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Design of Resolving Reagents: *p*-Substituted Mandelic Acids as Resolving Reagents for 1-Arylalkylamines

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Abstract: The resolution of 1-arylalkylamines **2**–**10** by mandelic acid **1** was studied. It was found that a substituent, which elongated the molecular length of the amines, diminished the resolution efficiency. On the basis of these results, (*S*)-*p*-methylmandelic acid (*S*)-**11** and (*R*)-*p*-methoxymandelic acid (*R*)-**12** were selected as new resolving reagents for the 1-arylalkylamines; these acids were found to have a higher resolving ability than (*R*)-**1**.

Resolution via diastereomeric salt formation is the most widely used method for separating enantiomers of a given racemic acid or base.[1] Despite the practical importance of this method, the choice of a suitable resolving reagent for a racemic target compound is achieved mainly by time-consuming trial-and-error procedure, even at present. Therefore, the prediction and/or rational design of a suitable resolving reagent is a matter of importance, and much attention has been attracted during the recent decade.[2]

Mandelic acid **1** is one of the most frequently used resolving reagents.[3] During the course of our study concerning the resolution of racemic amines,[4] we recently found that enantiomerically pure **1** could resolve 1-(3-methoxyphenyl)ethylamine as well as 1-phenylethylamine via diastereomeric salt formation, and that the crystal structures of their less-soluble salts are very similar to each other.[5] These results suggested that **1** would resolve a variety of 1-arylalkylamines on the basis of the same chiral discrimination mechanism, and that a study concerning the resolution of the 1-arylalkylamines by **1** would subsequently afford a way to design a more suitable resolving reagent for these amines.

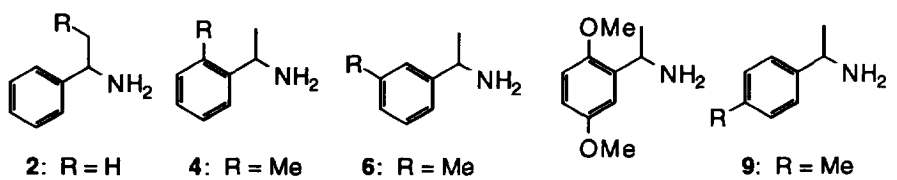
Here we describe the resolution of 1-arylalkylamines by enantiomerically pure **1**, and the design of resolving reagents for 1-arylalkylamines based on experimental results.

We at first addressed our attention to elucidate the effect of a substituent in 1-arylalkylamines on the resolution efficiency via diastereomeric salt formation with **1**. The resolutions of 1-arylalkylamines **2**–**10** were performed upon a single crystallization at 38.0 °C from an appropriate protic solvent[6] for an equimolar mixture of (*R*)-**1** and the corresponding racemic amines, respectively. The amount of the solvent was controlled so that the resulting diastereomeric salt was obtained in a range of 70–90% yield as close as possible (based on a half amount of the racemic amine to be resolved). The results are summarized in Table 1.

Table 1. Resolution of 1-Arylalkylamines **2**–**10** by (*R*)-**1**

entry	racemic amine	solvent	amount of solvent[a]	yield (%)[b]	e.e. (%)[c]	resolution efficiency[d]
1	**2**	H_2O	2.1	76	87[e]	0.66
2	**3**	H_2O	2.6	81	92[e]	0.75
3	**4**	H_2O	1.6	71	100[f]	0.71
4	**5**	H_2O	1.9	69	81[e]	0.56
5	**6**	MeOH	1.2	94	12[g]	0.11
6	**7**	MeOH	3.1	70	89[e]	0.62
7	**8**	H_2O/MeOH	4.8/2.7	71	92[g]	0.65
8	**9**	MeOH	1.9	88	4[f]	0.04
9	**10**	MeOH	3.0	84	4[g]	0.03

[a]Weight ratio of the solvent to the racemic amine. [b]Yield of the crystallized diastereomeric salt based on the half amount of the racemic amine. [c]Enantiomeric excess (e.e.) of the liberated amine, which was determined by an HPLC analysis (Daicel Crownpak CR). [d]Defined as a product of the yield of the diastereomeric salt and the e.e. of the liberated amine. [e](*R*)-Amine was obtained as a major enantiomer. [f](*S*)-Amine was obtained as a major enantiomer. [g]The absolute configuration of the major isomer has not been determined.



2: R = H, **3**: R = Me — **4**: R = Me, **5**: R = OMe — **6**: R = Me, **7**: R = OMe — **8** — **9**: R = Me, **10**: R = OMe

These results indicated a close relationship between the position of the substituent on **2**–**10** and the resolution efficiency: (*R*)-**1** could efficiently resolve 1-phenylpropylamine **3** and 1-arylethylamines **4** and **5**, having a substituent at the *o*-position of the phenyl group, as well as **2** (entries 1–4), whereas 1-arylethylamines **9** and **10**, having a substituent at the *p*-position of the phenyl group, could be scarcely resolved by (*R*)-**1** (entries 8 and 9); the results of *m*-substituted 1-arylethylamines **6**–**8** depended on the amines (entries 5–7).

It seems that this relationship between the position of the substituent and the resolution efficiency would be interpreted on the basis of the molecular length of the amines; the molecular length of the *p*-substituted 1-arylalkylamines is longer than that of (*R*)-**1**, whereas the *β*- or *o*-substituted 1-arylethylamines has similar molecular length to (*R*)-**1**, as illustrated in Figure 1. In the cases of the *m*-substituted amines, the molecular length of the amines would depend on the conformation of the aryl group. Thus, it is strongly suggested that 1-arylalkylamines, which have similar molecular length to that of (*R*)-**1**, could be efficiently resolved by (*R*)-**1**.

