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Preparative separation of structurally related and racemic hydroxyl-containing compounds through the formation of crystalline molecular complexes

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Abstract. The published data concerning the development of the methods for preparative separation of structurally related and racemic hydroxyl-containing organic compounds through the formation of crystalline molecular complexes are generalised. Special attention is focused on the resolution of racemic alcohols and phenols into enantiomers. The bibliography includes 85 references.

I. Introduction

Separation of structurally related hydroxyl-containing organic compounds, *i.e.*, alcohols and phenols, cannot often be performed by such traditional methods as distillation and crystallisation. This is particularly true for the resolution of racemates into enantiomers. In modern organic synthesis, preparation of homochiral synthons including hydroxyl-containing compounds is of increasing importance. In addition to extensively developing asymmetric synthesis, first of all catalytic, methods for the resolution of racemates remain topical. These methods include 'spontaneous' separate crystallisation of enantiomers of a racemic compound, fractional crystallisation of diastereomeric derivatives, for example, esters of alcohols with optically active carboxylic acids, kinetic resolution of racemates by the reaction with a homochiral reagent or in the presence of a chiral catalyst, enzymatic resolution, preparative chromatographic separation on columns with chiral phases and, finally, resolution into enantiomers by selective co-crystallisation to form crystalline molecular complexes (CMC). The latter method is characterised by simplicity and can be applied to separate neutral racemic compounds such as alcohols, esters, lactones without their preliminary derivatisation.

In order to isolate an optically active hydroxyl-containing compound from a crystalline complex with a chiral separating agent (SA), the complex is subjects to thermal dissociation (usually under reduced pressure) or selective extraction of one of the complex components with an appropriate solvent. Both processes proceed under mild conditions preventing possible racemisation. Selective co-crystallisation is often termed in the literature as inclusion crystallisation [1, 2] or as separation through the formation of crystalline 'host – guest' complexes, which, in our opinion, is not always justified. It is probably worth using these terms only in the cases where SAs, for example, cyclodextrins, already contain cavities matching the inclusion of a substrate under separation or these cavities are formed during crystallisation of SA, for example, urea. It is noteworthy that, due to a great diversity of processes of the formation of crystalline molecular complexes, they cannot often be unambiguously assigned to a specific type and occupy intermediate position.

In this review, the known examples of the separation of structurally related hydroxyl-containing substrates by selective co-crystallisation with chiral and achiral agents are generalised for the first time. Until now, this method has not yet find sufficiently wide use for preparative purposes.

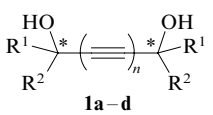
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II. Types of separating agents

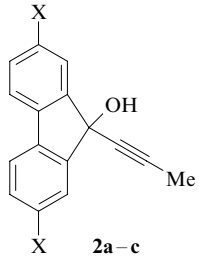
Different classes of compounds can be used as chiral separating agents. The most popular are oxygen-containing (alcohols, phenols and their derivatives) and nitrogen-containing (amines, amides) SAs. The structures of the most popular separating agents: alcohols **1** – **9**, phenols and their derivatives **10** – **12**, amines and amides **13** – **24**, phosphonium salts **25**, **26** and sulfoxide **27** are presented below.

Alcohols and their derivatives



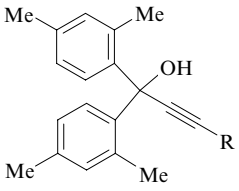
1a – **d**

n = 2: $R^1 = R^2$ = Ph (**a**), 2,4-$Me_2C_6H_3$ (**b**); R^1 = Ph, R^2 = 2-ClC_6H_4 (**c**); n = 1, $R^1 = R^2$ = Ph (**d**).



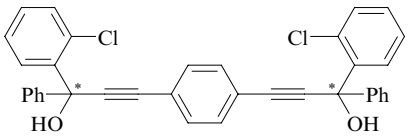
2a – **c**

X = H (**a**), Cl (**b**), Br (**c**).

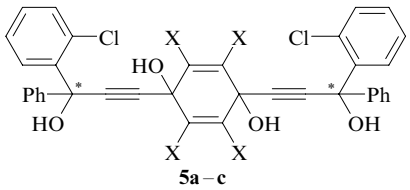


3a,**b**

R = H (**a**), Me (**b**).

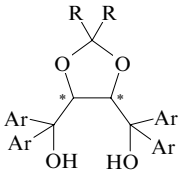


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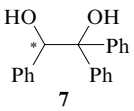
5a–**c**

X = H (**a**), Cl (**b**), Br (**c**).

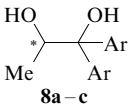


6a–**f**

Ar = Ph: R = Me (TADDOL) (**a**), Et (**b**); R–R = $(CH_2)_4$ (**c**), $(CH_2)_5$ (**d**); R = Me: Ar = 4-MeC_6H_4 (**e**), 4-$Bu^tOC_6H_4$ (**f**).

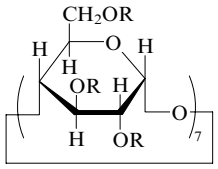


7



8a–**c**

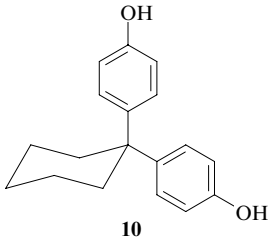
Ar = Ph (**a**), 4-$Bu^tC_6H_4$ (**b**), 1-naphthyl (**c**).



