The Aromatic CH/π Hydrogen Bond as an Important Factor in Determining the Relative Stability of Diastereomeric Salts Relevant to Enantiomeric Resolution − A Crystallographic Database Study[‡]

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Keywords: Chiral resolution / Hydrogen bonds / Pi interactions / Supramolecular chemistry

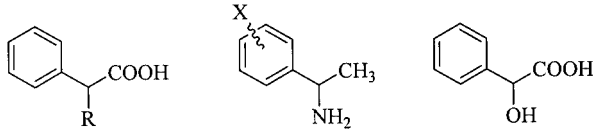
A systematic study was carried out to understand the principle underlying the process of enantiomeric resolution by the use of the Cambridge Structural Database. The crystal structures of fourteen pairs of diastereomeric salts, containing the mandelate anion, or its analogues, as the chiral acid component, were analyzed in the context of the aromatic CH/π hydrogen bond. The mean aromatic C–H···π distance parameters of the less-soluble salts are shorter than in the more-soluble ones. Also, the C–H···π-ring access angle, on average, is more acute in the less-soluble salts than in the more-soluble ones. Nontrivial discrepancies, on the other hand, have been noted in case-by-case comparisons of the parameters of several pairs. It was concluded that the contribution from the aromatic CH/π hydrogen bond should at least be taken into account when considering enantiomeric separation.

Introduction

A DL mixture of chiral acids or bases can be resolved into its enantiomers by the use of diastereomeric salts due to the differences in their solubilities. This classical method was introduced by Pasteur more than 150 years ago[1] and has been utilized since then for the resolution of various racemic materials.[2]

In order to elucidate the mechanism of enantiomeric resolution, Leclercq and Jacques have compared the physical properties of a number of diastereomeric salts. Table 1 summarizes the data relevant to this issue.[3−5] In every case the less-soluble salt melts at a higher temperature (with larger enthalpy of fusion) than the more-soluble one.[6] It was not possible, however, to reach any general conclusion about the origin of this difference in the solubility and thus the theoretical basis of the enantiomeric resolution.

Brianso has determined the crystal structure of (*S*)- and (*R*)-hydratropic acid (**1**, R = CH_3) salts of (*S*)-1-phenylethylamine (**2**).[7] She reported that the anion and the cation components possess an identical conformation in the respective diastereomers; no appreciable difference was found with respect to the hydrogen-bond pattern between the diastereomeric salts. A significant difference was found, however, in the relative orientation of the aromatic rings of the acid and the base components in these salts: the phenyl groups are almost perpendicular to each other in the less-soluble salt (Figure 1a), while they are nearly parallel in the more-soluble one (Figure 1b).



1 **2** **3**

The crystal structure of the (*S*)-mandelic acid (**3**) salt of **2** has also been determined.[8,9] The (*S*)-**3**/(*S*)-**2** salt is less soluble and has a higher melting point than the more-soluble diastereomer (*S*)-**3**/(*R*)-**2**. Lopez de Diego has determined the crystal structure of (*S*)-**3**/(*R*)-**2**[10] and compared this with that of (*S*)-**3**/(*S*)-**2**; she found no appreciable difference between their hydrogen-bond patterns. However, the access angle between an aromatic C−H and the plane of a

[‡] A comprehensive literature list for the CH/π hydrogen bond is available at http://www.tim.hi-ho.ne.jp/dionisio

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  DOI: 10.1002/ejoc.200400373

Table 1. Solubility, melting point and enthalpy of fusion of diastereomeric salts (**1**: hydratropic acid (R = CH_3) and homologues; **2**: 1-phenylethylamine (X = H); **3**: mandelic acid)

Acid	Base	Solubility[a]		M.p. (°C) (Enthalpy of fusion)[b]	
		p-salt[c]	*n*-salt[c]	*p*-salt	*n*-salt
1 (R = CH_3)	**2** (X = H)	7.8	11.3	165 (11.9)	146 (10.1)
1 (R = *n*-C_3H_7)	**2** (X = H)	30	5.6	134 (8.2)	165 (12.4)
1 (R = *n*-C_4H_9)	**2** (X = H)	17.4	6.0	129 (6.5)	166 (13.2)
3	**2** (X = H)	23	4.0	109 (6.6)	178 (11.3)
3	Ephedrine	6.0	77.5	170	91
3	Propadrine	6.1	7.0	172	165
3	ψ-Propadrine	11.95	6.2	164	170

[a] g/100 mL ethanol at 30 °C;[5] g/100 mL water at 25 °C.[4] [b] kcal·mol^{-1}. [c] *p*-Salt and *n*-salt denote, according to Jacques, Collet and Wilen, the salt formed between an acid and a base of the same and opposite sign, respectively.

