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

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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 obtaining of enantiomerically pure 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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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.

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]

Crystalization 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.

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).[13] In Figure 3, the area that would lead to 100% de value in the less soluble salt, without

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

![Scheme 2. Resolution of (rac)-mandelic acid (1) with (S)-phenylethylamine (2), with or without 10 % (S)-o-nitrophenylethylamines (3).](image)

![Figure 1. Turbidity measurements on the less soluble diastereomer 4; 10 mol % (S)-o-NO2PEA (5: PEA = phenylethylamine) or (R)-o-NO2PEA (6) used as inhibitors.](image)

![Figure 2. Turbidity measurements on the more soluble diastereomer 7: 10 mol % (S)-o-NO2PEA (5).](image)
additives, is represented by the triangle $nE_4$. Starting from the 1:1 mixture (the line $Se$), 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 $Se$ 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 0.50m in 2-propanol, whereas the resolution efficiency without additive drops dramatically to between 0.25 and 0.33m, 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.[9] The 2-nitrosobstituted 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 8a/b. Only for the resolution of $p$-chloromandelic acid, as shown in entries 4a/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 diastereomERICAL 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]

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 diastereomERICAL 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>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Resolving agent</th>
<th>Additive</th>
<th>Concentration</th>
<th>Yield [%]</th>
<th>ee value [%]</th>
<th>S factor</th>
<th>HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td></td>
<td></td>
<td></td>
<td>0.20 m EtOH</td>
<td>23</td>
<td>68</td>
<td>0.31</td>
<td>2</td>
</tr>
<tr>
<td>1b[a]</td>
<td></td>
<td></td>
<td></td>
<td>0.20 m EtOH</td>
<td>29</td>
<td>86</td>
<td>0.50</td>
<td>2</td>
</tr>
<tr>
<td>1c</td>
<td></td>
<td></td>
<td></td>
<td>0.20 m EtOH</td>
<td>30</td>
<td>88</td>
<td>0.53</td>
<td>2</td>
</tr>
<tr>
<td>2a</td>
<td></td>
<td></td>
<td></td>
<td>0.10 m iPrOH</td>
<td>40</td>
<td>74</td>
<td>0.59</td>
<td>2</td>
</tr>
<tr>
<td>2b[a]</td>
<td></td>
<td></td>
<td></td>
<td>0.10 m iPrOH</td>
<td>39</td>
<td>93</td>
<td>0.73</td>
<td>2</td>
</tr>
<tr>
<td>2c</td>
<td></td>
<td></td>
<td></td>
<td>0.10 m iPrOH</td>
<td>36</td>
<td>89</td>
<td>0.64</td>
<td>2</td>
</tr>
<tr>
<td>3a</td>
<td></td>
<td></td>
<td></td>
<td>0.25 m iPrOH</td>
<td>41</td>
<td>14</td>
<td>0.11</td>
<td>1</td>
</tr>
<tr>
<td>3b</td>
<td></td>
<td></td>
<td></td>
<td>0.25 m iPrOH</td>
<td>33</td>
<td>28</td>
<td>0.18</td>
<td>1</td>
</tr>
<tr>
<td>3c[a]</td>
<td></td>
<td></td>
<td></td>
<td>0.25 m iPrOH</td>
<td>29</td>
<td>53</td>
<td>0.31</td>
<td>1</td>
</tr>
<tr>
<td>4a</td>
<td></td>
<td></td>
<td></td>
<td>0.10 m iPrOH</td>
<td>39</td>
<td>73</td>
<td>0.57</td>
<td>3</td>
</tr>
<tr>
<td>4b</td>
<td></td>
<td></td>
<td></td>
<td>0.10 m iPrOH</td>
<td>34</td>
<td>76</td>
<td>0.52</td>
<td>3</td>
</tr>
<tr>
<td>5a</td>
<td></td>
<td></td>
<td></td>
<td>0.25 m iPrOH</td>
<td>58</td>
<td>49</td>
<td>0.57</td>
<td>1</td>
</tr>
<tr>
<td>5b[a]</td>
<td></td>
<td></td>
<td></td>
<td>0.25 m iPrOH</td>
<td>45</td>
<td>63</td>
<td>0.57</td>
<td>1</td>
</tr>
<tr>
<td>6a</td>
<td></td>
<td></td>
<td></td>
<td>0.20 m iPrOH/H_2O 4:1</td>
<td>61</td>
<td>12</td>
<td>0.15</td>
<td>4</td>
</tr>
<tr>
<td>6b</td>
<td></td>
<td></td>
<td></td>
<td>0.20 m iPrOH/H_2O 4:1</td>
<td>39</td>
<td>38</td>
<td>0.30</td>
<td>4</td>
</tr>
</tbody>
</table>
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 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 ¹H 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 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 I, 2-phenylbutyric acid, and 2 were obtained from Aldrich. A standard Suzuki
The dissolution temperatures differ somewhat, owing to the high
concentrations in this experiment (1.6
°C for this
sample).  The experimentally determined error limit is ±0.5°C.


[2] a) R. A. Sheldon, Chirotechnology, Marcel Dekker, New York, 1993,
chap. 6; b) Chirality in Industry II (Eds.: N. A. Collins, G. N. Shel-

Kellogg, Q. B. Broxterman, A. Minnaard, B. Kaptein, S. van der Sluis,
DSM).


[5] The cyclic phosphoric acids (Pmix) were developed as resolving
agents in our lab and have been patented: W. ten Hoeve, H. Wynberg,


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

[9] Analogous experiments with pure (S)-o-nitrophenylethylamine (S)
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 op 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°C); the experimentally deter-
mined 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. Eisenberg, J. W. Nieuwenhuijzen, R. M.

6651; b) K. Kinbara, Y. Harada, K. Saigo, Tetrahedron: Asymmetry
1998, 9, 2219.

Leiserowitz, Nature 1982, 296, 21; b) Z. Berkovich-Yellin, L. Addadi,
Soc. 1982, 104, 4610; d) D. Zbaida, M. Lahav, K. Drauz, G. Knaup,


The synthesis of nanoparticles is of fundamental impor-
tance for the development of novel technologies based on
nanomaterials. This is particularly true for magnetic nano-
materials which could be used, amongst other things, for high-
density information storage.[10] 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] and chemical methods
involving synthesis in a solution of nano-
particles.[5,4] 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 dis-
playing 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 Pil
nen 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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