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(2-Naphthyl)glycolic acid: a tailored resolving agent for *p*-substituted 1-arylethylamines

Kazushi Kinbara, Yoshiko Harada and Kazuhiko Saigo *

Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

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Abstract

A tailored resolving agent for *p*-substituted 1-arylethylamines, which was designed on the basis of a criterion derived from our crystal-structure study, namely that the racemate and the resolving agent should have similar molecular lengths, is described. The designed enantiopure (2-naphthyl)glycolic acid (2-NGA) showed excellent resolving ability for a wide variety of *p*-substituted 1-arylethylamines.

Resolution via diastereomeric salt formation is one of the most practical methods for obtaining enantiopure compounds.[1] Despite its importance, the method, however, requires a lot of trial-and-error to choose a suitable resolving agent, since the chiral discrimination mechanism during resolution is not clear at present. In order to clarify the chiral discrimination mechanism during resolution via diastereomeric salt formation and to present criteria for the selection of a suitable resolving agent, we recently carried out a systematic study on the resolution of 1-arylalkylamines with enantiopure mandelic acid.[2,3] As a result, it was found that the resolution efficiency depended on the position of the substituent of the amines to a considerable extent, and a further detailed study on the basis of the crystallographic analyses of the diastereomeric salts revealed that complementarity in molecular length between the resolving agent and the target racemates was essentially the most important factor for a successful resolution. On the basis of these results, we established a criterion for designing a resolving agent for 1-arylethylamines, namely that the racemate and the resolving agent (α-hydroxy acid) should have similar molecular lengths.

Our previous study showed that even though mandelic acid could efficiently resolve non- and *o*-substituted 1-arylethylamines, the resolution efficiency for *p*-substituted 1-arylethylamines was poor.[2] The resolution efficiency for these amines was significantly improved by using *p*-substituted mandelic acids as resolving agents. The results were, however, not sufficient for practical resolution;[2] it is considered that the flexibility of the substituent on the *p*-position of the aromatic ring of the resolving agents makes its molecular length ambiguous, diminishing the resolution efficiency. We then designed a

* Corresponding author. Fax: 81-3-5802-3348; e-mail: saigo@chiral.t.u-tokyo.ac.jp

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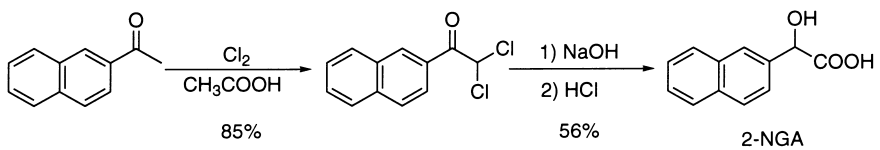
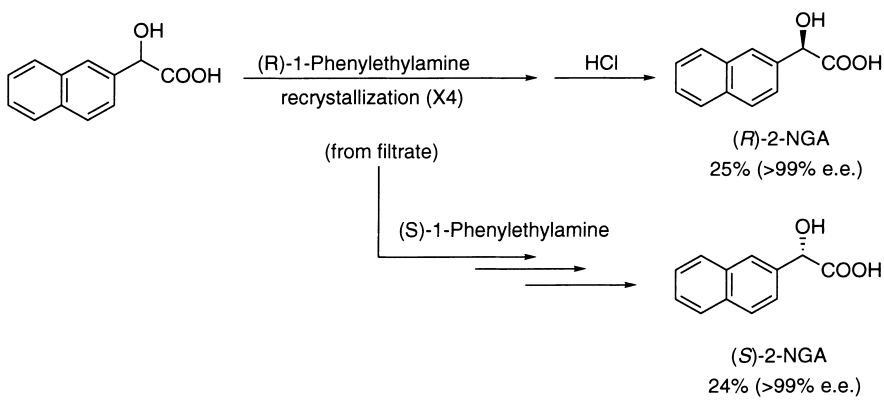
novel resolving agent, (2-naphthyl)glycolic acid (2-NGA), which has a rigid skeleton and an appropriate molecular length according to the above-mentioned criterion.

Although some procedures have been reported for the preparation of optically active 2-NGA, they could not be applied to the synthesis of enantiopure 2-NGA on a practical scale.[4] We then tried to develop a new method for the practical-scale preparation of enantiopure 2-NGA. At first, the synthesis of racemic 2-NGA was examined. As a result, the synthesis of racemic 2-NGA could be accomplished, following the procedure reported for the synthesis of mandelic acid (Scheme 1);[5] racemic 2-NGA could be prepared in 48% overall yield from commercially available 2-acetonaphthone. For a large-scale preparation this method was found to be more convenient than other known procedures.[6]



Scheme 1.