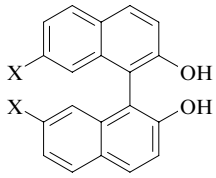
9a,**b**

R = H (**a**), Me (**b**).

Phenols and their derivatives

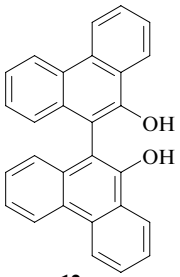


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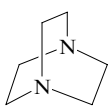
11a,**b**

X = H (BINOL) (**a**), OBn (**b**).

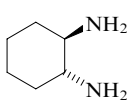


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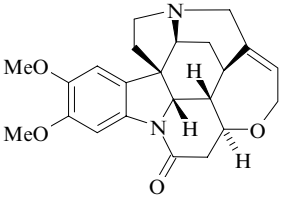
Amines and amides



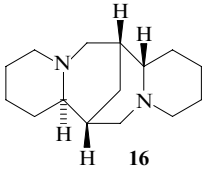
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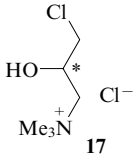
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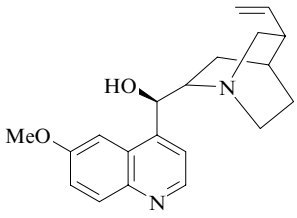
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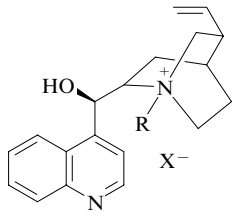
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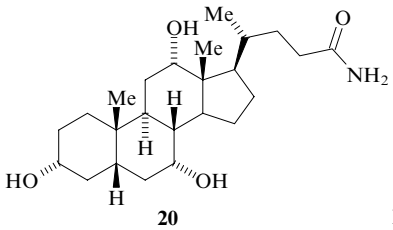


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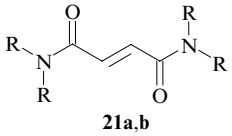


19a,**b**

R = Bn, X = Cl (**a**),
R = Bu^n, X = Br (**b**).

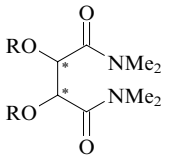


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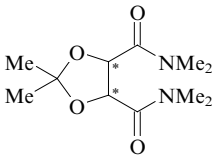
21a,**b**

R = cyclo-C_6H_{11} (**a**), Pr^i (**b**).

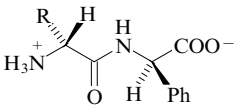


22a,**b**

R = Me (**a**),
cyclo-C_6H_{11} (**b**).



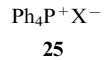
23



24

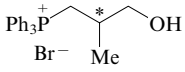
R is 1-naphthyl.

Phosphorus- and sulfur-containing reagents

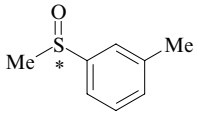


25

X = Cl, Br.



26



27

III. Preparative separation of hydroxyl-containing organic compounds

1. Separation of alkanols, cycloalkanols and alkylaromatic alcohols

Toda and Akagi [3] started systematic studies on the separation of organic compounds by the selective co-crystallisation method. They found that diols **1a**–**d** form crystalline complexes with a number of simple organic compounds. Acetylenic alcohols **1a**,**b**, **2**–**5**, as well as TADDOL (**6a**) give crystalline complexes with EtOH,[2,4–6] but do not bind water. This permitted the isolation of ethanol from 50% aqueous solution as a solvate complex {**3a**·EtOH}; on thermal dissociation of the latter, ethanol was recovered in 96% yield and purity of 99%.[2,7]

Primary long-chain aliphatic alcohols $C_mH_{2m+1}OH$ (m = 8–18) form crystalline 1:1 complexes with alkyltrimethylammonium bromides $(C_nH_{2n+1})Me_3N^+Br^-$ (n = 10–18).[8] IR spectroscopic data indicate that the hydrogen bond between the OH group and Br^- is weak, but hydrophobic interactions between the alkyl groups of the alcohol and tetraalkylammonium salt play a more important role. Ammonium salts with relatively long alkyl chains (n = 14–18) do not form complexes with alcohols having significantly shorter alkyl chains (m = 8–10). For example, hexadecyltrimethylammonium bromide forms complexes only with alcohols C_{14}–C_{17}. This provides possibility to separate homologous alcohols with similar properties. Thus dodecan-1-ol was isolated from a 1:1 mixture with heptan-1-ol in a yield of 22%

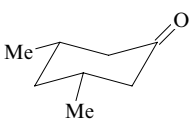
and purity of 97% using the complexation with dodecyltrimethylammonium bromide in acetone. In addition, separation of primary and secondary alcohols appeared to be possible. For example, tetradecan-1-ol was isolated from a mixture with tetradecan-2-ol (Ref. 8) through complexation with dodecyltrimethylammonium bromide.

Separating agent having amide fragments appeared to be helpful for the separation of *cis*- and *trans*-isomers of unsaturated alcohols. Since the *cis* isomer of but-2-ene-1,4-diol (**28a**) (b.p. 132 °C/16 Torr) and its *trans* isomer (**28b**) (b.p. 132 °C/13 Torr) have very close boiling points, it is virtually impossible to separate them by fractional distillation. This problem was solved [9] through selective complexation with bisamides **21**. Thus, the CMC {2 (**21a**)·**28b**} was isolated from a solution of bisamide **21a** and a mixture of *cis* and *trans* diols **28a** and **28b** (in a ratio of 25.5 : 74.5) in acetone; heating of this CMC in vacuum gave the pure *trans* isomer **28b** in a yield of 72%.

