BATCH: cg5a13 USER: eap69 DIV: @xyv04/data1/CLS_pj/GRP_cg/JOB_i05/DIV_cg050139r DATE: March 9, 2006

CRYSTAL GROWTH & DESIGN
XXXX
VOL. 0, NO. 0
1−5

Dutch Resolution: Nucleation Inhibition in an Ephedrine−Cyclic Phosphoric Acid System

Joanne S. C. Loh,† Willem J. P. van Enckevort,* and Elias Vlieg*

IMM Department of Solid State Chemistry, Radboud University Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands

Claire Gervais,‡ Reinier F. P. Grimbergen,§ and Bernard Kaptein

DSM Research, Life Sciences-Advanced Synthesis & Catalysis, PO Box 18, 6160 MD Geleen, The Netherlands

Received April 8, 2005; Revised Manuscript Received February 21, 2006

ABSTRACT: While the significant improvements in diastereomeric salt resolution using Dutch resolution have been experimentally established, little is known about the mechanism involved when more than one member of a family of resolving agents are added to a racemate. Investigation into the (−)-ephedrine−cyclic phosphoric acid resolution system has revealed a nucleation inhibition effect introduced by a member of the family that hinders the crystallization of the more soluble diastereomeric salt. In this way, the less soluble diastereomer is obtained with largely improved enantiomeric excess and yield. Comparison between experimental results and known phase diagrams indicates that for this system nucleation inhibition only occurs between compounds that are able to form (partial) solid solutions. It is suggested that adsorbed inhibitor molecules block the growth of the (super)critical 3D nuclei at the earliest stages of their development and thus delay the nucleation of the undesired salt.

Introduction

Separation of enantiomers via "classical" resolution[1,2] is the most common and generally most cost-effective method used in industry. Classical resolution involves the addition of one resolving agent to a racemate (an equal mixture of the two "mirror images") to form diastereomeric salts (Scheme 1A). However, since in many cases the type of resolving agent required for a given enantiomeric compound is not known, classical resolution is a time-consuming method and is largely based on trial and error investigations.[3]

"Dutch resolution" is a relatively new technique[4−6] where more than one member (usually three) of a "family" of resolving agents is used simultaneously (Scheme 1B). This technique leads to precipitation of crystalline diastereomeric salts in high yield and enantiomeric purity. The mechanism behind Dutch resolution is not clear at the moment. The fact that in many cases the resulting diasteromeric salts are solid solutions suggests a thermodynamic origin.[7] It has, however, recently become clear that kinetics certainly play an important role. Nieuwenhuijzen et al.[8] found that nucleation inhibition is a key factor in Dutch resolution, where the inhibitor was found to be a compound *not* incorporated in the diastereomeric salt.

Since by definition, Dutch resolution involves many compounds, it is in general difficult to separate thermodynamic and kinetic effects, because the relevant phase diagrams are usually not available. The system we investigate here was chosen to avoid such uncertainties. It consists of (−)-ephedrine and four members of the cyclic phosphoric acid family of resolving agents. Specifically, we resolve a racemic mixture of (±)-phencyphos by using (−)-ephedrine. This system is eutectic in nature with a eutectic composition very close to 50:50, which means that resolution is not possible on thermodynamic grounds. We can thus focus on the change in crystallization kinetics by adding enantiopure family members of (±)-phencyphos.

Scheme 1. "Classical" (A) and "Dutch" (B) Resolution[a]

$$R_BR'_B + A \rightarrow R_BA + R'_BA\downarrow \quad (A)$$

$$R_BR'_B + A_1 + A_2 + A_3 \rightarrow R_BA_x + R'_BA_y\downarrow \quad (B)$$

[a] R_B and R'_B are basic enantiomers, A and A_{1-3} are acidic resolving agents, R_BA_x and R'_BA_y are the resulting diastereomeric salt mixtures remaining in the solution and crystallizing, respectively, with A_x and $A_y = A_1 + A_2 + A_3$.

