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Resolutions of sibutramine with enantiopure tartaric acid derivatives: chiral discrimination mechanism

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ABSTRACT

The resolution of sibutramine **1** was investigated with enantiopure tartaric acid derivatives. Based on the resolving efficiency assay using a 'Dutch resolution', *O*,*O*′-di-*p*-anisoyl-(*R*,*R*)-tartaric acid (*R*,*R*)-DMTA was identified as an effective resolving agent, which is easily obtained from natural and inexpensive (*R*,*R*)-tartaric acid. Compound (*R*)-**1** was obtained with high enantiomeric purity and yield. The chiral discrimination mechanism and resolving effect in the process were explained with X-ray crystallographic studies. The crystal structures of the conglomerate salts revealed that the more soluble diastereomer (*S*)-**1**·(*R*,*R*)-DMTA formed a parallel ribbon supramolecular structure while the less soluble diastereomer (*R*)-**1**·(*R*,*R*)-DMTA formed a spiral net packing structure by enantio-differentiation self-assembly. The effect of the side substituent of the resolving agent on the enantioseparation of **1** via a supramolecular chiral host consisting of tartaric acid analogues is discussed.

1. Introduction

Approximately half of all commercial drugs are chiral. Many racemic medicines have been researched and upgraded in the domain of chiral preparation and application. Sibutramine **1**, as an anti-obesity drug, is a serotonin and noradrenaline re-uptake inhibitor. It has been proven to be effective in weight reduction.[1] The stereogenic carbon atom of sibutramine has two enantiomeric isomers. Its enantioselective behaviors have been revealed in the pharmacokinetic and pharmacodynamic characteristics.[2,3] Compound (*R*)-**1** decreases body weight and food uptake, whereas the (*S*)-isomer increases body weight and food uptake.[4,5] Animal experiments show that (*R*)-**1** can reduce dosage and lower side effects.[6] Meanwhile, it has been found that (*R*)-**1** can potentially be used in the treatment of depression, Parkinson's disease, cerebral function disorders and diabetes.[7] For efficiency and safety, sibutramine should be developed and administered as a single isomer drug. Although asymmetric synthesis is one way to obtain (*R*)-**1**,[8] it is unsuitable for commercial production. Alternatively, the racemate has some well-established preparation methods and is manufactured on a large scale. Therefore, the resolution of the racemate via diastereomeric intermediates is a reasonable method for the commercial synthesis of chiral sibutramine.

Tartaric acid and its derivatives are well known to be good resolving agents for racemic amines. The *rac*-**1** was first resolved with *O*,*O*′-dibenzoyl-tartaric acid (DBTA),[9] and enantiomerically pure **1** was prepared with >99.5% enantiomeric excess in 40% overall yield. However, (*R*)-**1** was obtained only by (*S*,*S*)-DBTA, which is not as abundant as natural (*R*,*R*)-tartaric acid. Herein, we explored the resolution with (*R*,*R*)-tartaric acid derivatives for the first time. A very efficient method was reported for the resolution of *rac*-**1**. *O*,*O*′-Di-*p*-anisoyl-(*R*,*R*)-tartaric acid (*R*,*R*)-DMTA **4** was found to be the best resolving agent among (*R*,*R*)-DBTA **2**, *O*,*O*′-di-(*p*-toluoyl)-(*R*,*R*)-tartaric acid (*R*,*R*)-DTTA **3** and **4** (Scheme 1).

Classical resolution depends on the different solubility of diastereomeric salt pairs, which is the result of the molecular interactions of the corresponding diastereomeric salt.[10] Over the past two decades, the crystal structures of paired diastereomeric salts were investigated to clarify the mechanism of chiral discrimination.[11–15] Few studies have probed the crystal structures of the resolving salts with 'Dutch resolution' to gain insights into chiral recognition mechanism.[16] Herein, the effect of the side substituent of the resolving agent on the enantioseparation of **1** is discussed. The crystal structures of the less-soluble salts were compared in using DBTA and DMTA. To elucidate chiral discrimination, we studied the crystal structures of paired diastereomeric salts of chiral sibutramine with **4** by X-ray crystallographic analysis. We investigated the supramolecular structure of these resolving salts and the relationships between structure and molecular

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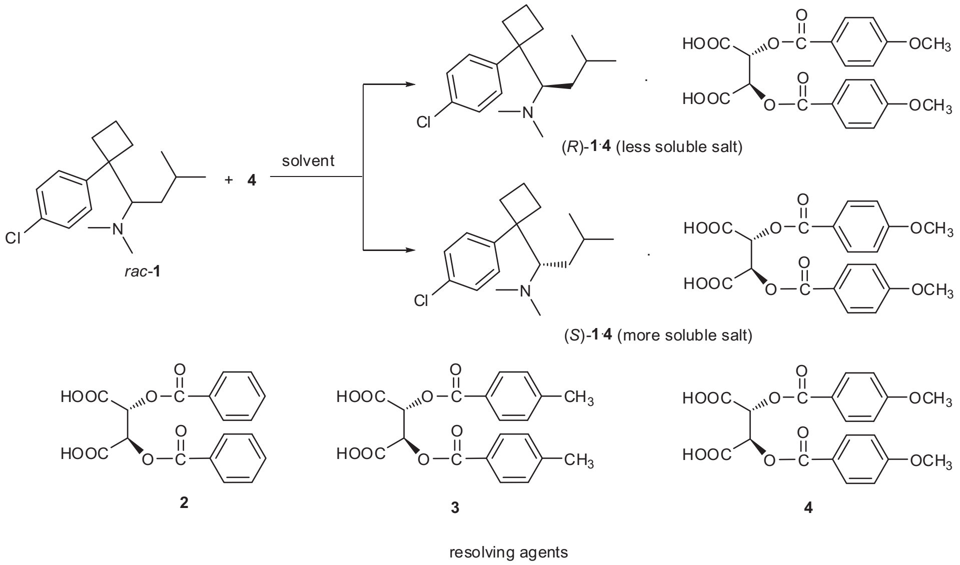

