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Efficient resolution of naproxen by inclusion crystallization with *N*-octyl-glucamine and structure characterization of the inclusion complex

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Abstract—(*S*)-(+)-Naproxen was directly resolved from the racemate with high enantiopurity (>95% e.e.) by inclusion crystallization using *N*-octyl-D-(−)-glucamine as the chiral host. The crystal structure of the inclusion complex was determined.

1. Introduction

Naproxen (6-methoxy-α-methyl-2-naphthaleneacetic acid, **1**) is one of the most popular non-steriodal anti-inflammatory and analgesic drugs. It is an arylpropionic acid with a stereogenic centre. (*S*)-(+)-**1** is about 28 times more effective than its (*R*)-enantiomer[1] an there has thus been extensive research on **1** in order to prepare the enantiopure (*S*)-form. For example, (*S*)-(+)-**1** can be obtained by enantioselective synthesis[2] but this is costly and time-consuming. The racemate of **1**, (±)-**1**, can be prepared easily using a well developed and optimized method and can be manufactured on a large scale.[3] Currently, most of the enantiopure drug is prepared from the resolution of (±)-**1**.

Crystallization of diastereomeric salts was adopted commercially for the production of (*S*)-(+)-**1**.[4] This process usually consumes large amounts of resolving agent and is complicated by recycling of the (*R*)-enantiomer. There have been several different methods for the resolution of (±)-**1** based on preferential-crystallization, including the combination of racemization and preferential-crystallization.[5] Manimaran et al. disclosed an optimal approach for the separation of racemic mixtures of certain aliphatic carboxylic acids or esters.[6] First, the racemic acid was treated with 1 equiv. of achiral organic amine to form a salt solution. Then 0.5 equiv. of (−)-α-methylbenzylamine (MBA) was added to give the salt of the D-acid and (−)-MBA, which precipitated with high diastereomeric excess. The mother liquid was heated and the achiral amine base catalyzed the racemization of the undesired L-acid; Patil et al. reported another unique separation process of (±)-**1** using *N*-methyl-D-(−)-glucamine D-(−)-**2a** as the resolving agent.[7] This process involved forming a diastereomeric salt of one of the enantiomers of the aliphatic acid by reacting a solution of the racemic mixture with about 0.25 equiv. of D-(−)-**2a**, which is sufficient to preferentially combine with one of the enantiomers of the racemic mixture but not the other. The resolving agent can be recycled. However, the yield of resolved material was too low to be viable for industrial application.

These previous works threw light on our efforts to explore an alternative approach for extending and simplifying the resolution procedure of (±)-**1**. Since the early 1980s, inclusion crystallization has proven to be an effective method for the separation of structural isomers and the enantiomeric resolution of racemic mixtures.[8] In contrast to the formation of

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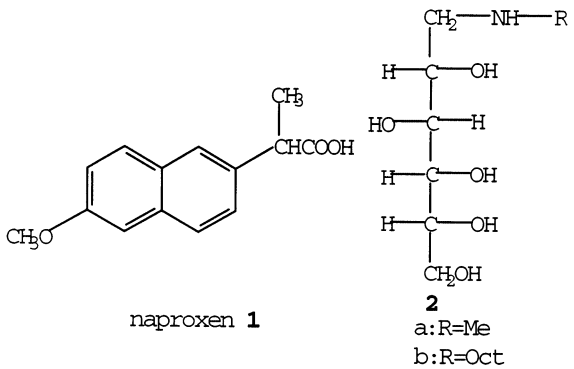
diastereomeric salts, this method can be applied to compounds with almost any functional group. Molecular recognition between host and guest is directed by specific intermolecular forces (e.g. hydrogen bonding, π–π-interaction and T-shaped interaction) as well as steric complementarity.[9] Recently, we have found that this method could be used for the effective resolution of (±)-**1**, which formed an inclusion complex with the chiral host *N*-octyl-D-(−)-glucamine **2b**. (*S*)-(+)-**1** was directly resolved from the racemate with high enantiopurity. We report herein this new simple and commercially feasible process and the crystal structure of the 1:1 inclusion complex of (*S*)-(+)-**1** and D-(−)-**2b**, which is described for the first time.