Scheme 2. Reciprocal Dutch resolution[a]

$$R_B + A_1A_1' + A_2A_2' + A_3A_3' \rightarrow R_BA_y\downarrow + R_BA_x'$$

[a] R_B is a basic enantiomerically pure resolving agent, (−)-ephedrine; A_{1-3} and A'_{1-3} are acidic compounds to be resolved; R_BA_x' is the resulting diastereomeric salt mixture remaining in the solution.

The resolution using cyclic phosphoric acids as resolving agent has been well established.[4,9−11] However in this study, the system is a reciprocal Dutch resolution system. Here the enantiomerically pure (−)-ephedrine is the resolving agent and the cyclic phosphoric acids are the racemates of interest (compare Scheme 2 to Scheme 1B). We reported on the crystal morphology of some of the diastereomeric salt compounds earlier.[12] By comparing the results of crystallization experiments with and without additives, we determined the effect of the additives on the kinetics. In all cases, the composition of the resulting crystals is analyzed in detail and discussed in the context of the corresponding phase diagrams. Apart from a better understanding of Dutch resolution, our study also provides additional criteria for searching crystallization inhibitors in many other systems.

Experimental Procedures

Model Compounds. The system investigated comprises (−)-ephedrine (**1**) and phencyphos (**2**, **3**), a member of the cyclic phosphoric

* To whom correspondence should be addressed. E-mail addresses: w.vanenckevort@science.ru.nl; e.vlieg@science.ru.nl. Telephone: +31-2436-53433. Fax: +31-2436-53067.

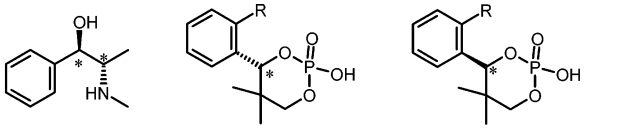
† Current address: AJ Parker CRC for Hydrometallurgy, CSIRO Minerals, P.O. Box 90, Bentley, WA 6982, Australia.

‡ Current address: Institute for Chemistry and Biochemistry, University of Bern, Freiestrasse 3, CH-3014 Bern, Switzerland.

§ Current address: DSM Composite Resins, PO Box 615, 8000 AP Zwolle, The Netherlands.

10.1021/cg050139r CCC: $33.50
Published on Web 00/00/0000

Table 1. The Structures and Nomenclature of (−)-Ephedrine Base and Cyclic Phosphoric Acids and the (−)-Ephedrine−Cyclic Phosphoric Acid Compounds



(-)-Ephedrine (**1**) (+)-Cyclic Phosphoric Acid (-)-Cyclic Phosphoric Acid

R group	cyclic phosphoric acid	stereochemistry of acid	(−)-ephedrine−acid compound name[a]
−H	phencyphos	(+) (**2**)	Inam (**6a**)
		(−) (**3**)	Inap (**6b**)
$-OCH_3$	anicyphos	(+) (**4**)	Aninam (**7a**)
		(−) (**5**)	Aninap (**7b**)

[a] Same nomenclature as used by Geravais et al.[7].

acid family (Table 1). An ephedrine−phencyphos compound consists of a 1:1 mix of the two components to produce Inam (**6a**, (+)-phencyphos) and Inap (**6b**, (−)-phencyphos). Another member of the cyclic phosphoric acid family of resolving agents, anicyphos, was added to the system as part of reciprocal Dutch resolution. The 1:1 mix of ephedrine−anicyphos produced Aninam (**7a**, (+)-anicyphos) and Aninap (**7b**, (−)-anicyphos). Crystal structures of compounds **6a,b** and **7a,b** have been previously reported.[7,13,14]

The model system consists of an equimolar mixture of Inam (**6a**) and Inap (**6b**). Aninam (**7a**) or Aninap (**7b**) are added in 5 or 10 mol % concentrations as additives to the model system.

The purified cyclic phosphoric acid compounds were kindly donated by Syncom BV. The (−)-ephedrine was obtained from Sigma Chemicals (anhydrous, purity ≥ 98%).