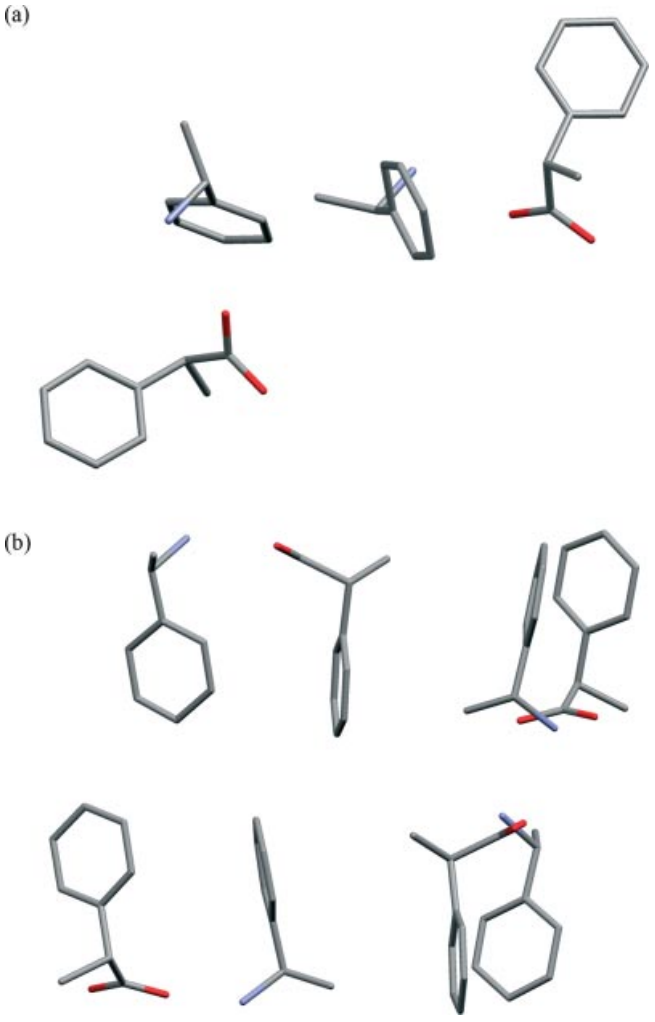


Figure 1. Crystal structures of (a) (*S*)- and (b) (*R*)-hydratropic acid (**1**; R = CH_3) salts of (*S*)-1-phenylethylamine (**2**); CSD refcode: (a) PMACEP, (b) NMACEP

nearby phenyl ring (α in Figure 2) was found to be smaller in the (*S*)-**3**/(*S*)-**2** salt than in the more soluble (*S*)-**3**/(*R*)-**2** salt. This is reminiscent of the observation by Brianso (vide supra) that the relative orientation of the aromatic rings of the acid and the base components in (*S*)- and (*R*)-**1** salts of (*S*)-**2** differs significantly.

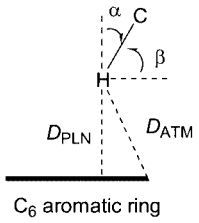
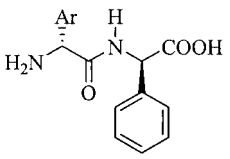


Figure 2. Relative disposition of a C−H bond to the plane of a C_6 aromatic ring

The above data suggest a possibility that the aromatic CH/π interaction[11] plays a role in the mechanism of enantiomeric resolution. The CH/π interaction is a kind of weak hydrogen bond[12,13] occurring between soft acids (CHs) and soft bases (π-systems). Although the contribution from a single CH/π bond is small (0.5−2 kcal·mol^{-1}), the enthalpy of the total interaction may become appreciable as a result of the interplay of many interactions. Evidence has, in fact, accumulated that the CH/π hydrogen bond plays an important role in crystal packing, the structure of clathrates, solid-state reactions, etc.[14]

With regard to the present issue, Ogura and his group have reported on the importance of CH/π hydrogen bonds in the enantiomeric discrimination, by (*R*)-arylglycyl-(*R*)-phenylglycine (**4**; aryl = phenyl or naphthyl), of racemic mixtures of sulfoxides,[15,16] 1-arylethylamines,[17] and hydroxy esters.[18] They also resolved racemic dibenzopyrazinoazepine by the use of chiral 2,3-di-*O*-(arylcarbonyl)tartaric acids (**5**).[19] Hirayama has reported on the role of CH/π hydrogen bond in the separation of DL-amino acids by optically active 1,1′-binaphthalen-2,2′-diyl phosphate (**6**).[20] The naphthalene moieties of **6** were reported to pack together in a specific way through aromatic CH/π hydrogen bonds in the crystals.

Saigo and co-workers have determined the crystal structure of diastereomeric salts composed of optically active 2-naphthylglycolic acid (**7**)[21] and 3′,4′-methylenedioxymandelic acid (**8**)[22] with a series of 1-phenylethylamine deriva-



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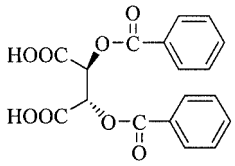

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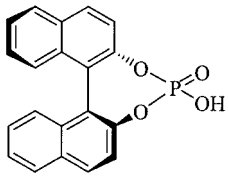

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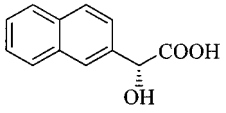

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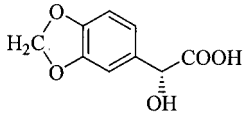

