



Nucleation inhibition in attrition-enhanced Pope-Peachey type of diastereomeric resolutions

Michel Leeman^a, Bernard Kaptein^b, Richard M. Kellogg^{a,*}

^aSyncom BV, Kadijk 3, 9747 AT Groningen, The Netherlands

^bDSM Pharmaceutical Products, Innovative Synthesis & Catalysis, PO Box 18, 6160 MD Geleen, The Netherlands

ARTICLE INFO

Article history:

Received 19 March 2009

Accepted 26 May 2009

Available online 21 June 2009

ABSTRACT

The resolution of racemic 1-(3-methoxyphenyl)ethylamine with (*S*)-mandelic acid by diastereomeric salt formation can be made more economical by application of the Pope-Peachey method. This resolution was further improved upon by the addition of small amounts of a nucleation inhibitor, which prevents the formation of crystals of the more soluble diastereomer. The mandelic acid left in the solution is then used for further crystal growth of the less soluble diastereomer, furnishing high yields and diastereomeric excesses. Slow cooling and grinding of the crystals formed lead to increased secondary nucleation and thus to more consumption of the less soluble diastereomer and even better results.

© 2009 Elsevier Ltd. All rights reserved.

1. Introduction

A relatively new insight into diastereomeric resolutions is that nucleation inhibitors that resemble structurally either the resolving agent or racemate can effectively inhibit the crystallization of the more soluble diastereomer in a resolution. Application of this principle in classical resolutions has been described for several systems.^{1–3} Recently we described this principle in detail for the resolution of racemic 1-(3-methoxyphenyl)ethylamine (3MeOPEA) with (*S*)-mandelic acid (MA) as depicted in Figure 1. The standard resolution at high concentration and using 1 equiv of MA resulted in a solid in 72% yield and 10% de (thus to 40% less soluble diastereomer and 32% of the more soluble diastereomer). The mother liquor (28%) was then saturated in both diastereomers with a eutectic composition of 29% de. However, on addition of a small amount (as little as 1 mol %) of (*S*)-2-acetoxy-2-phenylacetic acid (AcMA), one of the best nucleation inhibitors for this resolution, the crystallization of the more soluble diastereomer was inhibited for more than three weeks. The result was that the diastereomeric excess (de) of the isolated salts increased from 10% to 97%.⁴

2. Results and discussion

Inhibition of the crystallization of the more soluble diastereomer under these conditions by addition of only 1 mol % of (*S*)-AcMA results in a supersaturation of 278%⁵, the result being that the less soluble diastereomer is obtained in 42% yield and 97% de.

The resolution might be further improved if less of the resolving agent remained in the solution. In this way, less of the nucleation

inhibitor can be used and/or even higher concentrations can be applied.

A variation of a classical resolution frequently applied on an industrial scale is the use of half of the resolving agent (in practice usually 0.7 equiv) or optionally the Pope-Peachey approach in which half of the resolving agent is replaced by a (low cost) achiral acid or base.^{6,7} The role of the achiral acid or base is to form highly soluble salts with the enantiomer remaining in the solution. Note that on crystallization of the less soluble diastereomer the resolving agent is depleted in the solution and the solution equilibria shift to the salts of the achiral acid or base. The crystallization yield will never exceed 50%—the maximum yield of a perfect resolution without racemization. Since only half of an equivalent of the resolving agent is available the solubility of the diastereomeric salt will also be increased and therefore the resolution conditions need to be changed by using higher concentrations or less polar (poorer) solvents. A search for a solvent that would dissolve the less soluble salt, (*S*)-3MeOPEA-(*S*)-MA at a reasonable concentration at reflux temperature but only a small part of this salt at room temperature, led us to toluene as the most suitable solvent.

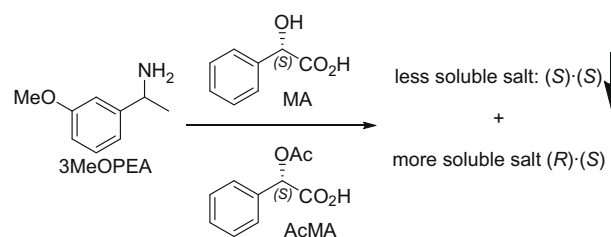


Figure 1. Resolution of (\pm)-3MeOPEA with (*S*)-MA, using (*S*)-AcMA as a chiral nucleation inhibitor.