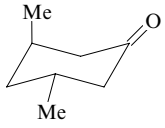
Tetraphenylphosphonium salts **25** also manifest the ability to efficient molecular recognition, which can be used for the separation of hydroxyl-containing isomers.[10] With the use of these salts, isomeric *cis* (**29a**) and *trans* cyclohexane-1,4-diols (**29b**) were successfully separated (from a mixture with the composition 1 : 1) through the formation of the CMC {**25**·**29b**} in an EtOH – EtOAc solution. After the decomposition of the complex with aqueous Et_2O, the pure *trans* isomer was isolated in a yield of 36%.

Separation of a mixture of cyclohexanol (cyclo-$C_6H_{11}OH$) (b.p. 161 °C) and cyclohexanone (cyclo-$C_6H_{10}O$) (b.p. 155.6 °C) by common distillation is a complicated task due to the proximity of their boiling points. Efficient separation of these compounds was successfully performed [11] through selective complexation with SA **1a**, which gives a stable CMC only with the ketone. Co-crystallisation of SA **1a** and equimolar amounts of cyclohexanol and cyclohexanone from a 1 : 1 Et_2O – petroleum ether mixture gave the CMC {**1a**·2 (cyclo-$C_6H_{10}O$)}. Its recrystallisation and heating in vacuum resulted in cyclohexanone (yield 95%) containing insignificant impurity (0.15%) of the alcohol.

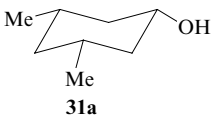
The method of selective co-crystallisation allows the separation [12, 13] of methyl-substituted cyclohexanols and cyclohexanones of similar structures. It appeared that the reagent **1a** selectively forms CMC with isomers **30a** and **31a** having equatorial substituents, but does not give complexes with isomers **30b**, **31b** and **31c** containing at least one substituent (Me or OH) in the axial position.



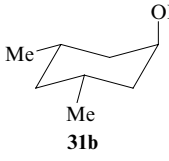
30a



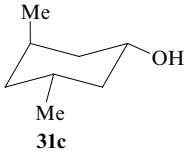
30b



31a



31b



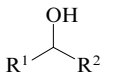
31c

Thus, the addition of diol **1a** to a solution of a mixture of isomers **31a** (63%), **31b** (22%) and **31c** (15%) in Et_2O – petroleum ether (1 : 1) results in the formation of only one CMC {**1a**·2 (**31a**)}. After two recrystallisations and heating of this complex in vacuum, isomer **31a** was isolated in a yield of 65% and purity of 99.7%. Similarly, a mixture of isomeric cyclohexanols **31a** and **31b**, the reduction products of ketone **30a** with $NaBH_4$, was separated.[12]

The use [2] of chiral TADDOL-type 1,4-diols **6a**–**f**, D-(−)- or L-(+)-tartaric acid derivatives, appeared to be extremely fruitful for the development of the selective co-crystallisation method; among them, the most important are compounds **6a**,**c**,**d**.

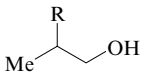
It is interesting to note that the racemic SA **6a** forms CMC with the composition 1 : 1 with alkanols having different lengths and branching of hydrocarbon chains, while the optically active SA **6a** gives 1 : 1 complexes only with low alcohols (MeOH and EtOH).[14] Derivatives of diol **6a** in both racemic and optically active forms having substituents (Me, Cl, F, CF_3) in the phenyl groups also form CMC with lower alcohols of different stoichiometric compositions.[14]

Chiral TADDOL-type diols appeared very efficient in the resolution of racemic alcohols **32**–**34** into enantiomers.



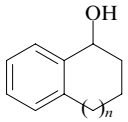
32a–**k**

R^1 = Ph: R^2 = Me (**a**), Et (**b**), C≡CH (**c**), CCl_3 (**d**), Bu^t (**e**), Bu^i (**f**);
R^1 = 4-MeC_6H_4, R^2 = Et (**g**);
R^1 = 3-$PhOC_6H_4$, R^2 = C≡CH (**h**);
R^2 = Me: R^1 = 4-BrC_6H_4 (**i**),
3,5-$(CF_3)_2C_6H_3$ (**j**), cyclo-C_3H_5 (**k**).



33a,**b**

R = Et (**a**), Ph (**b**).



34a,**b**

n = 0 (**a**), 1 (**b**).

Resolution of secondary alcohols **32a**–**c** into enantiomers by co-crystallisation with diol (*R*,*R*)-**6a** can be performed under heterogeneous conditions in hexane (suspension co-crystallisation).[15–17] Diol **6a** is insoluble in hexane, while the compounds that are to be separated, in this case, secondary alcohols, are hexane-soluble. This suspension method is often more efficient than co-crystallisation in solution, because separation occurs in higher yields. In some cases, aqueous suspension of a chiral SA was used for the resolution of racemic alcohols. The results of the resolution of alcohols **32**–**34** by co-crystallisation with chiral diols **5b**,**c** and **6a**,**c** are presented in Table 1.