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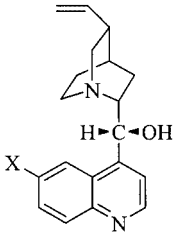
tives. They found that the relative orientation of the aromatic ring of **2** to that of **7** and **8** is different between the less-soluble and the more-soluble diastereomeric salts. In the former salts, a more compact packing of the aromatic groups is found than in the latter. In the case of 1-*p*-tolylethylamine salts (**7**/**2**, X = *p*-Me), the interplanar angle between an aromatic *meta* C−H moiety of **2** with respect to the π-plane of **7** (β in Figure 2) was found to be 84° in the less-soluble crystals, while it is 54° in the more-soluble one. They argued the result in the context of the CH/π hydrogen bond and suggested that the origin of the differing solubility can be attributed, primarily, to the aromatic CH/π interaction and hydrogen bonding. This agrees also with our earlier suggestion[23] that the CH/π hydrogen bond is more effective when the C−H group approaches co-axially from the direction perpendicular to the π-molecular plane (α = 0° for $CHCl_3$ and acetylenic CH, and 30−40° for sp^2 or aromatic CH).[24]

It is certain that the difference in the physicochemical properties of the diastereomeric salts is related to the difference in their dissolution entropies. However, from the above results we felt it plausible that the difference in the aromatic CH/π hydrogen bonds could also be one of the primary causes of the solubility difference of these salts. To explore the involvement of the CH/π hydrogen bond in the mechanism of enantiomer discrimination, we have analyzed CH/π hydrogen bonds in relevant molecules, particularly those in various ion-pairs of frequently used resolving agents. The results are reported here.

Results and Discussion

General Survey

Various compounds have been used in the separation of racemic materials into their enantiomers. Natural substances such as tartaric acid, brucine, ephedrine, cinchonine (**9**), cinchonidine (**10**), or synthetic compounds such as optically pure **2**, **3**, and **6** are often used as the resolving agents.[25]



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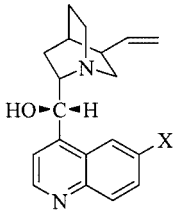
quinine: X = OCH_3
cinchonidine: X = H



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quinidine: X = OCH_3
cinchonine: X = H

As the first step of this study, we edited database subsets including substructures of **2** (subset 1), **3** (subset 2), **6** (2,2′-disubstituted 1,1′-binaphthyl: subset 3), brucine (subset 4),

Table 2. Short CH/π distances (< 3.05 Å) disclosed in subsets including substructures of several resolving agents

Database subset		Hit (ratio)	Fragment	D_{ATM} (Å)	α (°)
1 (121 entries)[a]	any CH	117 (97)	681	2.92 ± 0.12	40 ± 22
	aromatic CH	102 (84)	385	2.93 ± 0.12	40 ± 28
2 (77 entries)[b]	any CH	76 (99)	585	2.91 ± 0.12	38 ± 20
	aromatic CH	69 (90)	303	2.91 ± 0.11	37 ± 22
3 (201 entries)[c]	any CH	198 (99)	2005	2.89 ± 0.13	38 ± 17
	aromatic CH	190 (95)	1294	2.89 ± 0.13	37 ± 17
4 (16 entries)[d]	any CH	16 (100)	93	2.88 ± 0.12	32 ± 15
	aromatic CH	4 (25)	8	2.91 ± 0.17	47 ± 17
5 (40 entries)[e]	any CH	37 (93)	215	2.89 ± 0.14	40 ± 18
	aromatic CH	17 (43)	61	2.88 ± 0.16	42 ± 18

[a] Entries including 1-phenylethylamine (**2**) and derivatives. [b] Entries including mandelic acid (**3**) and derivatives. [c] Entries including the substructure 2,2′-disubstituted 1,1′-binaphthyl. [d] Entries including brucine. [e] Entries including cinchona alkaloids [cinchonine (**9**), cinchonidine (**10**), quinine and quinidine].

