MOLECULAR RECOGNITION AND RESOLUTION OF GEOMETRICAL ISOMERS OF BENZOIC ACIDS BY BRUCINE

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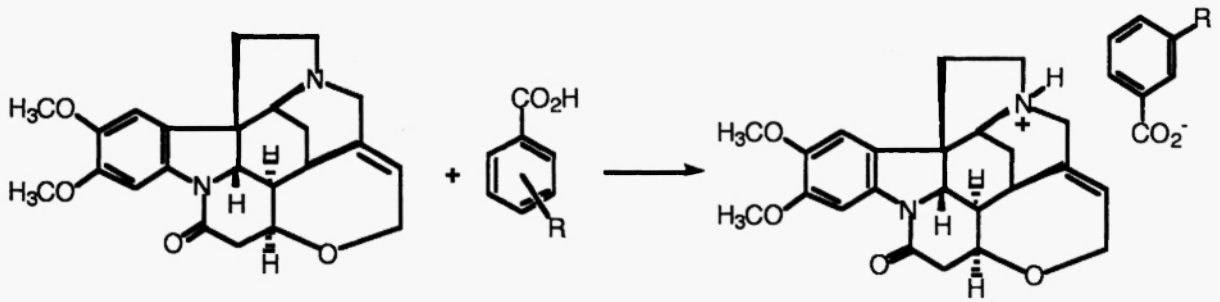
Abstract: Brucine recognized specifically *m*-substituted benzoic acid derivatives among other geometrical isomers. Crystalline clathrates were produced as single crystals from the reaction mixture solutions.

The search for new building blocks and structural motifs for crystal engineering has been growing as an intensive research area in recent several years [1]. The optical resolution of enantio mixtures of acids by an optically active basic compound was often reported [2] from mid-20th century. For example, brucine **1** known as an alkaloid derivative is essential compound for an optical resolution agent [3]. However, the molecular recognition of geometrical isomers of mono-substituted benzoic acids by brucine **1** has not been known. We examined the molecular recognition of mono-substituted benzoic acid derivatives **2** with brucine **1**. Mono-substituted benzoic acid derivatives used were *ortho*, *metha*, and *para* isomers with chloro-, bromo-, or nitro-substituent. After equimolar amount mixture of enantiomerically pure brucine **1** and a *m*-substituted benzoic acid was completely dissolved in methanol, the solution was allowed to stand quietly (without stirring) at room temperature. The precipitation of a solid material was observed from the initial complete solution after 0.5-3 hours. The results of complex formation by combination of substituted

benzoic acids **2** with brucine **1** is summarized in the Table. In the case of only *m*-nitrobenzoic acid **2b** (entry 2 in Table), the crystal of the clathrate compound **3b** immediately precipitated. Surprisingly, the crystal of the clathrate compound from the reaction mixture in methanol formed a good single crystal. Compounds **3e** and **3h** (entries 5 and 8 in Table) afforded single crystals similarly under the same conditions as described above. Thus, the specific self-assembling between m-substituted benzoic acid **2** and brucine **1** was confirmed, however, attempts to obtain crystalline clathrate compounds of o- and *p*-substituted benzoic acids with brucine **1** were all unsuccessful as shown in the Table.



1 2 3

Scheme

Table. Summary of complex and mono-substituted benzoic acids **2** with brucine **1**.

Entries	Benzoic acid			Crystal		Product	
	2	R	pKa	**3**	Crystal	Molecular Ratio (**1**:**2**:MeOH)	Yield (%)
1	**2a**	o-NO_2	2.17	**3a**	—	—	—
2	**2b**	*m*-NO_2	3.45	**3b**	crystal	1:1:1	quant
3	**2c**	*p*-NO_2	3.44	**3c**	—	—	—
4	**2d**	*o*-Cl	2.94	**3d**	—	—	—
5	**2e**	*m*-Cl	3.82	**3e**	crystal	1:1:1	quant
6	**2f**	*p*-Cl	3.98	**3f**	—	—	—
7	**2g**	*o*-Br	2.85	**3g**	—	—	—
8	**2h**	*m*-Br	3.81	**3h**	crystal	1:1:1	quant
9	**2i**	*p*-Br	4.00	**3i**	—	—	—
10	**2j**	*m*-CH_3	—	**3j**	—	—	—
11	**2k**	3,5-dinitro	—	**3k**	crystal	1:1	quant

We examined an X-rays crystallographic analysis to clarify the structure of complex **3b** being obtained as a single crystal. The single crystalline **3b** was mounted into sealed capillary sample holder. Precise lattice constants and three dimensional intensity data were collected on a RIGAKU AFC7R controlled by four circle diffractometer with Ni-filtered CuKα radiation at 293K [4]. Phase determination was

made by direct method (SHELX 86) [5] , and using Fourier techniques. The molecular structure drawing for complex **3b** was shown in Fig. 1, and the complex composition was determined to be consisted of molecular ratio of *m*-nitrobenzoic acid / brucine / methanol in 1 / 1 / 1. The molecular structure obtained from X-ray analysis of crystal **3b** revealed that acidic proton of *m*-nitrobenzoic acid (entry 2 in Table) had been transferred to the amine nitrogen atom (N1) of brucine **1** and that the resulting ammonium forms carboxylate via a hydrogen-bonding between O6 and hydrogen on N atom to afforded the intimate ion pair of benzoic acid and brucine **1** in a 1:1 ratio (Fig. 1). A methanol molecule forms an intermolecular hydrogen bonding with oxygen atom (O4) of the carbonyl group of brucine **1**.