Cholanamide (**20**) stereoselectively forms CMC with a series of secondary alcohols **32**.[20, 21] The best results were obtained for the resolution of racemic alcohols **32a** and **32f** (*ee* of isolated isomers exceeded 85%).[21]

Stereoselective co-crystallisation of enantiomerically enriched alcohol (*R*)-(+)-**32d** (*ee* 36%) with achiral 1,4-diazabicyclo[2.2.2]octane (**13**) resulted in the homochiral alcohol (*R*)-(+)-**32d** in a yield of 32%.[22]

Upon the resolution of racemic *trans*-2-methoxycyclohexanol (**35**) with SA (*R*,*R*)-**6e**, the CMC with the stereoisomer (*R*,*R*)-**35** is stereoselectively formed, which was isolated with *ee* 94%.[23] Reduction (solvent-free) of alkyl aryl ketones involved into the CMC with the chiral agents **1c** and **6a** (reducing agent was the complex of BH_3 with ethylenediamine) gave the corresponding optically active alcohols in yields up to 96% and *ee* up to 60%.[24]

Enantioselective reduction of acetophenone with monohydride complex **36** combined with the enantiomeric enrichment of the alcohol formed through co-crystallisation of the latter with the chiral ligand **6a**, the hydrolysis product of the complex in the reaction mixture, has been carried out.[25] Later, this process was modernised [17] using aluminium dihydride complex

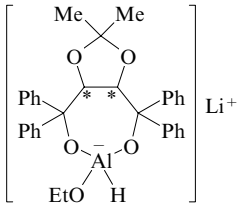
Table 1. Resolution of racemic alcohols **32**–**34** into enantiomers through co-crystallisation with chiral diols **5b**,**c** and **6a**,**c**.

Racemic substrate	Separating agent	Resolution conditions	Yield of isolated enantiomer (%)	Isolated enantiomer, *ee* (%)	Ref.
32a	(*S*,*S*)-**5b**	*a*	48	(*S*)-(−)-**32a**, 95	18
	(*S*,*S*)-**5c**	*a*	39	(*S*)-(−)-**32a**, 90	18
	(*R*,*R*)-**6a**	*b*	85	(*S*)-(−)-**32a**, 95	15
	(*R*,*R*)-**6a**	*c*	85	(*S*)-(−)-**32a**, 98	15
	(*S*,*S*)-**6a**	*d*	90 [a]	(*R*)-(+)-**32a**, 98	17
	(*R*,*R*)-**6a**	*e*	72	(*S*)-(−)-**32a**, 75 (98) [b]	19
32b	(*R*,*R*)-**6a**	*b*	75	(*S*)-(−)-**32b**, 100	15
	(*R*,*R*)-**6a**	*c*	75	(*S*)-(−)-**32b**, 98	15
	(*S*,*S*)-**6a**	*d*	78 [a]	(*R*)-(+)-**32b**, 88	17
	(*R*,*R*)-**6a**	*e*	39	(*S*)-(−)-**32b**, 91	19
32c	(*R*,*R*)-**6a**	*b*	89	(*R*)-(+)-**32c**, 92	15
	(*R*,*R*)-**6a**	*c*	76	(*R*)-(+)-**32c**, 100	15
	(*R*,*R*)-**6a**	*e*	69	(*R*)-(+)-**32c**, 97	19
32g	(*R*,*R*)-**6c**	*e*	79	(*S*)-(−)-**32g**, 63	19
32h	(*R*,*R*)-**6c**	*e*	65	(*S*)-(−)-**32h**, 92 (100) [b]	19
33a	(*S*,*S*)-**5b**	*a*	42	(*S*)-(−)-**33a**, 32	18
34a	(*R*,*R*)-**6c**	*e*	79	(*S*)-(+)-**34a**, 78	19
34b	(*R*,*R*)-**6c**	*e*	45	(*S*)-(+)-**34b**, 78	19

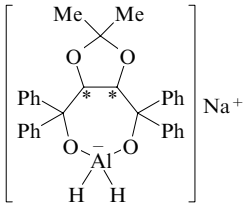
Note. (*a*) Single co-crystallisation from toluene; (*b*) single co-crystallisation in a suspension of SA in hexane; (*c*) single co-crystallisation in a suspension of SA in water; (*d*) double co-crystallisation in a suspension of SA in hexane; (*e*) single co-crystallisation from a mixture toluene–hexane (1 : 1).

[a] Yield of CMC; [b] values in parentheses refer to double co-crystallisation.

37, which appeared to be significantly more stable as compared to monohydride complex **36**. The tandem process provides possibility for increasing enantioselectivity of the reduction of those carbonyl compounds that react with TADDOL-containing aluminium hydride complexes with lower enantioselectivity than alkyl aryl ketones.[26]



36



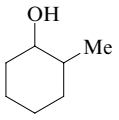
37

1,2-Diols **7** and **8** derived from mandelic and lactic acids, respectively,[27–29] were used as chiral SA significantly more seldom than 1,4-diols **6** derived from tartaric acid. Homochiral diol (*R*)-**7** forms CMC with acyclic alcohols (the composition of CMC is shown in parentheses): MeOH (1 : 1), Pr^nOH (2 : 1), Bu^nOH (1 : 1) and Bu^tOH (2 : 1), whereas racemic diol **7** does not form these complexes. At the same time cyclohexanol and 2-methylcyclohexanol do not form CMC with both homochiral and racemic diol **7**. On the other hand, 1,2-diols (*S*)-**8a** and (±)-**8a** give CMC with the composition 1 : 1 with these cyclic alcohols.[27] These data demonstrate the possibility of separating mixtures of acyclic and cyclic alcohols using appropriate

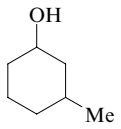
Table 2. Resolution of racemic alcohols into enantiomers through stereoselectice co-crystallisation with 1,2-diols **8a**–**c**.[28,29]