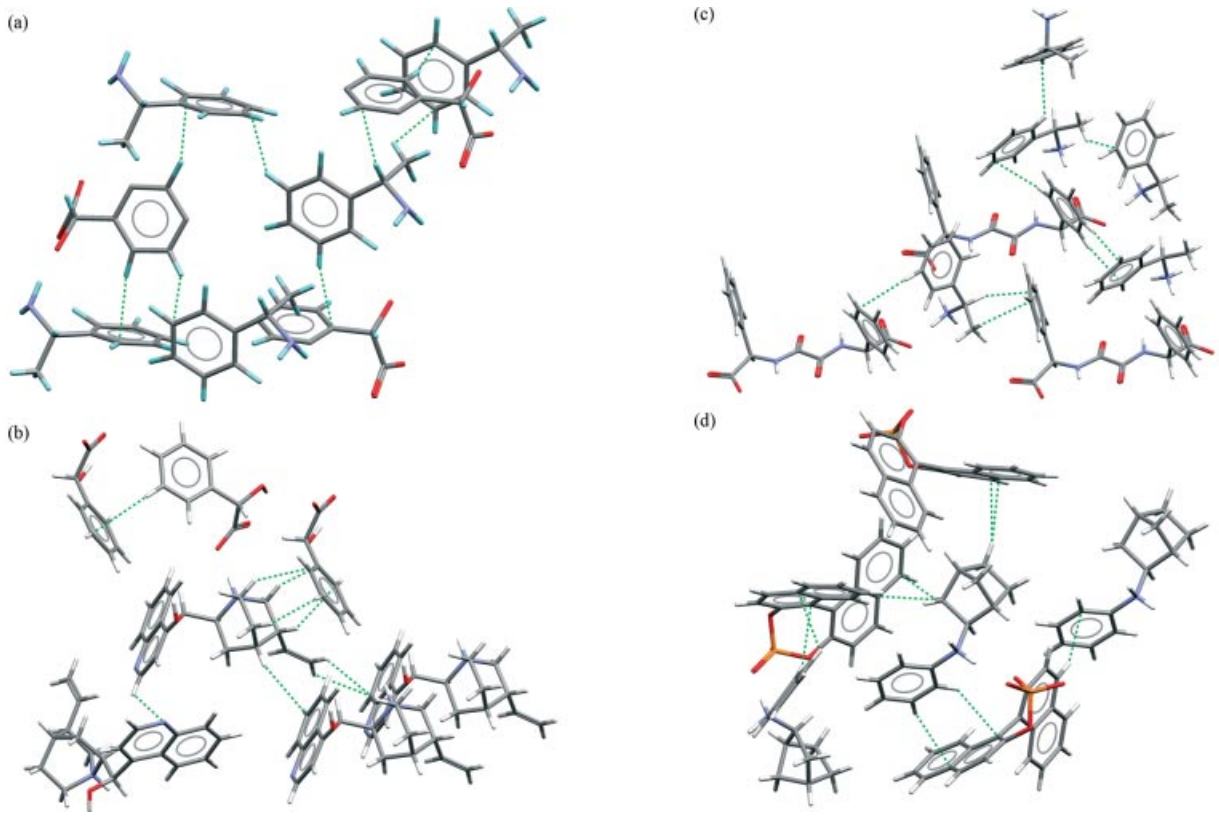

Figure 3. Typical examples showing CH/π contacts in diastereomeric salts; dotted lines indicate short CH/π distances (<3.05 Å). (a) CSD refcode PEAMAN: (*S*)-1-phenylethylammonium (*S*)-mandelate; (b) RERXUH: cinchonidinium (*S*)-mandelate; (c) DOJQOI: bis[(*R*)-1-phenylethylamine] (*R*,*R*)-*N*,*N*′-oxalylbis(phenylglycine) monohydrate; (d) NOWCAD: (2*S*)-(2-phenylammonium)norbornane (*R*)-(−)-(1,1′-binaphthalene-2,2′-diyl)phosphate

and cinchona alkaloids (subset 5). Structures with crystallographic disorder and *R* values greater than 10% were excluded. According to the procedure described in the Exp. Sect. we surveyed intermolecular CH/π contacts in the above database subsets. Table 2 summarizes these results.

Short CH/π distances have very frequently been found in these entries: 117/121, 76/77, 198/202, 16/16 and 37/40, for subsets 1−5, respectively. In Figure 3 we give typical examples from the above search. The ratio of hits (93−100%) was larger than that recorded in a general survey.[26] This may suggest that CH/π hydrogen bonds play a considerable role in the enantiomeric discrimination. The ratio of hits decreased slightly for subsets 1−3 (84−95%) when only aromatic CHs are concerned. The decrease in the ratio is significant, however, for subsets 4 (25%) and 5 (43%). This is understandable since the aromatic moiety constitutes a minor portion of the molecule in brucine and cinchona alkaloids. In view of this finding and the results reported by others,[7−9,15−22] we hypothesized that the aromatic CH/π interaction, in essence, is responsible for the mechanism of enantiomeric resolution.

To minimize complications, we decided to confine ourselves to examining diastereomeric salts of mandelate **3**. The crystal structures of diastereomeric salts of **3** with various amines were found in a number of studies aimed at the elucidation of the discrimination mechanism. Subset 6 was edited by collecting entries with the substructure of mandelate anion with hydrogen coordinates. The results are summarized in Table 3. Fifty-four structures out of 60 entries were found to involve CH/π distances shorter than 3.05 Å when the aromatic CH is concerned. The high proportion of hits (90%) suggests that the aromatic CH/π hydrogen

Table 3. Distance and angle parameters obtained by surveying aromatic CH/π contacts in diastereomeric salts of mandelate and derivatives

	Hit	Nr.1[a]	D_{ATM} (Å)	α (°)	Nr.2[b]	D_{ATM} (Å)	D_{PLN} (Å)	D_{CNT} (Å)	α (°)
Subset 6 (60 entries)[c]	54	252	2.91 ± 0.12	36 ± 19	153	2.92 ± 0.13	2.80 ± 0.14	2.90 ± 0.17	30 ± 15
Less soluble (20 entries)[d]	20	106	2.88 ± 0.13	27 ± 22	29	2.88 ± 0.13	2.74 ± 0.14	2.83 ± 0.18	21 ± 17
More soluble (15 entries)[d]	14	94	2.93 ± 0.11	41 ± 23	26	2.98 ± 0.12	2.83 ± 0.12	2.91 ± 0.17	32 ± 14

[a] Number of short aromatic CH/π atomic contacts (<3.05 Å). [b] Number of aromatic CH/π contacts where H is above the phenyl ring (region 1). [c] These include (*S*)-, (*R*)- and (*R*,*S*)-mandelate, diastereomeric salts of unreported solubility difference, mixtures of diastereomers, etc. [d] Six less-soluble salts and one more-soluble salt (without partner) are included.