Scheme 1. Resolution of racemic **1**.

recognition to understand why the resolving efficiency of **4** is the best for the resolution of **1**.

2. Results and discussion

2.1. Resolution of sibutramine

Tartaric acid and its diaryl carboxylate derivatives **2**, **3,** and **4** are among the most widely used chiral acids for the resolution of racemic amines,[17] such as DBTA for racemic sibutramine **1**.[9] To improve the resolution efficiency, the three compounds were explored with diastereomeric salts. At first, we explored a mixed group of **2**, **3,** and **4** as the resolving agent. The mixture of resolving agents was added to a solution of equimolar amounts of *rac*-**1** in ethyl acetate, and the precipitate was analyzed by ^{1}H NMR and HPLC. Compound (*R*)-**1** was obtained with 43.4% yield and 62.3% enantiomeric excess (Table 1, entry 1). According to ^{1}H NMR results, Dutch resolution of *rac*-**1** was carried out with a mixture of **2**, **3,** and **4**. After recrystallization of the salt, **4** became the major component in the complex, in which the molar ratio of **2**, **3,** and **4** changed from 3:7:20 to 2:11:50 (Table 1, entries 1 and 2). When the mixture of **3** and **4** was used with equimolar *rac*-**1**, the resolving efficiency increased to 38.2% (Table 1, entry 3). Meanwhile, the resolution was carried out with **3** or **4** alone. The salt of **1**·**3** was difficult to precipitate out and the resolving efficiency of **4** was better than others (Table 1, entry 4). These demonstrated that **4** was the best resolving agent. Compound (*R*)-**1** could be obtained with up to 75.3% efficiency with **4**.

Furthermore, several solvents, such as methanol, ethanol, isopropanol, acetone, and dichloromethane were studied, and the mixed solvent of ethanol and *n*-hexane was found to be an excellent solvent system. In the resolution with tartaric acid derivatives, the usual molar ratio of racemic amine and resolving agent was 1:1. To improve the resolving efficiency of **4**, we tested several ratios between host and guest during the resolution of *rac*-**1**. Optimization experiments showed that the ratio of 0.9:1 was the best (Table 1, entries 5–11). In the experiments, ^{1}H NMR demonstrated that the ratios of **4** and **1** in the less-soluble salts were close to 1:1. After recrystallization in isopropyl alcohol, the less soluble diastereomer (*R*)-**1**·(*R*,*R*)-DMTA was treated with alkali to release (*R*)-**1** with >98% enantiomeric excess. Thus, utilizing **4** as a resolving agent, enantiomerically pure (*R*)-**1** was prepared with 98.6%

Table 1
Results of resolution of *rac*-**1**

Entry	**1**:**2**:**3**:**4**[a]	Solvent	ee[b] (%)	Yield[c] (%)	Eff.[d] (%)
1	3:1:1:1	Ethyl acetate	62.3	43.4	27.0 (3:7:20)[e]
2	—[f]	Ethyl acetate	83.1	58.2	– (2:11:50)[e]
3	4:0:1:3	Ethyl acetate	77.5	49.3	38.2
4	1:0:0:1	Ethyl acetate	78.7	95.6	75.3
5	1:0:0:1	Ethanol/*n*-hexane	82.8	95.9	79.4
6	1:0:0:0.9	Ethanol/*n*-hexane	89.4	91.3	81.6
7	—[g]	Isopropanol	98.6	92.5	–
8	1:0:0:0.8	Ethanol/*n*-hexane	88.5	88.0	77.9
9	1:0:0:0.7	Ethanol/*n*-hexane	87.9	80.4	70.7
10	1:0:0:0.6	Ethanol/*n*-hexane	89.1	74.7	66.6
11	1:0:0:0.5	Ethanol/*n*-hexane	91.4	68.9	63.0

[a] Initial molar ratio of *rac*-**1**, **2**, **3** and **4**.
[b] In all experiments, (*R*)-**1** was obtained and the enantiomeric purity was determined by HPLC.
[c] Yield of (*R*)-**1** based on half the initial amount of *rac*-**1**.
[d] Resolving efficiency, defined as a product of the yield of the diastereomeric salt and the ee of the liberated **1**.
[e] Molar ratio of **2**, **3** and **4** in the precipitated salts.
[f] Recrystallization from the mixed salt of entry 1.
[g] Recrystallization from the salt of entry 6.