* Corresponding author. Tel.: +31 0 50 5757272; fax: +31 0 50 57577399.
E-mail address: r.m.kellogg@syncom.nl (R.M. Kellogg).

Achiral acids were screened to deliver a salt with (*R*)-3MeOPEA and which would dissolve in toluene at high concentrations. Acetic acid was chosen as the achiral acid since it is cheap, non-toxic, readily available, and produced oils that did not crystallize, at least within a period of 3 weeks.

In the first experiments, a half equivalent of AcOH, a half equivalent of (*S*)-MA, varying amounts of (*S*)-AcMA (replacing the AcOH) as a nucleation inhibitor, and 1 equiv of racemic 3MeOPEA were mixed with toluene in stirred reactor tubes, heated at reflux (~111 °C) to dissolution, and the tubes were stirred for 30 min at 70 °C during which time crystallization started. The tubes were subsequently stirred and further cooled to 20 °C at 0.1 °C min⁻¹. After eight more hours of stirring at 20 °C, the solids were collected, washed, and the yields and de's were determined as shown in Table 1.⁸

Table 1
The effect of (*S*)-AcMA on the resolution efficiency

Entry	(<i>S</i>)-AcMA (%)	Yield ^a (%)	de ^a (%)	S-factor ^b
1	None	47	54	0.51
2	0.01	46	56	0.50
3	0.10	47	61	0.56
4	1.00	43	97	0.83

^a The results are averages of duplicates.

^b S-factor = 2 × yield × de.

For entry 1 in Table 1, no additive was added and, as explained in the introduction, the crystalline salt cannot be isolated in more than 50% yield. As expected, the isolated salts only have moderate de's. However, as seen in entry 4, only 1% of (*S*)-AcMA blocks the nucleation of the more soluble diastereomer (*R*)-3MeOPEA-(*S*)-MA and almost all of (*S*)-MA in the solution is used for the precipitation of the less soluble (*S*)-3MeOPEA-(*S*)-MA yielding nearly enantiomerically pure material. Lower concentrations of (*S*)-AcMA (entries 2 and 3) were not effective with this setup.

On the basis of a recent discovery⁹ of attrition-enhanced deracemization, we turned our attention to a different protocol. When the mixtures were heated to dissolution at 100 °C and then cooled to 20 °C at 0.1 °C min⁻¹, instead of fast cooling from 111 °C to 70 °C and subsequently cooled to 20 °C at 0.1 °C min⁻¹, the resolution efficiency increased dramatically as shown in Table 2.

Table 2
The effect of (*S*)-AcMA with slow crystallization

Entry	(<i>S</i>)-AcMA (%)	Yield ^a (%)	de ^a (%)	S-factor ^b
1	None	42–43	92–99	0.79–0.83
2	0.05	41–42	98–99	0.81–0.83
3	0.10	41–42	99	0.81–0.83

^a The results are extremes of triplicates.

^b S-factor = 2 × yield × de.

As can be concluded from the differences between Table 1, entry 1 and Table 2, entry 1 the temperature profile used in the resolution is essential. This can be explained⁹ by the crystallization of the less soluble diastereomer together with the grinding action of the magnetic stirrer,^{10,11} which delivers more crystal surface (secondary nucleation) and promotes the consumption of the (*S*)-MA in the solution, therefore reducing (but not eliminating) the supersaturation of the more soluble diastereomer. The results seen here are thus strictly kinetic in nature.

During the cooling, the crystallization was observed. In Table 2, entry 1, the reaction mixture with the lowest de (92%), started to crystallize at 84 °C whereas both reaction mixtures with >98% de started to crystallize above 85 °C. Screening Pope-Peachey resolu-

tions in a test tube without slow cooling or grinding, will most likely result in far from optimal (thermodynamic) results as a result of higher supersaturation. Faster cooling might be possible if the grinding action on the first formed crystals is more intense, for example, by the addition of solid glass beads and vigorous stirring.⁹

Entries 2 and 3 in Table 2 show that addition of a small amount of (*S*)-AcMA seems to result in more reproducible results and in higher de's as a result of the widening of the metastable zone width of the more soluble diastereomeric salt.