Crystallization Experiments. Crystallization was followed by turbidity experiments as described by Nieuwenhuizen et al.[8,15] The solutions were placed in double-walled glass vessels and were magnetically stirred. Temperature was controlled by a thermostatic water bath and was measured using a Pt100 temperature sensor. A condenser was used to reduce evaporation in the system at higher temperatures. The turbidity of the solutions was monitored using a laser source (He/Ne, $\lambda = 6328$ Å) and detector, where the intensity of the transmitted laser beam is a measure for the level of turbidity. Transitions between high and low turbidity with changes in solution temperature marked the crystallization and dissolution temperatures. A computer logged the temperature and the transmitted laser intensity data as a function of time.

In the pure model system, solutions were prepared to an initial concentration of 13.8 g of Inap (**6a**)/100 g of ethanol and 14.25 g of Inam(**6b**)/100 g of ethanol, or combined an equimolar solution of 13.8 g of Inap(**6a**) and 14.25 g of Inam(**6b**) in 100 g of ethanol. The additive (Aninam(**7a**) or Aninap(**7b**)) was added at a concentration of 10 mol % of the main compounds in the solution. In the mixed solution, this corresponds to 5% of both compounds together. For this small quantity, it was assumed that there was only a limited effect on the overall solubility of the main compound(s) in the system.

The appropriate (−)-ephedrine−cyclic phosphoric acid solutions (total solution mass was 40 g) were placed in the glass vessels at 60 °C. The solutions were cooled (10 °C/h) and heated (5 °C/h) for five cycles over a temperature range of 10−60 °C. At the end of five cycles, the precipitated solids were collected at 10 °C and analyzed for enantiomeric identification and purity using chiral high performance liquid chromatography (HPLC) and differential scanning calorimetry (DSC). The nature of the solid phases was determined by means of powder X-ray diffraction (PXRD). The crystallization and dissolution temperatures were averaged over at least three cycles and then used to calculate the metastable zone width (MSZW), which is the difference between these two temperatures. Note that the MSZW depends on the cooling and heating rates used.

To understand the resolution behavior better, supplementary crystallization experiments were performed. In these experiments, the products were collected at different temperatures without recording the turbidity and subsequently analyzed. The experiments were carried out in a similar vessel, using identical heating and cooling rates as for the turbidity experiments. Once crystallization had commenced, the solution temperature was held at the crystallization temperature for 5−10 min to ensure the nucleation and growth of a sufficient quantity of crystals for analysis.

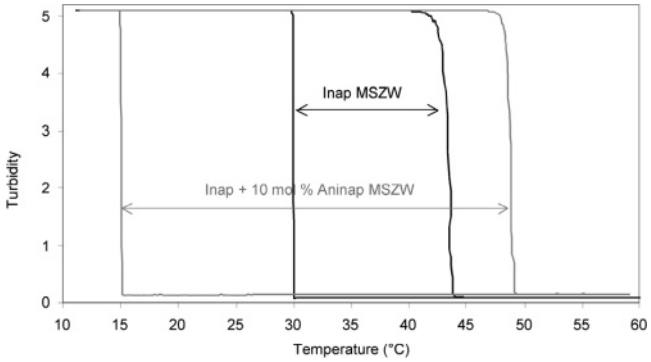


Figure 1. Crystallization and dissolution temperatures and MSZW for pure Inap (**6b**) solution with 10 mol % Aninap (**7b**) additive.

Product Characterization. For chiral HPLC an I. D. Chirobiotic R column (250 mm × 4.6 mm) with a mixture of buffer/methanol (90:10 vol %, where the buffer consisted of 15 mM ammonium acetate in water, pH 4.1) was used to separate the enantiomers. The flow rate used was 1 mL/min at a column temperature of approximately 21 °C and an injection volume of 20 μL. A wavelength of 210 nm was used for detection.

A Mettler Toledo 822e DSC was used to determine the melting point of the products. Standard aluminum crucibles were used, and a heating rate of 10 °C/min was employed. The estimated composition of the products from DSC measurements was based on the Inam−Inap eutectic having a composition of 50:50 (calculated from the Schröder−van Laar equation[16,17]).