2. Results and discussion

The key to success in this approach is the selection of a suitable solvent in which (*S*)-(+)-**1** preferentially forms an inclusion compound with D-(−)-**2b** and the complex has very low solubility. Suitably, (±)-**1** and the chiral host D-(−)-**2b** were dissolved in acetonitrile in a molar ratio of 1:0.45. Therefore, one could obtain (*S*)-(+)-**1** with reasonable yield and high enantiopurity, and only (*R*)-enriched **1** is left in the mother liquor. The (*R*)-enriched solid obtained by evaporating the solvent could be directly racemized in aqueous base solution for further resolution. The overall yield from (±)-**1** to (*S*)-(+)-**1** exceeded 90%. The enantiopurity of (*S*)-(+)-**1** meets the standard of British Pharmaceutical Version 1993 (e.e. ≥95%). At present D-(−)-**2b** is available commercially. The resolving agent could be recycled with almost no undesired effect on the resolution. Interestingly, however, D-(−)-**2a** did not form an inclusion complex with (*S*)-(+)-**1**.

The ^{1}H NMR spectra and elemental analysis showed that the molar ratio of (*S*)-(+)-**1** and D-(−)-**2b** in the inclusion complex is 1:1.[10] In the IR spectrum of the inclusion complex, the C=O stretching band in the guest (*S*)-(+)-**1** shifts to a lower wavenumber.[11] (±)-**1** exhibits a sharp and strong band of C=O stretching at 1727 cm^{-1}, while in the inclusion complex the corresponding C=O band occurs at 1637 cm^{-1}. The chiral host D-(−)-**2b** shows strong vibrational bands at around 3232 cm^{-1} (O–H absorption) and 3420 cm^{-1} (N–H absorption), while the absorptions for the inclusion complex are seen at 3242 and 3403 cm^{-1}, respectively. These results show that the carbonyl group of the guest (*S*)-(+)-**1**, and both the amine and hydroxyl groups of the host D-(−)-**2b** are involved in the formation of hydrogen bonds in the inclusion complex. X-Ray structural analysis of a single crystal of the inclusion complex (*S*)-(+)-**1**/D-(−)-**2b** shows the formation of hydrogen bonds between (*S*)-(+)-**1** and D-(−)-**2b**.[12] The asymmetric unit for (*S*)-(+)-**1**/D-(−)-**2b** is shown in Fig. 1. The guest (*S*)-(+)-**1** molecule interacts with the chiral host, D-(−)-**2b**, via hydrogen bonding between the carboxylic acid group and the hydroxyl and amino groups. The carbonyl oxygen of the guest **1** interacts with the hydroxyl group of host **2b**, with an OH···O distance of ca. 1.85 Å. The O–H group of the carboxylic acid is in contact with both the hydroxyl and amino groups of host **2b**. On the other hand, chiral host molecules are linked to each other by hydrogen bonding between hydroxyl groups to form