Table 4. Distance and angle parameter (D_{ATM} and α, respectively) in various salts resolved with the use of optically pure mandelic acid or derivatives; **2**: 1-phenylethylamine; **3**: mandelic acid; **7**: 2-naphthylglycolic acid; numbers that do not agree with the hypothesis are printed in ***bold italics***

	CSD refcode	Fragments[a]	D_{ATM} (Å)	α (°)	Acid/base	Symmetry	Solubility (g/100 mL)	M.p. (°C)	Ref.
Entry 1									
Less	PEAMAN	5	2.85 ± 0.17	35 ± 28	(*S*)-**3**/(*S*)-**2**	($P2_12_12_1$, $Z = 4$)	4[b]	178	[9]
More	PIVGEG	11	2.88 ± 0.13	51 ± 16	(*R*)-**3**/(*S*)-**2**	(P_1, $Z = 4$)	23[b]	109	[10]
Entry 2									
Less	JUXKIW	8	2.92 ± 0.17	38 ± 15	3 × (*S*)-**3**/(*R*)-**2**	($P2_12_12_1$, $Z = 4$)	3.7[c]	107	[28]
More	HIBVUJ	8	2.97 ± 0.12	40 ± 10	3 × (*S*)-**3**/(*S*)-**2**	($P2_12_12_1$, $Z = 4$)			[29]
Entry 3									
Less	VURBEP	1	3.03	43	(*R*)-**3**/(*R*)-2-*t*-3-imidazolidin-4-one	($P2_1$, $Z = 2$)		118	[30]
More	VURBIT	0			(*S*)-**3**/(*R*)-2-*t*-3-imidazolidin-4-one	($P2_1$, $Z = 2$)		79	[30]
Entry 4									
Less	PITZUN	5	***2.98 ± 0.12***	40 ± 5	(*R*)-**3**/(*R*)-2-amino-2-phenylethanol + H_2O	($C2$, $Z = 4$)			[31]
More	PIVBAX	21	2.91 ± 0.11	41 ± 15	(*R*)-**3**/(*S*)-2-amino-2-phenylethanol	($P1$, $Z = 4$)			[31]
Entry 5									
Less	LABXUH	5	2.84 ± 0.22	35 ± 8	(*R*)-**3**/cinchonine	($P2_12_12_1$, $Z = 8$)			[32]
More	LABXOB	4	3.03 ± 0.11	56 ± 19	(*S*)-**3**/cinchonine	($P2_1$, $Z = 2$)			[32]
Entry 6									
Less	RERXUH	1	***3.00***	***45***	(*S*)-**3**/cinchonidine	($C2$, $Z = 4$)		185	[33]
More	RERYAO	1	2.88	19	(*R*)-**3**/cinchonidine	($P2_1$, $Z = 4$)		185, 191	[33]
Entry 7									
Less	NONZOF	3	2.91 ± 0.04	36 ± 14	(*S*)-**3**/(*S*)-phenylalanine	($C2$, $Z = 4$)			[34]
More	NONZUL	6	2.92 ± 0.07	73 ± 27	(*S*)-**3**/(*R*)-phenylalanine	($C2$, $Z = 4$)			[34]
Entry 8									
Less	BAVDIL	3	2.83 ± 0.13	17 ± 8	(*R*)-**3**/deoxyephedrine	($P2_12_12_1$, $Z = 4$)	31.2[c]	110	[35]
More	BAVDOR	6	2.93 ± 0.12	33 ± 14	(*S*)-**3**/deoxyephedrine	($P2_1$, $Z = 6$)	32.4	99	[35]
Entry 9									
Less	MEGVOJ	8	2.91 ± 0.10	28 ± 37	(*R*)-**7**/(*R*)-**2** (X = *p*-CH_3)	($P2_12_12_1$, $Z = 4$)	0.8[d]	220	[21]
More	MEGWIE	4	2.97 ± 0.13	66 ± 28	(*S*)-**7**/(*R*)-**2** (X = *p*-CH_3)	($C2$, $Z = 4$)	5.7	156	[21]
Entry 10									
Less	MEGVUP	7	***2.90 ± 0.10***	17 ± 18	(*S*)-**7**/(*S*)-**2** (X = *p*-C_2H_5)	($P2_1$, $Z = 2$)			[21]
More	MEGWOK	6	2.83 ± 0.08	19 ± 21	(*R*)-**7**/(*S*)-**2** (X = *p*-C_2H_5)	($P2_1$, $Z = 2$)			[21]
Entry 11									
Less	MEGWAW	9	2.91 ± 0.11	26 ± 35	(*S*)-**7**/(*S*)-**2** (X = *p*-Cl)	($P2_12_12_1$, $Z = 4$)	0.7[d]	210	[21]
More	MEGWUQ	8	2.93+0.11	31 ± 36	(*R*)-**7**/(*S*)-**2** (X = *p*-Cl)	($P2_12_12_1$, $Z = 4$)	1.6	173	[21]
Entry 12									
Less	XEJKUS	6	***2.93 ± 0.12***	39 ± 24	(*R*)-*o*-F-**3**/pseudoephedrine	($P2_12_12_1$, $Z = 4$)	3.6[d]	170	[36]
More	XEJLAZ	5	2.91 ± 0.11	39 ± 20	(*S*)-*o*-F-**3**/pseudoephedrine	($P2_12_12_1$, $Z = 4$)	54	131	[36]
Entry 13									
Less	XEJLED	9	2.87 ± 0.17	***34 ± 12***	(*R*)-*m*-F-**3**/pseudoephedrine + 0.5H_2O	($P2_1$, $Z = 4$)	74[d]	81	[36]
More	XEJLIH	2	3.09 ± 0.13	23 ± 0	(*S*)-*m*-F-**3**/pseudoephedrine + 2H_2O	($P2_12_12_1$, $Z = 4$)	195	48	[36]
Entry 14									
Less	XEJMAA	8	***2.98 ± 0.07***	22 ± 3	(*S*)-*p*-F-**3**/pseudoephedrine + 2H_2O	($P2_12_12_1$, $Z = 20$)	46[d]	109	[36]
More	XEJLUT	6	2.87 ± 0.10	26 ± 13	(*R*)-*p*-F-**3**/pseudoephedrine	($P2_1$, $Z = 4$)	112	120	[36]