The PXRD patterns were collected on a Philips PW1820 diffractometer using Cu Kα_1 radiation ($\lambda = 1.540\,60$ Å). The scan range was 5°−40° with a step width of 0.02° and a scan step time of 5 s. The diffraction patterns were compared to reported crystal structures.

The additives (Aninam (**7a**) and Aninap (**7b**)) detected in the collected products may be present in two forms: as a separate crystalline solid or incorporated into the crystal structure. The resolution of the X-ray diffractometer used in these analyses is not enough to detect structural changes introduced by an incorporation of <1% of Aninam (**7a**) or Aninap (**7b**), which only differs from Inam or Inap by the presence of an added methoxy group on the cyclic phosphoric acid molecule.

Results

The present work is focused on the resolution of a diastereomeric mixture (50:50 mix) of Inam (**6a**) and Inap (**6b**). Our DSC and PXRD measurements indicate that Inam (**6a**) and Inap (**6b**) form a eutectic with a 50:50 composition and a melting temperature of 207 °C (as compared to the melting points of 230 and 234 °C of pure Inam and Inap, respectively). Thus no resolution is expected on thermodynamic grounds. To determine the crystallization kinetics, we performed turbidity experiments not only on the eutectic mixture but also on its pure components and all possible combinations with the two additives. Figure 1 shows the behavior for pure Inap (**6b**) with and without Aninap (**7b**) as additive. Upon cooling, the system starts to crystallize at a specific temperature; the dissolution occurs at a higher temperature after reheating. The difference between these two temperatures is the metastable zone width (MSZW) for our specific experimental conditions. The results of many of such experiments are summarized in Figure 2.

The pure Inam (**6a**) solution crystallizes more readily than pure Inap (**6b**). As Figure 2 shows, the onset of crystallization in the 50:50 mixture of Inam (**6a**) and Inap (**6b**) closely follows that of Inam (**6a**). The turbidity experiments do not reveal the nature of the crystals that are formed, but the experiments using

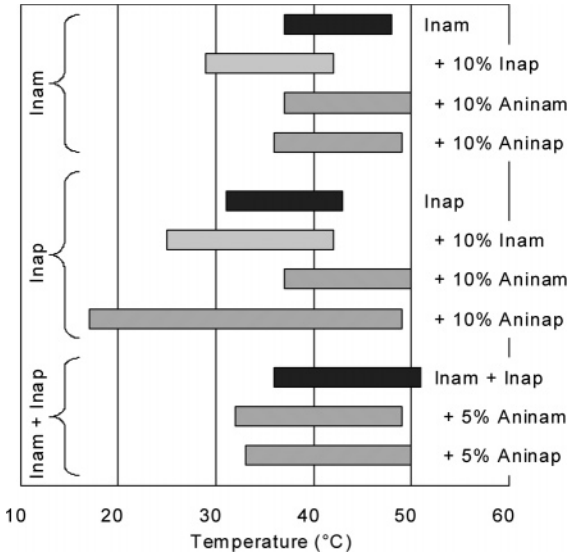


Figure 2. The position and width of the metastable zone as determined for 11 compositions of the solution. In all cases, the values are averaged over at least three crystallization/dissolution cycles, leading to error bars of ±2 °C.

pure Inam or Inap suggest that most likely in the mixture Inam (**6a**) will crystallize first, followed by Inap (**6b**) at a lower temperature. At the end of the experiment, the crystals are collected at 10 °C, a temperature at which also the Inap (**6b**) is expected to have crystallized. Indeed HPLC and PXRD experiments confirmed a global composition for the crystals close to 50:50.

Effects of the additives on the MSZW are summarized in Figure 2. For completeness, also Inap (**6b**) and Inam (**6a**) were used as additives in pure Inam (**6a**) and Inap (**6b**) solutions, respectively. Some changes in the behavior are observed in this case, but the MSZW is not strongly affected. The shift for Inam (**6a**) + 10% Inap (**6b**) probably indicates that the crystals are smaller on average. Small crystals are formed at higher undercooling and dissolve faster, which moves the metastable zone to lower temperatures.