Racemic substrate	Separating agent	Ratio SA : substrate in CMC	Yield of isolated enantiomer (%)	Isolated enantiomer, *ee* (%)
33b	(*S*)-**8c**	2 : 1	68	(*R*)-**33b**, > 99
38a	(*S*)-**8a**	1 : 1	50	(*S*)-**38a**, 53
38b	(*S*)-**8a**	1 : 1	64	(*S*)-**38b**, 35
	(*S*)-**8b**	1 : 2	85	(*R*)-**38b**, 18
39	(*S*)-**8a**	1 : 1	57	(*S*)-**39**, 56
40	(*S*)-**8a**	1 : 1	81	(*S*)-**40**, 68

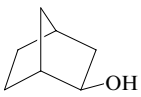
SA (**7** or **8**). Homochiral 1,2-diols **8** demonstrated high efficiency in the resolution of 2-phenylpropan-1-ol into enantiomers (**33b**)[29] and moderate efficiency in the resolution of racemic cycloalkanols **38**–**40**[28,29] (Table 2).



38a,**b**



trans-**39**



exo-**40**

cis- (**a**), *trans*- (**b**).

Resolution of 1-cyclopropylethanol (**32k**) into enantiomers was carried out; a series of esters of this alcohol exhibits pharmacological and other kinds of biological activity. Double co-crystallisation of alcohol **32k** with chiral diols **6a**,**b** through the formation of CMC {(*S*,*S*)-**6a**·(*R*)-(−)-**32k**} and {(*R*,*R*)-**6b**·(*S*)-(+)-**32k**} from a solution in a mixture Et_2O–hexane resulted in homochiral alcohols **32k** with *ee* ⩾ 98% and 97%, respectively, and the yields of 43%–45% of the parent racemate.[30] The CMC isolated withstand heating to 50 °C in vacuum, but after heating at 70 °C for 1 h they lose the alcohol completely; the yields of the latter and the remaining solid diol (SA) are virtually quantitative with complete retention of their enantiomeric purity.

Racemic 1-(*p*-bromophenyl)ethanol (**32i**) was resolved into enantiomers through inclusion crystallisation with per-*O*-methy-β-cyclodextrin (**9b**); crystal structures of inclusion complexes obtained were studied, as well as the mechanism of chiral recognition.[31] The 1 : 1 inclusion complex is crystallised from an aqueous solution containing equimolar amounts of the components. According to the X-ray diffraction data, the intermolecular interaction in these complexes occurs between the OH group of the substrate and the oxygen atom of one of the MeO groups in SA **9b**.

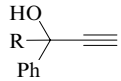
Sonication-assisted reduction of ketones RC(O)Me involved in complexes with β-cyclodextrin (**9a**) (reducing agent is $NaBH_4$ or the complex of BH_3 with ethylenediamine) in the absence of a solvent has been studied.[32] This resulted in alcohols RCH(OH)Me in yields from 30% (R is 1-naphthyl) to 100% (R = Ph) and *ee* up to 26%. Reduction of these ketones under the action of $NaBH_4$ in aqueous solution containing SA **9a** gave racemic alcohols.

(*R*)-3,5-Bis(trifluoromethyl)phenylethanol (**32j**) was prepared[33] from the corresponding prochiral ketone by the hydrogen-transfer catalytic asymmetric reduction in the presence of the catalytic system $[(p\text{-Cym})Ru^{II}Cl_2]_2$–(1*S*,2*R*)-*cis*-aminoindan-2-ol (*p*-Cym is *p*-cymene). Optically active alcohol **32j** (*ee* 90%–92%) was isolated from the reaction mixture through the formation of the CMC {2(**13**)·**32j**}, which

allowed further enantiomeric enrichment of the alcohol **32j** (*ee* > 99%).

2. Resolution of acetylenic alcohols

The process of resolution of acetylenic alcohols into enantiomers through the corresponding diastereomeric salts of monoesters of phthalic acid with chiral bases [34] is labourious and often does not give good results. At the same time, some of these alcohols form enantioselectively CMC with the composition 1 : 1 with brucine (**15**), which allowed the resolution of these alcohols into optical isomers. Single co-crystallisation of racemic acetylenic alcohols **41a – f** in which the hydroxyl group is bound to the tertiary carbon atom, with brucine (**15**) from acetone followed by decomposition of the CMC obtained with dilute HCl resulted in the isolation of both optical isomers in the yields of 38% – 65% and *ee* 15% – 93%. The second co-crystallisation in most cases gave homochiral alcohols.[35, 36]



41a – f

R = Bu^t (**a**), *tert*-C_5H_{11} (**b**), 2-MeC_6H_4 (**c**), 2-FC_6H_4 (**d**), 2-ClC_6H_4 (**e**), 2-BrC_6H_4 (**f**).

Partial resolution of racemic acetylenic alcohols **41a**,**d – f** into enantiomers was carried out by co-crystallisation with (–)-sparteine (**16**) from acetone (Table 3).[36] Packing diagram for the CMC {(–)-**16** · **41f**} is presented in Fig. 1.

Table 3. Resolution of acetylenic alcohols **41** into enantiomers through co-crystallisation with (–)-sparteine.