[a] Number of short aromatic CH/π atomic contacts (<3.05 Å). [b] In ethanol. [c] In water. [d] In 95% ethanol.

bond may play a role in the process of enantiomeric resolution.

Among the above 54 entries, we found crystal structures of 14 pairs of less- and more-soluble salts of **3** with various amines. The distance parameters (D_{ATM}, D_{CNT}, D_{PLN}) of the less-soluble salts were found to be shorter than those of the more soluble ones. The mean C−H···π-ring access angle, α, is smaller in the less-soluble salts than in the more-soluble ones. This result is in line with our hypothesis that aromatic CH/π hydrogen bonds work more effectively in the less-soluble (more stable) salts.

Comparison of the Less- and More-Soluble Salts

To analyze in more detail whether the relative disposition of the aromatic rings is important in the mechanism of enantiomeric resolution, we compared the distance and angle parameters D_{ATM} and α of the 14 pairs of salts of differing solubility. Table 4 lists the results.[27]

Entry 1: $\alpha = 35°$ for PEAMAN vs. 51° for PIVGEG. This result is consistent with our hypothesis and suggests that the large difference in the solubilities and melting points of these diastereomers largely originates from the difference in the aromatic CH/π hydrogen bonds.

Entry 2: $\alpha = 38°$ for JUXKIW[28] vs. 40° for HIBVUJ.[29] This result is compatible with our hypothesis. The difference is insignificant, however.

Entry 3: VURBEP vs. VURBIT.[30] VURBEP shows an aromatic CH/π contact with $\alpha = 43°$, whereas in VURBIT no short CH/π contact was found. This is compatible with the hypothesis.

Entry 4: $\alpha = 40°$ for PITZUN vs. 41° for PIVBAX.[31] This result is not incompatible with the expectation, even though the difference is insignificant. PITZUN co-crystallizes with 1 mol of water; this might affect the interactions between the molecules.

Entry 5: $\alpha = 35°$ for LABXUH vs. 56° for LABXOB.[32] This result is consistent with the difference in the solubility.

Entry 6: $\alpha = 45°$ for RERXUH vs. 19° for RERYAO.[33] This result does not agree with the experimental data, although the difference in the solubility was reported to be very small. At present we can find no clear reasoning for this discrepancy.

Entry 7: $\alpha = 36°$ for NONZOF vs. 73° for NONZUL.[34] This result is consistent with the difference in the solubilities of this diastereomeric pair.

Entry 8: $\alpha = 17°$ for BAVDIL vs. 33° for BAVDOR.[35] This result is consistent with the experimental data.

Entries 9−11:[21] MEGVOJ ($\alpha = 28°$) vs. MEGWIE (66°); MEGVUP (17°) vs. MEGWOK (19°); MEGWAW (26°) vs. MEGWUQ (31°). The above data are consistent with the difference in the solubilities reported for these diastereomers.

Entries 12−14:[36] XEJKUS ($\alpha = 39°$) vs. XEJLAZ (39°); XEJLED (34°) vs. XEJLIH (23°); XEJMAA (22°) vs. XEJLUT (26°). For entry 13, the result is incompatible with the solubility data reported for these diastereomers. The distance data are incompatible with the solubility data for entries 12 and 14. The NH/F hydrogen bonds may occur between N^+H and the fluorine atom in the aromatic ring. Further, these compounds differ in the state of hydration. The above conditions might have affected the crystal structure and thus the stability of the salts.