Addition of Aninam (**7a**) to the pure Inam (**6a**) and Inap (**6b**), as well as to the Inam/Inap mixture does not lead to significant changes in MSZW. Aninap (**7b**), on the other hand, has a dramatic effect on the crystallization of Inap (**6b**). This follows directly from the turbidity measurement shown in Figure 1. Figure 2 shows that the addition of 10% Aninap (**7b**) to Inap (**6b**) leads to a metastable zone width that has aproximately twice the width compared with the other cases. Adding Aninap (**7b**) to a pure Inam (**6a**) solution has little effect on its crystallization behavior. The addition of Aninap (**7b**) to the Inam/Inap mixture does not lead to a large change in MSZW. This is as expected, because the crystallization of Inam (**6a**) prevents observation of the delayed crystallization of Inap (**6b**).

At the (too low) collection temperature of 10 °C also, Inap (**6b**) was fully crystallized. To determine the crystallization behavior as a function of temperature, we performed an additional set of crystallization experiments for the pure mixture and for the mixture plus additive with the largest effect, that is, Aninap (**7b**). Now crystals were collected at different temperatures and subsequently analyzed. From these measurements, we determined the enantiomeric excess (ee) of (+)-phenocyphos as a function of collection temperature. In this case, the enantiomeric exess is defined as ee = (Inam − Inap)/(Inam + Inap), with Inam (**6a**) and Inap (**6b**) the crystallized fractions of the solid compounds. The results are shown in Figure 3.

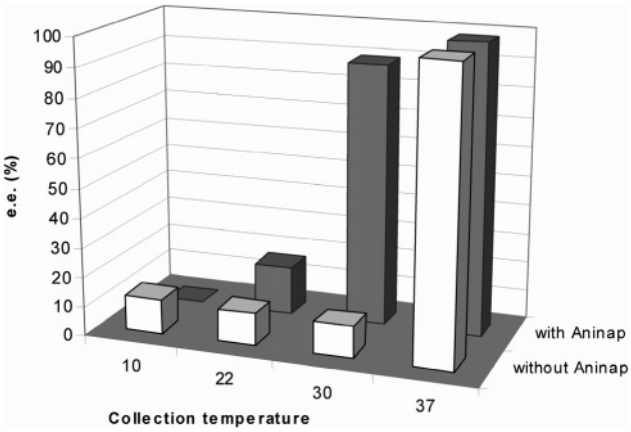


Figure 3. The enantiomeric excess (ee) of Inam (**6a**) at different collection temperatures for a 50:50 Inam−Inap mixture with and without 5 + 5 mol % Aninap (**7b**) added. The value without Aninap at 22 °C was not measured but interpolated from the data at 10 and 30 °C to obtain a better graph.

Discussion

Resolution Promoted by Nucleation Inhibition. The values shown in Figure 3 can be explained by considering the metastable zones in Figure 2. In the case where no additive is added, the first crystals that are formed are diastereomerically pure Inam (**6a**), giving an ee near 100% at a collection temperature of 37 °C. Lowering the temperature leads to the crystallization of Inap (**6b**) as well, such that at collection temperatures below 30 °C the ee is less than 10%. Adding 10% of Aninap (**7b**) delays the formation of Inap (**6b**) crystals, giving a high ee at a collection temperature of 30 °C and a small but significant value at 22 °C. In the crystallization experiment of pure Inap (**6b**) with 10% Aninap (**7b**) added, crystallization was observed at 17 °C. The fact that the ee at 22 °C is already strongly reduced shows that in the 50:50 Inam−Inap mixture Inap (**6b**) has a different crystallization behavior. A possible explanation for this difference might be a higher supersaturation for the mixed solutions as a consequence of the twice as high (−)-ephedrine concentration in the liquid.