3. Conclusion

The results in Table 1, entry 1 represent the thermodynamic end-state of the resolution. The resolutions that give better results are kinetically steered and after prolonged stirring (days–years), these will produce the same thermodynamical end-state. Thus, in large-scale Pope-Peachey resolutions, a precise cooling profile, grinding of the less soluble crystals, seeding, and/or addition of a nucleation inhibitor might be essential to obtain reproducibly good results. The addition of a small amount of a proper nucleation inhibitor can dramatically increase the success rate even without precise cooling.

Acknowledgments

Partial financial support for this work was provided by the Samenwerkingsverband Noord- Nederland (Cooperation Northern Netherlands) and the European Fund for Regional Development (EFRO).

References

- 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.
- Dalmolen, J.; Tiemersma-Wegman, T. D.; Nieuwenhuijzen, J. W.; van der Sluis, M.; van Echten, E.; Vries, T. R.; Kaptein, B.; Broxterman, Q. B.; Kellogg, R. M. *Chem. Eur. J.* **2005**, *11*, 5619.
- Addadi, L.; Weinstein, S.; Gati, E.; Weissbuch, I.; Lahav, M. *J. Am. Chem. Soc.* **1982**, *104*, 4610.
- Leeman, M.; Brasile, G.; Gelens, E.; Vries, T.; Kaptein, B.; Kellogg, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 1287.
- A resolution without nucleation inhibitor yielded 18% (total 50%) of the more soluble diastereomer in the saturated mother liquor. The remaining 32% of the more soluble diastereomer had thus crystallized. This resolution with 1% (*S*)-AcMA as nucleation inhibitor where the more soluble diastereomer did not crystallize therefore produced a supersaturation of: 50%/18% × 100% = 278%, relative to 100% for a saturated solution.
- Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Krieger: Malabar, Florida, 1994.
- Pope, W. J.; Peachey, S. J. *J. Chem. Soc.* **1899**, 75, 1066.
- A typical Pope-Peachey resolution experiment was performed by charging a Kimble reactor tube (Ø 25 × 150 mm) with a PTFE-coated egg-shaped magnetic stirring bar (19 mm × 10 mm), (±)-3MeOPEA (322 mg, 2.13 mmol, 1.0 equiv), (*S*)-MA (162 mg, 1.06 mmol, 0.5 equiv), and AcOH (63 mg, 1.06 mmol, 0.5 equiv) in toluene (10 mL). This mixture was stirred and after some minutes, crystals started to form. When additives were used, an equimolar amount of AcOH and toluene were replaced by a solution of (*S*)-AcMA (41.35 mg·10 mL⁻¹ toluene) ensuring that the whole system remained neutral and of equal volume. The suspension was heated at reflux (dissolution) and placed in a Reactiv8 computer-controlled reactor station and stirred magnetically at 600 rpm and at 70 °C (Table 1) or 100 °C (Table 2) for 30 min. The tubes were then cooled to 20 °C at 0.1°/min and kept at 20 °C for an additional 8 h. The crystals formed were collected on pre-weighed disposable filters and washed with 2 × 2.0 mL Et₂O. The solids were dried in vacuo, weighed, and subsequently the de of the salts was determined. Chiral HPLC analysis of 3MeOPEA salts was carried out on a Crownpak CR(-) column with an aqueous solution of HClO₄ (pH 2) as eluent at 20 °C and 0.6 mL min⁻¹. UV-vis detection was performed at 192 nm. The salts were dissolved in eluent and injected as such. (*R*)-3MeOPEA R_f: 39.59 min, (*S*)-3MeOPEA R_f: 42.98 min.
- (a) Noorduin, W. L.; Izumi, T.; Millimaggi, A.; Leeman, M.; Meekes, H.; van Enckevort, W. J. P.; Kellogg, R. M.; Kaptein, B.; Vlieg, E.; Blackmond, D. B. *J. Am. Chem. Soc.* **2008**, *130*, 1158; (b) Leeman, M.; Noorduin, W.L.; Kaptein, B.; Vlieg, E.; Meekes, H.; van Enckevort, W.J.P.; Zwaagstra, K.; de Gooijer, J.M.; Boer, K.; Kellogg, R.M.; submitted for publication.
- Kondepudi, D. K.; Kaufman, R. J.; Singh, N. *Science* **1990**, *250*, 975.
- McBride, J. M.; Carter, R. L. *Angew. Chem., Int. Ed.* **1991**, *30*, 293.