To summarize, D_{ATM} of the less-soluble salt is shorter in nine entries than that of the more-soluble partner. In entries 4, 6, 10, and 12, however, the data do not agree with our hypothesis. The C−H···π-plane access angle α is smaller in the former than in the latter except for entries 6 and 13. A more in-depth analysis is therefore necessary to clarify the origin of the disagreement in the individual cases. Needless to say, weak molecular forces other than the CH/π bond, such as the dispersion force, ordinary hydrogen bond, and CH/*n* (CH/O, CH/N, CH/F, etc.) hydrogen bonds may also operate. It may also not be appropriate to compare diastereomeric salts that differ in chemical composition. Differences in the crystal packing, the state of hydration (entries, 4, 13, and 14), and the ion-pair interactions in the solvent may give rise to a difference in the dissolution entropy.

Conclusion

The crystal structures of compounds bearing the substructure of currently used resolving agents were analyzed in the context of the aromatic CH/π hydrogen bond. More specifically, short aromatic CH/π contacts were looked for in the crystal structures of diastereomeric salts of mandelic acid and its analogues. The aromatic C−H···π distance and C−H···π-plane access angle, α, have, in general, been found to be smaller in the less-soluble salts than in the more-soluble ones. Some discrepancies were noted, however, in the case-by-case comparison of the diastereomeric pairs. In spite of this, we think it probable that the aromatic CH/π hydrogen bond plays a nontrivial role in the mechanism of enantiomer discrimination. It is pertinent to point out in this regard that compounds bearing a large π-surface, such as the naphthyl group,[18,20,21] are often much more effective than the corresponding phenyl analogues. Furthermore, aroyl derivatives of tartaric acid[19] are good resolving agents. Contribution from the CH/π bonds should at least be taken into account in the consideration of enantiomeric separation. More systematic and in-depth studies are necessary in the future for providing a useful approach to the enantiomeric resolution.

Experimental Section

The CSD version 5.24 (May 2003 release, 272066 entries) was used. A program was composed, with the CSD software QUEST3D, to examine the spatial relationship of C−H bonds with respect to a C_6 aromatic ring (Figure 4). Several kinds of distance and angle parameters were defined to cover every possibility.[37] Nonbonded CH/π contacts were sought with the distance and angle cut-offs $D_{max} = 3.05$ Å[38] and $\angle H-C-C^1 < 70°$.

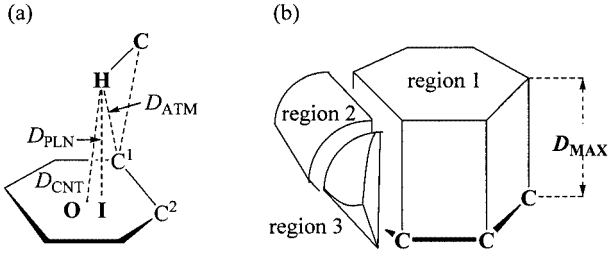

Figure 4. Method of surveying CH/π contacts in the CSD. (a) O: center of the ring; C^1: carbon closest to H; C^2: next closest carbon; D_{PLN}: distance from H to the aromatic π plane (line HI); D_{ATM}: distance from H to the closest carbon (line HC^1); D_{CNT}: distance from H to the center of the ring (line HO); θ: π-plane−H−X angle ($\angle$IHX). (b) The program was run to search for H/π distances shorter than a cut-off value, D_{max}, in every region. $D_{pln} < D_{max}$, $\theta < 60°$, for the region just above the ring (region **1**). $D_{lin} < D_{max}$, $\theta < 60°$, $90° < |\omega| < 130°$ for the region slightly offset from the ring (region **2**). $D_{atm} < D_{max}$, $\theta < 60°$, $50° < \varphi < 90°$ for another possible region φ: HX^1I (region **3**)

Acknowledgments

We thank Dr. Kazumasa Honda (National Institute of Advanced Industrial Science and Technology) for useful discussions.