The addition of Aninap (**7b**) leads thus to a wider temperature window in which Inam (**6a**) with high diastereomeric purity can be collected. This complies with the "rule of reversal", which states that the crystal that precipitates in excess (Inam (**6a**), (+)-phencyphos)) is of opposite absolute configuration to that of the chiral impurity (Aninap (**7b**), (−)-anicyphos))[18,19]. The wider temperature window not only facilitates resolution experiments but also gives a higher yield of Inam (**6a**) as a result of a lower solubility at reduced temperatures. Figure 3 also demonstrates the importance of the temperature at which crystals are collected. In most laboratory resolution experiments, the crystals are collected at room temperature, but a higher ee (albeit with lower yield) is obtained in the temperature interval immediately after crystals are formed. If the solubility and nucleation curves are known, the optimum collection temperature may also be tuned by changing the initial concentration.

Aninap (**7b**) clearly acts as a nucleation inhibitor of Inap (**6b**), which is in line with the mechanism proposed by Nieuwenhuijzen et al.[8] But why is Aninap (**7b**) an effective nucleation inhibitor for Inap (**6b**), while the other combinations are not? The solution phase diagram of Inam (**6a**) and Aninam (**7a**) shows a eutectic crystallization behavior; thus the addition of Aninam (**7a**) will not lead to a solid solution of Aninam (**7a**) in Inam (**6a**)[7]. For both the Inam−Aninap and the Inap−Aninam

combinations, no solution phase diagram is available, but our DSC data (not presented here) show that both systems are eutectic as well. The phase diagram of Inap (**6b**) and Aninap (**7b**)[7], on the other hand, shows that this system does form a partial solid solution in which the Aninap (**7b**) is incorporated in the Inap (**6b**) crystal at the concentrations used in our experiment. *So, we find for the system investigated here that the only additive that is effective as a nucleation inhibitor is the one that forms a partial solid solution with the compound for which it acts as an inhibitor.*

For a nucleation inhibitor to be effective, it needs to interact with the solid nucleus. An ideal eutectic phase diagram indicates little or no interaction, while a partial solid solution of course evidences a significant affinity. The family concept in Dutch resolution can thus be identified with the fact that one or more family members will interact sufficiently strongly with (one of) the diastereomeric salts to affect the nucleation process. For the model system investigated here, the interaction for the only effective additive is so strong that a partial solid solution is formed. Since the additive has to be effective at the growing *interface*, there is, however, no need to form a solid solution in the *bulk*. Therefore, solid solution formation as such is not a necessary condition for retarding the nucleation and growth process. A perfect solid solution is even not expected to show nucleation inhibition, because in that case the additive will be readily incorporated.

The fact that Aninap (**7b**) dissolves in Inap (**6b**) only up to approximately 15% (partial solid solution) indicates a mismatch between the two molecules, which means that the presence of Aninap (**7b**) could well hamper the growth of Inap (**6b**). The inhibition effect of Aninap (**7b**) on the nucleation of Inap (**6b**) is reminiscent of the "tailor-made additives" effect[20]. That additives can influence the crystallization behavior of diastereomeric salts has also been reported by Sakai et al.,[21] who found a crystal habit modification, and by Weissbuch et al.,[22] who observed twinning, which was explained by stereospecific inhibition of nucleus growth. A theory of conglomerate crystallization in the presence of chiral impurities has recently been formulated by Kondepudi and Crook.[23]

Our study not only explains the success of Dutch resolution but also gives an alternative approach for finding suitable crystallization inhibitors. Namely, a possible inhibitor might be found by searching for a compound that forms a partial solid solution with the nondesired solid product. This approach may be helpful for any system where crystallization of one or more compounds needs to be suppressed.

Mechanism of Nucleation Inhibition. In classical nucleation theory, the activation barrier for the formation of crystal nuclei increases with the surface energy.[24] From this perspective, one would expect that additives lead to enhanced nucleation, since the adsorption of an additive leads to a decrease in surface energy as follows from the Gibbs isotherm.[25] However, in our experiments the formation of nuclei is blocked, so this effect appears to be unimportant.