Next, the resolution of racemic 2-NGA by enantiopure amines was studied. As a result, enantiopure 2-NGA could be obtained using (*R*)- or (*S*)-1-phenylethylamine (PEA) as a resolving agent (Scheme 2). Recrystallization of the 2-NGA·(*R*)-PEA salt from aqueous ethanol four times gave pure (*R*)-2-NGA·(*R*)-PEA salt in 28% overall yield. Treatment of the (*R*)-2-NGA·(*R*)-PEA salt with hydrochloric acid afforded crystalline crude (*R*)-2-NGA, which was further purified by recrystallization from chloroform/ethanol to give enantiopure (*R*)-2-NGA in 25% overall yield.[7] Moreover, enantiopure (*S*)-2-NGA could also be obtained by repeated recrystallization (three times) of the salt of (*S*)-enriched 2-NGA, recovered from the filtrate of the first recrystallization of the (*R*)-2-NGA·(*R*)-PEA salt, with (*S*)-PEA.[7]



Scheme 2.

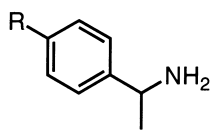
The resolution of various *p*-substituted 1-arylethylamines was performed using (*R*)- or (*S*)-2-NGA as a resolving agent. The results are summarized in Table 1. In order to make crystallization conditions as similar as possible and to avoid the problem of polymorphs, crystallization was performed only once from a protic solvent at a constant temperature (30°C). The amount of the solvent was adjusted to control the yield of the precipitated salt as close as possible within the range 50–80%.

As can be seen from Table 1, 2-NGA has excellent resolving ability over a range of amines, although the crystallization conditions were not optimized at all. In the case of the resolution of 1-(*p*-chlorophenyl)ethylamine (entry 6), which is a valuable intermediate for pharmaceuticals,[8] an additional recrystallization afforded diastereomerically pure (*S*)-2-NGA·(*S*)-1-(*p*-chlorophenyl)ethylamine salt (67% overall yield). Since the absolute configurations of the amines in the less-soluble salts per-

Table 1
Optical resolution of *p*-substituted 1-arylethylamines by 2-NGA[a]

entry	configuration of 2-NGA	R	yield(%)[b]	e.e. (%)[c]	resolution efficiency[d]
1	*R*	Me	81	95 (*R*)	0.77
2	*S*	Et	62	>99	0.61
3	*S*	Pr	80	>99	0.79
4	*R*	OMe	58	87 (*R*)	0.50
5	*S*	c-Hex	50	91	0.46
6	*S*	Cl	77	98 (*S*)	0.75
7	*S*	Br	81	93	0.75
8	*S*	NO_2	80	70	0.56
9	*S*	Ar=1-Naphthyl	77	96 (*S*)	0.74

[a]Solvent: Alcohol/H_2O. [b]Yield of the salt based on a half amount of the amine. [c]Absolute configuration of the amine. [d]Product of the yield and e.e.



fectly correlated with that of 2-NGA used, it is strongly implied that the resolution of *p*-substituted 1-arylethylamines occurs via a common chiral discrimination mechanism. Noteworthy is that even amines having a largely bulky substituent in the *p*-position could be efficiently resolved by 2-NGA (entry 5). In addition, even when a group capable of strong hydrogen bond formation such as a nitro group was present on the phenyl group of the amine, the resolution efficiency remained very high (entry 8). Since a slight change in the molecular structure of a racemate usually exerts a dramatic effect on the resolution efficiency,[2] this high resolving ability of 2-NGA for such a wide variety of amines is remarkable.

As is described, we have succeeded in the design of a tailored resolving agent, 2-NGA, which shows excellent resolving ability for a variety of *p*-substituted 1-arylethylamines. This result indicates that systematic study on the correlation between the crystal structures of diastereomeric salts and their resolution efficiencies would provide direction for the design of new resolving agents.

Acknowledgements

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7. Enantiomeric excesses were determined by HPLC on Daicel CHIRALCEL OJ-R. (a) (*R*)-2-NGA: m.p.: 162.0–163.5°C; IR (KBr): ν=3350–3250, 1690, 1400, 1280, 830 cm^{-1}; ^1H NMR (300 MHz, [D_6]DMSO): δ=5.21 (s, 1H, C*H*), 6.00 (br s, 1H, O*H*), 7.50–7.58, 7.88–7.94 (m, 4H, $C_{10}H_7$); ^{13}C NMR (300 MHz, [D_6]DMSO): δ=72.80 (*C*H), 125.08, 125.64, 126,27, 126.49, 127.78, 127.96, 128.08, 132.78, 132.93, 138.05, ($C_{10}H_7$), 174.30 (*C*OOH); $[\alpha]^{20}_D$ −144.7 (c 0.98 in EtOH). (b) (*S*)-2-NGA: m.p.: 163.5–167.0°C; IR (KBr): ν=3350–3250, 1690, 1400, 1280, 830 cm^{-1}; ^1H NMR (300 MHz, [D_6]DMSO): δ=5.21 (s, 1H, C*H*), 6.00 (br s, 1H, O*H*), 7.50–7.58, 7.88–7.94 (m, 4H, $C_{10}H_7$); ^{13}C NMR (300 MHz, [D_6]DMSO): δ=72.80 (*C*H), 125.08, 125.63, 126.27, 126.49, 127.78, 127.96, 128.08, 132.78, 132.93, 138.05, ($C_{10}H_7$), 174.30 (*C*OOH); $[\alpha]^{20}_D$ +145.6 (c 0.98 in EtOH).
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