Racemic substrate	Yield of isolated enantiomer (%) [a]	Isolated enantiomer, *ee* (%) [b]
41a	49	(*S*)-(–)-**41a**, 59 (100)
	51	(*R*)-(+)-**41a**, 57
41d	36	(–)-**41d**, 34 (85)
	61	(+)-**41d**, 23
41e	51	(–)-**41e**, 55 (100)
	44	(+)-**41e**, 60
41f	61	(–)-**41f**, 50 (100)
	37	(+)-**41f**, 81

Note. CMC have the composition 1 : 1.

[a] After single co-crystallisation; [b] results of triple co-crystallisation are given in parentheses.

Resolution of acetylenic alcohols **41** by co-crystallisation with (–)-sparteine appeared to be more efficient than complexation with brucine, which is important because (–)-sparteine is a less toxic SA. In turn, racemic sparteine prepared by the Leonard method [37] can be resolved into enantiomers by optically active acetylenic alcohols through co-crystallisation of equimolar amounts of homochiral alcohol (–)-**41f** and racemic sparteine from acetone.[36]

Co-crystallisation of achiral bicyclic diamine **13** and scalemic alcohol (+)-**41e** (*ee* 72.5%) resulted in the CMC {**13** · 2 [(+)-**41e**]}, from which the homochiral alcohol (+)-**41e** was isolated in the yield of 36%.[22] Similarly, co-crystallisation of scalemic alcohols (+)-**41f** (*ee* 78%) and (*S*)-(+)-**31d** (*ee* 36%) with achiral diamine **13** provided the possibility for increasing the enantiomeric purity in the course of this 'spontaneous' resolution and for obtaining pure alcohols in the yields of 37% and 32%, respectively.

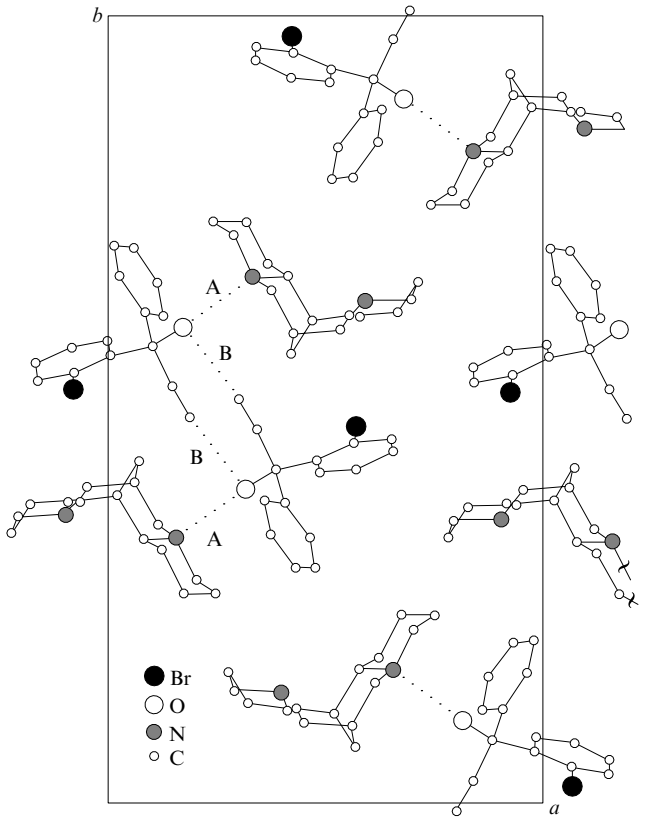
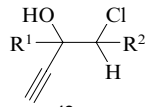


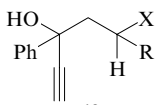
Figure 1. The projection of the crystal structure of the inclusion complex {(–)-**16** · **41f**} onto the *xy* plane (according to the X-ray diffraction data, here and in Fig. 2, the H atoms are omitted for simplicity).[36]
Two hydrogen bonds are shown: OH – N (A) and C≡CH···OH (B).

Brucine (**15**) is capable of recognising not only one, but two chiral centres in molecules of α-chloro-, β-chloro-, β-bromo- and β-methoxyacetylenic alcohols **42** and **43** prepared by the reaction of ethynylmagnesium bromide with the corresponding α- or β-substituted ketones. Enantioselective binding of one diastereomer of alcohol **42** or **43** to brucine into the CMC with the composition 1 : 1 through co-crystallisation from acetone underlies [38] the resolution of racemic α- or β-substituted acetylenic alcohols in the yields of 28% – 50% and *ee* 100%.



42a – c

R^1 = Ph: R^2 = Me (**a**), Ph (**b**);
R^1 is 2-thienyl, R^2 = Me (**c**).



43a – c

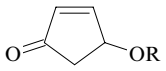
R = Ph, X = Cl (**a**);
R = Me: X = Br (**b**), OMe (**c**).

3. Resolution of functionally substituted alkanols and cycloalkanols

a. Hydroxy ketones and their derivatives, hydroxy carboxylic acid derivatives

Compound (*S*,*S*)-**1c** appeared efficient in the resolution of racemic unsaturated hydroxy ketone **44a** into enantiomers in the form of its butyrate **44d**.[39] The CMC {(*S*,*S*)-**1c** · (*S*)-(–)-**44d**} is selectively crystallised from a mixture Et_2O – petroleum ether (1 : 1). After crystallisation of the complex and its thermal dissociation, the enantiomerically pure compound (*S*)-(–)-**44d**

was isolated in a yield of 56%. After the addition of diol (*R*,*R*)-**1c** to the filtrate and decomposition of the CMC formed, the enantiomerically pure keto ester (*R*)-(+)-**44d** was obtained in a yield of 60%.