The correct explanation most likely relates to the well-known mechanism for growth inhibition by impurities[26,27]. By pinning growth steps or through similar mechanisms, adsorbed impurities lead to a so-called dead zone of supersaturation values that depends on the impurity concentration. This dead-zone has also important consequences for nucleation. In this process, first a critical nucleus needs to be formed, the size of which depends strongly on the supersaturation. By definition, the critical nucleus is in (labile) equilibrium with the supersaturated solution; thus its effective supersaturation is zero, and it has an equal chance to grow or disappear. However, when a dead-zone occurs owing to impurities, such a nucleus cannot grow. Thus in the presence of adsorbed impurities, a higher supersaturation is needed to nucleate a crystal phase. This model predicts that, once crystals are formed, growth will continue largely unaffected as long as the supersaturation is above the dead-zone value. This agrees with our experimental observations, where Aninap (**7b**) slows nucleation of Inap (**6b**) to a great extent but does not seriously hinder further growth of the Inap (**6b**) crystals.

Nucleation inhibition has also been observed in the resolution of racemic mandelic acid by (*S*)-phenylethylamine.[8,15] In that case, the additives were selected to be those that were not incorporated in the resulting crystals when using a mix of many resolving agents. This is consistent with our findings. In a resolution experiment, the collected crystals will predominantly be of the least-soluble type, so the fact that an additive is not incorporated means that it does not interact with the least-soluble salt. This screens for one condition for a favorable additive. The second condition is an interaction with the most-soluble salt, which can be derived from turbidity experiments or phase diagrams.

Conclusions

The present investigation has revealed the presence of nucleation inhibition in a reciprocal Dutch resolution system. The observed kinetic effect of Aninap on the crystallization of Inap is derived from the thermodynamic behavior in which Aninap forms a partial solid solution in Inap. For combinations of compounds with a eutectic phase diagram, no significant kinetic effects were observed. The kinetically delayed crystallization of the nondesired salt leads to a wider temperature range over which the desired product can be collected with a high chiral purity and thus increases the yield of the process as well.

The system investigated here and the one reported by Nieuwenhuijzen et al.[8] are the only Dutch resolution systems studied in sufficient detail to identify nucleation inhibition as the dominant mechanism. It is too early to conclude that this holds for all resolution methods involving a family of resolving agents. For nucleation inhibition, the additive should interact with the nondesired salt and less or not at all with the desired product. In principle, a nucleation promoter acting on the desired product only could provide an alternative kinetic route to efficient resolution, and such additives may still be found. Unfortunately, a nucleation promoting agent is expected to be incorporated in the crystals of the desired compund, which is an unwanted side effect. For both inhibitors and promoters, an affinity of the additive for one of the diastereomeric salts is required, which agrees with the family concept of Dutch resolution.

The observation that an active nucleation inhibitor forms a partial solid solution with the nondesired solid not only is important for understanding Dutch resolution but also can be relevant for many other systems in which crystallization of a component has to be suppressed.

Acknowledgment. The authors thank the following people for their assistance in the experimental work, for stimulating discussions, or both: José Nieuwenhuijzen, Carla Koopman, Lucien Duchateau, Zjak van Eupen, Alle Bruggink, Gerry Ariaans, and Quirinius B. Broxterman. Further the authors acknowledge DSM and The Netherlands Organization for Scientific Research (STW-NWO) for financial support.

References

(1) Pasteur, L. *Ann. Chim. Phys.* **1848**, *24*, 442−459.
(2) Pasteur, L. *C. R. Hebd. Seances Acad. Sci.* **1853**, *37*, 162−169.

