particles in the solid state or in solution (self-assembly) should be controllable as desired for the intended application.

Several methods are available for the production of magnetic nanomaterials. They can be divided into physical methods, which produce essentially thin layers,[2,3] template methods, which involves the growth of nanorods or nanowires by different approaches, frequently electrochemical, within the channels of inorganic or track-etch organic matrixes,[4] and chemical methods involving synthesis in a solution of nanoparticles.[5,6] The latter may generally allow, after size selection, the formation of self-assembled superlattices. Sun and Murray[5] have, for example, recently reported a high-temperature preparation of 9 nm cobalt nanoparticles displaying a long-range self-organization. This method has been extended to the synthesis of Fe/Pt particles to increase the magnetic anisotropy of the materials, with the goal of producing high-density memories.[7] Self-organized cobalt nanoparticles have also been reported by the group of Pileni by reverse micelle synthesis.[8]

In all cases, as a result of their small dimension, the particles are superparamagnetic at room temperature and thus not usable for many applications, such as magnetic recording. One way to increase the magnetic anisotropy of the particles is to modify their shape. This problem has been addressed by Alivisatos who initially demonstrated the importance of reaction conditions, in particular the concentration of the

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[*] Dr. B. Chaudret, F. Dumestre, Dr. C. Amiens
Laboratoire de Chimie de Coordination du CNRS
205, route de Narbonne, 31077 Toulouse Cédex 04 (France).
Fax: (+33) 5-61-55-30-03
E-mail: chaudret@lcc-toulouse.fr

F. Dumestre, Dr. P. Renaud
Digital DNA Labs, Semiconductor Products Sector, Motorola
le Mirail B.P. 1029, 31023 Toulouse Cédex (France)

M.-C. Fromen, Dr. M.-J. Casanove
CEMES-CNRS
29 Rue Marvig, BP 4347, F 31055 Toulouse, France.

Dr. P. Zurcher
Digital DNA Labs, Semiconductor Products Sector, Motorola
2100 E. Elliot Road, Tempe, AZ-85824 (USA)

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