[1] L. Pasteur, *C. R. Acad. Sci.* **1853**, *37*, 162.
[2] J. Jacques, A. Collet, S. M. Wilen, *Enantiomers, Racemates, and Resolutions*, Wiley, New York, **1981**.
[3] Data retrieved from tables 5, 6, and 7 of chapter 5 in J. Jacques, A. Collet, S. M. Wilen, *Enantiomers, Racemates, and Resolutions*, Wiley, New York, **1981**.
[4] C. Jarowski, W. H. Hartung, *J. Org. Chem.* **1943**, *8*, 564.
[5] M. Leclercq, J. Jacques, *Bull. Soc. Chim. Fr.* **1975**, 2052.
[6] J. Jacques, A. Collet, S. M. Wilen, *Enantiomers, Racemates, and Resolutions*, Wiley, New York, **1981**, pp. 287−289.
[7] M.-C. Brianso, *Acta Crystallogr., Sect. B* **1976**, *32*, 3040. See also: J. Jacques, A. Collet, S. M. Wilen, *Enantiomers, Racemates, and Resolutions*, Wiley, New York, **1981**, pp. 283−285.
[8] M.-C. Brianso, M. Leclercq, J. Jacques, *Acta Crystallogr., Sect. B* **1979**, *35*, 2571.
[9] S. Larsen, H. Lopez de Diego, *Acta Crystallogr., Sect. B* **1993**, *49*, 303.
[10] H. Lopez de Diego, *Acta Chim. Scand.* **1994**, *48*, 306.
[11] M. Nishio, M. Hirota, Y. Umezawa, *The CH/π Interaction. Evidence, Nature, and Consequences*, Wiley-VCH, New York, **1998**.
[12] G. R. Desiraju, T. Steiner, *The Weak Hydrogen Bond in Chemistry and Structural Biology*, Oxford University Press, Oxford, **1999**.
[13] M. Nishio, *Weak Hydrogen Bonds* in *Encyclopedia of Supramolecular Chemistry* (Eds.: J. L. Atwood, J. W. Steed), Marcel Dekker Inc., New York, **2004**, 1576.
[14] Review: M. Nishio, *Cryst Eng Comm* **2004**, *6*, 130.
[15] K. Ogura, T. Uchida, M. Noguchi, M. Minoguchi, A. Murata, M. Fujita, K. Ogata, *Tetrahedron Lett.* **1990**, *31*, 3331; M. Akazome, Y. Ueno, H. Ooiso, K. Ogura, *J. Org. Chem.* **2000**, *65*, 68.
[16] M. Akazome, M. Noguchi, O. Tanaka, A. Sumikawa, T. Uchida, K. Ogura, *Tetrahedron* **1997**, *53*, 8315.
[17] M. Akazome, H. Matsuno, K. Ogura, *Tetrahedron: Asymmetry* **1997**, *8*, 2331.
[18] M. Akazome, T. Takahashi, K. Ogura, *J. Org. Chem.* **1999**, *64*, 2293.
[19] H. Tomori, H. Yoshihara, K. Ogura, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 3581.
[20] I. Fujii, N. Hirayama, *Helv. Chim. Acta* **2002**, *85*, 2946.
[21] K. Kinbara, Y. Harada, K. Saigo, *J. Chem. Soc., Perkin Trans. 2* **2000**, 1339.
[22] K. Kinbara, K. Oishi, Y. Harada, K. Saigo, *Tetrahedron* **2000**, *56*, 6651.
[23] M. Nishio, M. Hirota, Y. Umezawa, *The CH/π Interaction. Evidence, Nature, and Consequences*, Wiley-VCH, New York, **1998**, pp. 52, 60 (see figure 3.7).
[24] O. Takahashi, Y. Kohno, S. Iwasaki, K. Saito, M. Iwaoka, S. Tomoda, Y. Umezawa, S. Tsuboyama, M. Nishio, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2421 (see figures 6, 10).
[25] J. Jacques, A. Collet, S. M. Wilen, *Enantiomers, Racemates, and Resolutions*, Wiley, New York, **1981**, pp. 254−257.
[26] 72% for entries including transition metal compounds: H. Suezawa, T. Yoshida, Y. Umezawa, S. Tsuboyama, M. Nishio, *Eur. J. Inorg. Chem.* **2002**, 3148. 43−54% for CH_3/π short contact in organic entries: Y. Umezawa, S. Tsuboyama, K. Honda, J. Uzawa, M. Nishio, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1207.
[27] The crystal structure and energetics of association in the crystalline states was studied for mandelate salts of ephedrine and pseudoephedrine: S. P. Zingg, E. M. Arnett, A. T. McPhail, A. A. Bothner-by, W. R. Gilkerson, *J. Am. Chem. Soc.* **1988**, *110*, 1565. The crystal structure was determined (DINKUG01, DINLAN01, GAJPIQ, GAJPOW) and the relevant thermochemical parameters were discussed. Unfortunately, however, we did not find coordinates of the above crystals in the present version of the CSD.
[28] S. Larsen, H. Lopez de Diego, *J. Chem. Soc., Perkin Trans. 2* **1993**, 469.
[29] H. Lopez de Diego, *Acta Crystallogr., Sect. C* **1995**, *51*, 253.
[30] M. Acs, E. Novotny-Bregger, K. Simon, G. Argay, *J. Chem. Soc., Perkin Trans. 2* **1992**, 2011.
[31] S. Larsen, D. Kozma, M. Acs, *J. Chem. Soc., Perkin Trans. 2* **1994**, 1091.
[32] S. Larsen, H. Lopez de Diego, D. Kozma, *Acta Crystallogr., Sect. B* **1993**, *49*, 310.
[33] A. Gjerlov, S. Larsen, *Acta Crystallogr., Sect. B* **1997**, *53*, 708.
[34] K. Okamura, K. Aoe, H. Hiramatsu, N. Nishimura, T. Saito, K. Hashimoto, *Anal. Sci.* **1997**, *13*, 315.
[35] E. J. Valente, M. E. Harris, K. Goubitz, H. Schenk, *Z. Kristallogr.* **1999**, *214*, 402.
[36] E. J. Valente, M. C. Moore, *Chirality* **2000**, *12*, 16.
[37] This is necessary since a C−H group may interact in regions where the hydrogen is slightly offset outside the π-plane.
[38] 2.9 Å [(1.2 Å for C−H plus 1.7 Å for a half width of the aromatic ring) × 1.05]. The C−H bond length and angle were normalized to standard values in the CSD software.

Received May 26, 2004