These results indicates that resolving reagents, which have longer molecular length than that of (*R*)-**1**, would be efficient for the resolution of *m*- and/or *p*-substituted 1-arylalkylamines. On the basis of this consideration, we then prepared (*S*)-*p*-methylmandelic acid (*S*)-**11**[7,8] and (*R*)-*p*-methoxymandelic acid (*R*)-**12**,[7,8] which have similar molecular length to that of **9**, and performed the resolution of **9** as well as **2** with these acids upon crystallization at 38.0 °C from a protic solvent[6] for an equimolar mixture of the acid and the amine. The results are summarized in Table 2.

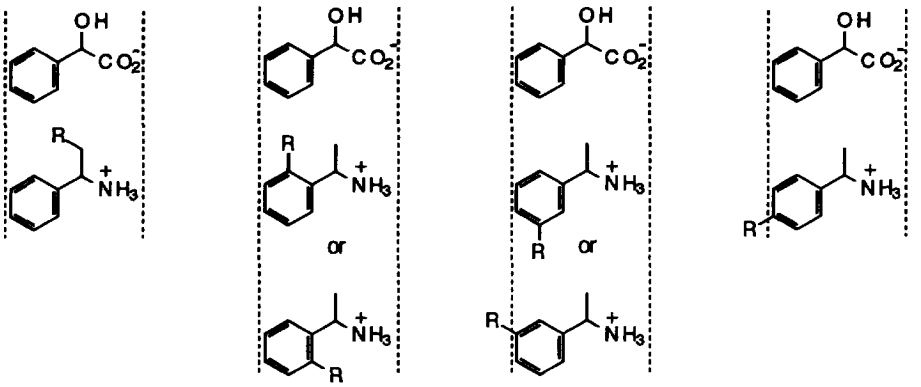
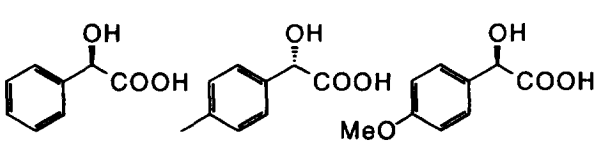


Figure 1 Comparison of the molecular length of 1-arylalkylamines with that of (*R*)-**1**. R represents a substituent of the amine.

Table 2. Resolution of 1-Arylethylamines **2**, **6**, **9**, and **10** by *p*-Substituted Mandelic Acids **11** and **12**

entry	racemic amine	resolving reagent	solvent	amount of solvent[a]	yield (%)[b]	e.e. (%)[c]	resolution efficiency[d]
1	**2**	**11**	MeOH	3.7	74	80[f]	0.59
2	**9**	**11**	MeOH	3.4	85	63[f]	0.54
3	**2**	**12**	MeOH	4.7	70	89[e]	0.62
4	**9**	**12**	MeOH	15.9	72	85[e]	0.61
5	**6**	**12**	MeOH	7.4	76	75[e]	0.57
6	**10**	**12**	MeOH	6.8	62	46[g]	0.29

[a]Weight ratio of the solvent to the racemic amine. [b]Yield of the crystallized diastereomeric salt based on the half amount of the racemic amine. [c]Enantiomeric excess (e.e.) of the liberated amine, which was determined by a chiral HPLC analysis (Daicel Crownpak CR). [d]Defined as a product of the yield of the diastereomeric salt and the e.e. of the liberated amine. [e](*R*)-Amine was obtained as a major enantiomer. [f](*S*)-Amine was obtained as a major enantiomer. [g]The absolute configuration of the major isomer has not been determined.



1 **11** **12**

As a result, these acids were found to have a considerably higher resolving ability for **9** than (*R*)-**1**, as we had expected (compare Table 2, entries 2 and 4 with Table 1, entry 8). The resolving ability increased in the order (*R*)-**1**<<(*S*)-**11**<(*R*)-**12**. In addition, the resolution efficiencies of **6** and **10** were also tremendously improved by using (*R*)-**12** as the resolving reagent (compare Table 2, entries 5 and 6 with Table 1, entries 5 and 9, respectively). Thus, *p*-substituted mandelic acids were found to be quite efficient resolving reagents for 1-

arylalkylamines, which could scarcely be resolved by (*R*)-**1**. Moreover, it is noteworthy that (*S*)-**11** and (*R*)-**12** have a high resolving ability even for **2**, as does (*R*)-**1**. This result indicates that these resolving reagents can resolve 1-arylalkylamines, having somewhat shorter molecular length than their molecular length, as well as 1-arylalkylamines with similar molecular length.

The precise reason for such correlation between the efficiency of resolution and the length of resolving reagents is not known at present, although our previous study indicated that hydrogen-bond networks, formed in less-soluble salts, played a significant role in the chiral discrimination of 1-arylethylamines.[5] In order to elucidate this correlation more clearly, crystallographic studies concerning both more- and less-soluble diastereomeric salts are now in progress.

In summary, it was found that *p*-substituted mandelic acids (*S*)-**11** and (*R*)-**12** were suitable resolving reagents for *p*-substituted 1-arylalkylamines while (*R*)-**1** was suitable for non- or *o*-substituted 1-arylalkylamines. These results suggest that when one chooses a suitable resolving reagent for a given racemate, the complementarity in size between the resolving reagent and the racemate should be taken into account.

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6. Since there is a possibility that the resolution efficiency depends on the solvent to some extent, we restricted the solvent to protic one, such as water, methanol, or their mixture, which would play a similar role to each other in solvation etc. and control the solubility of the diastereomeric salts.
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8. Resolution of **11** and **12** were performed using 1-phenylethylamine as a resolving reagent, respectively.[7] (*S*)-**11** (95% e.e.) and (*R*)-**12** (95% e.e.) were obtained and used for the resolutions in the present study.

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