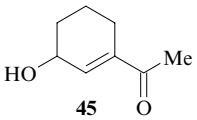
44a–e

R = H (**a**), MeC(O) (**b**), EtC(O) (**c**), Pr^{n}C(O) (**d**), tetrahydropyran-2-yl (**e**).

Resolution of hydroxy ketone **44a** and its derivatives **44b–e** was performed by co-crystallisation with biphenanthrenediol (*S*)-**12**.[39] Keto esters **44b–e** were resolved into enantiomers from methanolic solution at a twofold excess of the substrate with respect to the SA (*S*)-**12**. Recrystallisation of the CMC (1 : 1) obtained followed by heating in vacuum gave the corresponding optically active keto esters **44b–e** in high yields and enantioselectivity up to 100%. It is noteworthy that the CMC of the unsaturated hydroxy ketone **44a** with SA (*S*)-**12** appeared unstable. Preparation of the optically pure compound **44a** by hydrolysis of *O*-acyl derivatives **44b–d** was substantially complicated due to racemisation. Racemisation was avoided[40] through hydrolysis, under mild conditions, of optically active tetrahydropyranyl ether **44e** isolated from the CMC with the SA (*S*)-**12**. In this way, homochiral 4-hydroxycyclopent-2-enone (**44a**) was obtained. The X-ray diffraction data for the CMC {(*S*)-**12**·(*S*)-(−)-**44c**} are reported.[41]

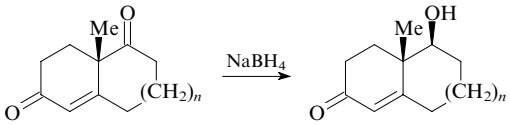
Interesting results have been obtained when using diol (*S,S*)-**4** as a SA that forms CMC with one enantiomer of the racemic substrate in the absence of MeOH, but binds the other enantiomer and MeOH into a three-component complex.[42] For example, co-crystallisation of the SA (*S*,*S*)-**4** with racemic hydroxy ketone **44a** from toluene gives the CMC {(*S,S*)-**4**·2[(*R*)-(+)-**44a**]}, from which enantiomer (*R*)-(+)-**44a** was obtained in a yield of 72% and *ee* 38%. When co-crystallisation was performed from MeOH, the CMC {(*S*,*S*)-**4**·(*S*)-(−)-**44a**·MeOH} was obtained, from which enantiomer (*S*)-(−)-**44a** was isolated in a yield of 44% and *ee* 42%. Co-crystallisation of diol (*S,S*)-**4** with the racemate (±)-**44a** from EtOH gave the three-component CMC {(*S*,*S*)-**4**·(*S*)-(−)-**44a**·EtOH}, from which the hydroxy ketone (*S*)-(−)-**44a** was isolated in a yield of 78% and *ee* 80%.

Co-crystallisation of SA (*S,S*)-**4** with racemic 3-acetylcyclohex-2-enol (**45**) from MeOH resulted in the CMC {(*S*,*S*)-**4**·(*S*)-(−)-**45**·MeOH},[42] from which enantiomer (*S*)-(−)-**45** was isolated in a yield of 55% and *ee* 58%. However, the complexation in toluene resulted in the CMC {(*S*,*S*)-**4**·(±)-**45**}, *i.e.*, no enantiomeric enrichment was observed. In contrast to diol (*S*,*S*)-**4**, diol (*S*,S)-**1a** gave CMC in different solvents,[42] the enantiomer (*R*)-(+)-**45** prevailing.



45

Hydroxy ketones **46a**,**b** are of significant interest as chiral 'building blocks', but their preparation even in the racemic form is often rather difficult. Solvent-free reduction of diketone (*R*)-**47a** involved in a CMC with diol (*R*,*R*)-**6a** with $NaBH_4$ affords only stereoisomer **46a** in a yield of 55%, but if the same reaction is carried out in an aqueous suspension of the SA (*R*,*R*)-**6a**, a mixture of stereoisomers is formed.[43] Similarly, solvent-free reduction of the CMC {(*R*,*R*)-**6a**·(*R*)-**47b**} with $NaBH_4$ affords only one stereoisomer **46b** in a yield of 54%.



47a,**b** **46a**,**b**

n = 0 (**a**), 1 (**b**).

Dipeptide (*R*,*R*)-**24** forms CMC with some esters of α-hydroxy carboxylic acids **48a–g** and pantolactone (**49**). Co-crystallisation was performed from MeOH. The structure of the CMC was determined by the X-ray diffraction. After decomposition of the complexes, the (*S*)-forms of compounds **48a–g** and **49** were isolated with *ee* 82%–99%.[44,45]



48a–g **49**

R^1 = Me: R^2 = Me (**a**), Et (**b**);
R^2 = Me: R^1 = Et (**c**), Pr^n (**d**), Bu^n (**e**), Bu^i (**f**), Bu^t (**g**).