(3) Sheldon, R. A. *Chirotechnology*; Marcel Dekker: New York, 1993; Chapter 6.
(4) Vries, T.; Wynberg, H.; van Echten, E.; Koek, J.; ten Hoeve, W.; Kellogg, R. M.; Broxterman, Q. B.; Minnaard, A.; Kaptein, B.; van der Sluis, S.; Hulshof, L.; Kooistra, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2349−2354.
(5) Broxterman, Q. B.; van Echten, E.; Hulshof, L. A.; Kaptein, B.; Kellogg, R. M.; Minnaard, A. J.; Vries T. R.; Wynberg, H. *Chimica Oggi (Chem. Today)* **1998**, *16*, 34−37.
(6) Kaptein, B.; Elsenberg, H.; Grimbergen, R. F. P.; Broxterman, Q. B.; Hulshof, L.; Pouwer, K. L.; Vries, T. R. *Tetrahedron: Asymmetry* **2000**, *11*, 1343−1351.
(7) Gervais, C.; Grimbergen, R. F. P.; Markovits, I.; Ariaans, G. J. A.; Kaptein, B.; Bruggink, A.; Broxterman, Q. B. *J. Am. Chem. Soc.* **2004**, *126*, 655−662.
(8) Nieuwenhuijzen, J. W.; Grimbergen, R. F. P.; Koopman, C.; Kellogg, R. M.; Vries, T. R.; Pouwer, K.; van Echten, E.; Kaptein, B.; Hulshof, L. A.; Broxterman, Q. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 4281−4286.
(9) ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* **1985**, *50*, 4508.
(10) Leusen, F. J. J. Rationalization of racemate resolution: A molecular modelling study. Ph.D. Thesis, University of Nijmegen, 1993; ISBN: 90-9005690-4, 181 pages.
(11) van der Haest, A. D. Classical resolution: Designs of resolving agents and studies of diastereomeric salts. Ph.D. Thesis, University of Nijmegen, 1992; 123 pages.
(12) Loh, J. S. C.; van Enckevort, W. J. P.; Vlieg, E. *J. Cryst. Growth* **2004**, *265*, 604−615.
(13) Kok, A. M. G.; Wynberg, H.; Smits, J. M. M.; Beurskens, P. T.; Parthasarathi, V. *Acta Crystallogr.* **1987,** *C43*, 1328−1331.
(14) Smits, J. M. M.; Beurskens, P. T.; Kok, A. M. G.; Wynberg, H. *Acta Crystallogr.* **1987,** *C43*, 1331−1333.
(15) Nieuwenhuijzen, J. W. Resolutions with families of resolving agents: principles and practice. Ph.D. Thesis, University of Groningen, Netherlands, 2002.
(16) Schröder, I. *Z. Phys. Chem.* **1893**, *11*, 449.
(17) van Laar, J. J. *Arch. Neerl. II* **1903**, *8*, 638.
(18) Addadi, L.; Weinstein, S.; Gati, E.; Weissbuch, I.; Lahav, M. *J. Am. Chem. Soc.* **1982**, *104*, 4610−4617.
(19) Addadi, L., van Mil, J.; Lahav, M.; *J. Am. Chem. Soc.* **1981**, *103*, 1249−1251.
(20) Addadi, L.; Berkovitch-Yellin, Z.; Domb, N.; Gati, E.; Lahav, M.; Leiserowitz, L. *Nature* **1982,** *296*, 21−26.
(21) Sakai, K.; Maekawa, Y.; Saigo, K.; Sukegawa, M.; Murakami, H.; Nohira, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1747−1750.
(22) Weissbuch, I.; Kuzmenko, I.; Vaida, M.; Zait, S.; Leiserowitz, L.; Lahav, M. *Chem. Mater.* **1994**, *6*, 1258−1268.
(23) Kondepudi, D. K.; Crook, K. E. *Cryst. Growth Des.* **2005**, *5*, 2173−2179.
(24) See, for instance: Mutaftschiev, B. In *Handbook of Crystal Growth, 1a Fundamentals*; Hurle D. T. J., Ed.; Elsevier: Amsterdam, 1993; pp 187−247.
(25) Liu, X. Y. *J. Phys. Chem. B* **2001**, *105*, 11550−11558.
(26) Cabrera, N.; Vermilyea, D. A. In *Growth and Perfection of Crystals*; Doremus, R. H., Roberts, B. W., Turnbull, D., Eds.; Wiley: New York, 1958; pp 393−410.
(27) van Enckevort, W. J. P.; van den Berg, A. C. J. F. *J. Cryst. Growth* **1998** *183*, 441−455.