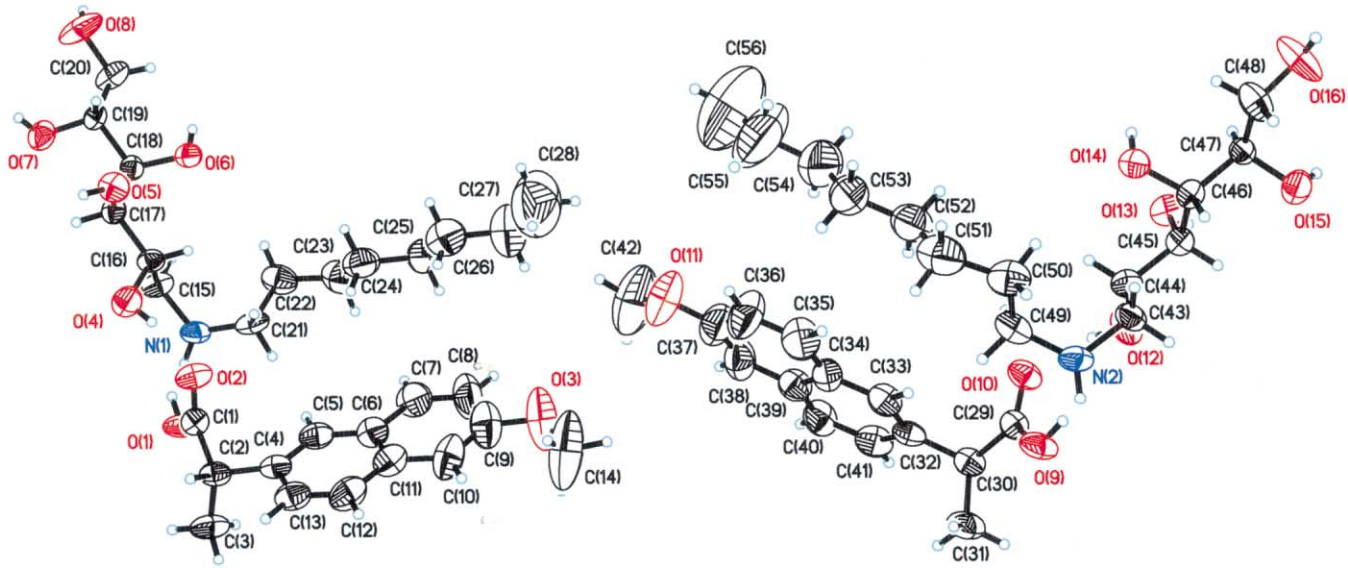


Figure 1. ORTEP drawing of (*S*)-(+)-**1** and D-(−)-**2b** (thermal ellipsoids at the 50% probability level).

host layers, and the H···O contact distances vary from 1.842 to 1.921 Å. The important hydrogen bonds are listed in Table 1. A stereoview of the crystal structure is shown in Fig. 2. The average distance between neighboring host D-(−)-**2b** molecules located at either side of an (*S*)-(+)-**1** molecule is about 8.78 Å. The approximate equivalence in the length of the *N*-octyl group and the length of the guest D-(−)-**2b** molecule (ca. 8.50 and ca. 8.90 Å, respectively) may also be beneficial to the formation of the inclusion complex.

Table 1. Important hydrogen bonds in the inclusion complex of (*S*)-(+)-**1** and D-(−)-**2b**

Nr	Donor-H···acceptor	H···A (Å)	D···A (Å)	∠D–H···A (°)
1	O(1)–H(1A)···N(1)	2.1124	2.812(5)	143.04
2	N(1)–H(1B)···O(1)	2.3982	2.812(5)	110.12
3	N(2)–H(2A)···O(9)	2.3851	2.802(5)	110.27
4	O(4)–H(4A)···O(2)	1.8467	2.650(5)	166.38
5	O(5)–H(5A)···O(16)[1]	1.9300	2.747(5)	173.86
6	O(6)–H(6A)···O(1)[2]	2.0424	2.827(4)	159.84
7	O(7)–H(7A)···O(12)[3]	1.8529	2.644(5)	161.35
8	O(8)–H(8A)···O(15)[4]	1.8416	2.657(6)	172.52
9	O(9)–H(9A)···N(2)	2.1040	2.802(5)	142.91
10	O(12)–H(12A)···O(10)	1.8497	2.652(5)	165.40
11	O(13)–H(13A)···O(8)[5]	1.9208	2.739(5)	174.78
12	O(14)–H(14A)···O(9)[2]	2.0279	2.814(4)	160.67
13	O(15)–H(15A)···O(4)[6]	1.8718	2.658(5)	160.23
14	O(16)–H(16A)···O(7)[7]	1.8511	2.667(5)	172.78

Translation of ARU-code to equivalent position: 1 = 2+*x*, 1+*y*, 1+*z*; 2 = *x*, −1+*y*, *z*; 3 = 2+*x*, *y*, 1+*z*; 4 = 3+*x*, *y*, 1+*z*; 5 = −2+*x*, *y*, −1+*z*; 6 = −2+*x*, −1+*y*, −1+*z*; 7 = −3+*x*, −1+*y*, −1+*z*.