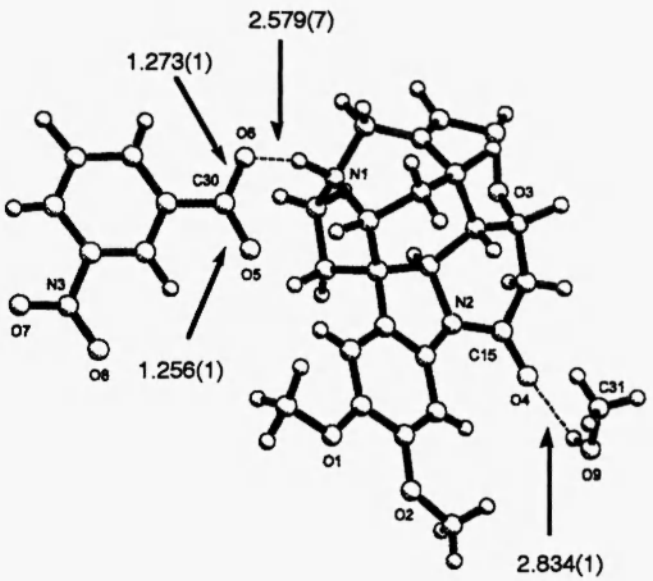


Fig. 1. Molecular structure of **3b** (dotted line indicates the possibility of intermolecular hydrogen bonding, and the number on arrow shows the distance of hydrogen-bonding (Å) and bond distances (Å) as discussed in the text.).

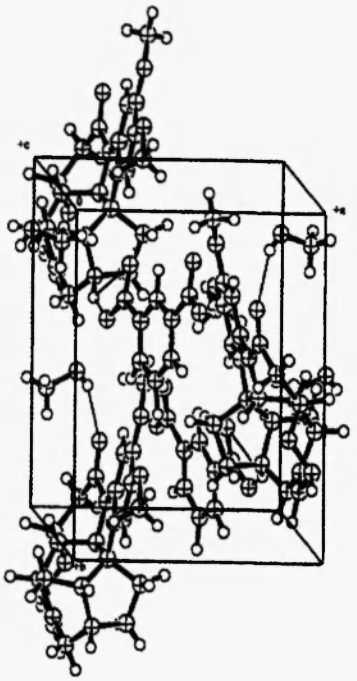


Fig. 2. Molecular structure of **3b** in a unit cell.

In Fig. 1, the bond length of C — O (C30 — O6 and C30 — O5) of the carboxyl group of the benzoic acid were 1.273(1) and 1.256(1) Å, respectively, and hence, the two oxygen atoms (O5 and O6) were clearly distinguished by molecular recognition with brucine molecule. Molecular packing in the unit cell is shown in Fig. 2. From the view of molecular arrangement in the unit cell, the nitro group of compound **3b** obviously does not contribute to the intermolecular hydrogen bonding. In contrast to the *m*-substituted

benzoic acid, no crystalline complex was separated from the methanol solution of the same initial concentration of *o*- or *p*- substituted benzoic acids, and only glassy complexes were obtained by slow evaporation of the solvent. This evidence suggests that molecular recognition and self-assembly of substituted benzoic acid with brucine **1** had been occurred for *m*-substituted benzoic acids, and because of the difference of crystal packing between these isomers *m*-substituted isomer alone produced crystalline product with brucine to give a less soluble aggregate, and then the resolution of geometrical isomer of substituted benzoic acid had been performed.

The pKa value of benzoic acids in Table are in the range of 3.4-3.9 except for the *ortho*-substituted benzoic acids **2a**, **2d**, and **2g**, and *m*-toluic acid **2j**. The pKa values imply that the conformation of complex crystals **3b**, **3e**, and **3h** of mono-substituted benzoic acids **2** with brucine **1** does not depend on the acidity of the geometrical isomer of benzoic acids, and brucine must be protonated with all of these mono-substituted benzoic acid. The reason for the formation of crystalline realized for the *m*-substituted isomer might be explained by making the small and tight package for the *m*-isomer but not for the *o*- and *p*-isomers, either by intra- and intermolecular steric hindrance of the substituents, respectively. Although brucine has been known to be an useful optical resolution agent, this is the first report that describes unique molecular recognition and resolution by brucine to distinguish only *m*-isomer selectively from the *o*-, *m*-, and *p*-isomer mixtures of substituted benzoic acids (e.g., a mixture of **2a**, **2b**, and **2c**) producing the corresponding clathrates as crystalline precipitates.

References.

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[4] Crystal data for **3b**: $C_{30}H_{31}O_8N_3 \cdot CH_3OH$, crystal dimension 0.20 X0.20 X0.30 mm, monoclinic, space group $P2_1$(#4), a = 9.695(2), b = 12.266(2), c = 12.063(2) Å, β = 99.93(1), V = 1413.0(4) Å^3, Z = 2, Dcalc = 1.395 g/cm^3, 293K, 2221 unique reflections having [$I > 2\sigma(I)$] R = 0.055, wR = 0.050 refined against F^2.

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