3. Conclusion

The (*S*)-(+)-enantiomer of naproxen **1** was obtained with high enantiopurity (>95% e.e.) by inclusion crystallization with D-(−)-**2b**. The method is simple and commercially feasible for the resolution of (±)-**1**. The crystal structure of inclusion complex (*S*)-(+)/**1**-D-(−)-**2b** was determined.

4. Experimental

A 100 mL flask equipped with a magnetic stirring bar was charged with (±)-**1** (9.20 g, 40 mmol) in acetonitrile (70 mL). To the solution, D-(−)-**2b** (5.30 g, 18 mmol) was added. The mixture was heated to 84°C and heated under reflux for 6 h. Cooling to room temperature, the white solid precipitate was isolated by filtration to obtain colorless crystal (9.16 g, 17.5 mmol, 97.2% recovery). Mp 138.5–139.0°C; 94.6% e.e.;[13] $[\alpha]_D^{23} = +5.2$ (*c* 0.5, DMSO). The solid was decomposed with 20 wt% NaOH solution, precipitation was filtered and washed with water to afford D-(−)-**2b** (5.10 g, 96.2% recovery); mp 123–124°C; $[\alpha]_D^{23} = -17.4$ (*c* 2, DMSO). The filtrate was treated with a 1N aqueous HCl solution and the white solid precipitated was isolated and dried to give a white solid. After recrystallization from 90 wt% alcohol, (*S*)-(+)-**1** was obtained as a colorless needle-like crystalline solid (3.93 g, 99.0 wt%, 85.4% recovery). Mp 154–155°C; e.e. = 95.8%;[13] $[\alpha]_D^{23} = +66.3$ (*c* 1, C_2H_5OH).

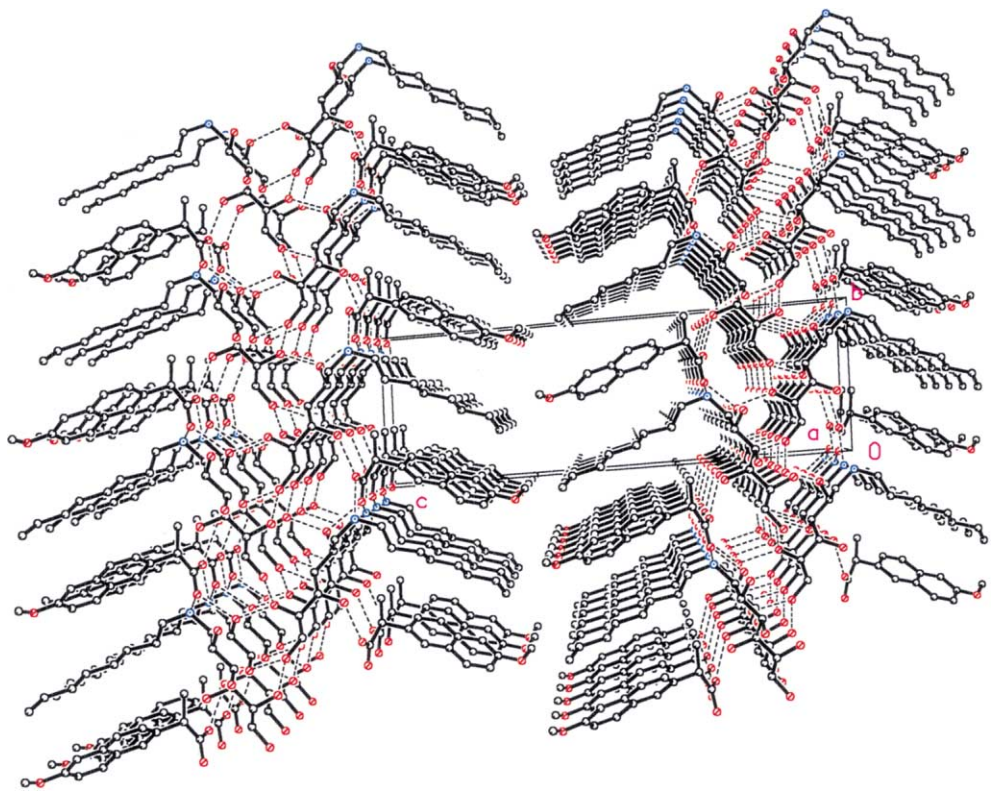


Figure 2. Diagram of crystal structure viewed down the *a*-axis.

The filtrate left after separation of the complex was evaporated, leaving a pale yellow solid of enriched (*R*)-**1**, which was racemized with a 25 wt% aqueous NaOH solution for recycling, to afford a white solid (5.10 g, 99.0 wt%, 110.2% recovery). Mp 154–155°C; $[\alpha]_D^{23}=0$ (*c* 1, C_2H_5OH).

Acknowledgements

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10. The inclusion complex (*S*)-(+)-**1**/D-(−)-**2b**: ^{1}H NMR (500 MHz, methanol-d_4), δ: 0.914 (3H, t, $J=12.5$ Hz), 1.330 (12H, m), 1.507 (3H, d, 12.5 Hz), 1.618 (2H, t), 2.875 (2H, m), 3.072 (2H, m), 3.641–3.751 (4H, m), 3.899 (3H, s), 4.019 (1H, q, $J=12.5$ Hz), 7.070–7.715 (6H, m) ppm; elemental analysis, calcd for $C_{28}H_{45}NO_8$: C, 64.17; N, 2.67; H, 8.59; found: C, 64.52; N, 2.42; H, 8.35%.
11. IR (KBr) of (*S*)-(+)-**1**/D-(−)-**2b**, ν_{max}: 3403 (br), 3243 (br), 3057, 2952 (s), 2854, 2450, 1637, 1608, 1560 (s), 1505, 1488 (br), 1396, 1338, 1290, 1259, 1214, 1162, 1135, 1111, 1026, 895, 856, 817 cm^{-1}.
12. Crystal data for 1:1 inclusion complex of (*S*)-(+)-**1** and D-(−)-**2b**: $C_{28}H_{45}NO_8$; colorless lamellar crystal (0.4×0.25×0.01 mm); Mr = 523.62; triclinic; space group *P*1 (no. 1), $a=6.1246(3)$, $b=8.7821(4)$, $c=27.1377$ (11) Å, $\alpha=92.707(1)$, $\beta=95.925(1)$, $\gamma=90.101(1)$°; $V=1450.20(11)$ Å^3; $Z=2$; $\rho_{calcd}=1.167$ g cm^{-3}, F (0 0 0) = 552; μ(MoKα) = 0.085 mm^{-1}; Bruker SMART CCD diffractometer; graphite-monochromated MoKα ($\lambda=0.71073$ Å) radiation; $T=295(2)$ K; 2θ range, 1.52–55.00°; total reflection collected 16658, in which 10163 unique reflection collected ($R_{int}=0.0418$); empirical adsorption corrections; data processing was accomplished with SAINT processing program. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using SHELX-97, including the positional and anisotropic thermal parameters of the nonhydrogen atoms. Hydrogen atoms were generated in idealized positions attached to the named C, N, O atoms and refined in riding model. The refinement calculations converged at $R=0.0590$, $wR_2=0.1112$.
13. Condition of HPLC: Chirex Phase 2005 (250×4.3 mm, Phenomenex Inc.) as chiral column, and 0.05 M ammonium acetate in methanol as an eluent.