Resolution of pantolactone into optical antipodes through the formation of CMC with the composition 1 : 1 with SA (*R*,*R*)-**6d** has been described.[46] The X-ray diffraction data for complex {(*R*,*R*)-**6d**·(*R*)-**49**} are presented in Fig. 2. After double co-crystallisation from a mixture benzene–hexane (1 : 1) followed by dissociation of the complex upon heating in vacuum, lactone (*R*)-**49** was obtained in a yield of 30% and *ee* 99%. Co-crystallisation of diol (*R*,*R*)-**6d** in aqueous suspension is facilitated in the presence of hexadecyltrimethylammonium bromide as a phase-transfer catalyst.[47]

Chiral diols **6b**,**f**, **7** and **8a** also co-crystallise with pantolactone, however, the efficiency of the resolution of the racemate (±)-**49** by the above SA is strongly different (*ee* from 4%

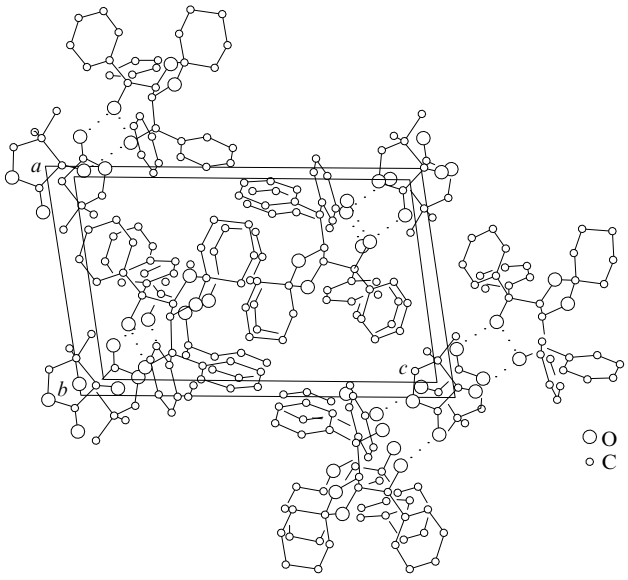
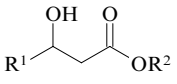


Figure 2. The crystal structure of the inclusion complex {(*R*,*R*)-**6d**·(*R*)-**49**}.[46]
Hydrogen bonds are shown as dotted lines.

to 74% after the first co-crystallisation).[48] The best results were achieved in the resolution of (±)-**49** with chiral SA **7**. Three co-crystallisations from a mixture benzene – hexane (1 : 2) afforded the CMC {(*S*)-**7**·(*R*)-**49**}. This was dissolved in Et_2O and the optically active lactone **49** was extracted with water;[49] the enantiomer (*R*)-(−)-**49** (*ee* 98%) was obtained in a yield of 67%. Notably that this is the first example of the use of chiral 1,2-diol **7** for the resolution of a racemic compound into enantiomers.

Esters of β-hydroxy carboxylic acids **50** in the optically active form are intermediates in the synthesis of a series of biologically active compounds.[50–52] Co-crystallisation of diol (*R*,*R*)-**6c** with esters **50a**,**b** resulted in (*S*)-enantiomers of the latter with *ee* 80% – 100% (Table 4).[53]



50a – d

R^1 = Me: R^2 = Me (**a**), Et (**b**); R^2 = Me: R^1 = CH_2Cl (**c**), CO_2Me (**d**).

Table 4. Resolution of racemic esters of β-hydroxy carboxylic acids into enantiomers.[39, 53]

Racemic substrate	Separation agent [a]	Resolution conditions	Yield of isolated enantiomer (%)	Isolated enantiomer, *ee* (%)
50a	(*R*,*R*)-**6c**	*a*	44	(*S*)-(+)-**50a**, 100
	(*R*,*R*)-**6c**	*b*	80	(*S*)-(+)-**50a**, 80
50b	(*R*,*R*)-**6c**	*a*	28	(*S*)-(+)-**50b**, 100
	(*R*,*R*)-**6c**	*b*	93	(*S*)-(+)-**50b**, 78
	(*S*)-**12**	*b*	86	(*S*)-(+)-**50b**, 93
50c	(*S*)-**12**	*b*	57	(*S*)-(−)-**50c**, 95
50d	(*S*)-**12**	*b*	81	(*R*)-(+)-**50d**, 60

Note. (*a*) Co-crystallisation of substrate and SA (from the mixture Et_2O – petroleum ether, 1 : 1), (*b*) co-crystallisation in suspension (in hexane).
[a] CMC {2(*R*,*R*)-**6c**·**50**} and {(*S*)-**12**·**50**}, respectively, are formed.

It is remarkable that thermal dissociation of the CMC {2[(*R*,*R*)-**6c**]·(*S*)-(+)-**50a**}, in which association between the substrate and SA is achieved through H-bonding, occurs with the liberation of the target compound at a substantially higher temperature than the boiling point of the ester **50a**.[53] It is noteworthy that, in contrast to the method of selective co-crystallisation, enzymatic degradation of racemic enantiomers **50b** (Ref. 54) and **50c** (Ref. 55) did not give pure enantiomers.

Biphenanthrenediol (*S*)-**12** appeared to be an efficient SA for the resolution of β-hydroxy esters **50b – d** (Table 4).[39] Second co-crystallisation of the CMCs formed gave enantiomerically pure hydroxyesters.

b. Cyanohydrins

Cyanohydrins **51** were resolved into enantiomers by co-crystallisation with SA (*R*,*R*)-**6a**,**c** (from a mixture toluene – hexane, 1 : 1) (Table 5).[19]

Table 5. Resolution of racemic cyanohydrins into enantiomers.[19]

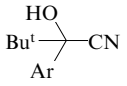
Racemic substrate	Separating agent	Yield of isolated enantiomer (%) [a]	Isolated enantiomer, *ee* (%)
51a	(*R*,*R*)-**6a**	52	(+)-**51a**, 100
51b	(*R*,*R*)-**6a**	47	(*R*)-(+)-**51b**, 100
51c	(*R*,*R*)-**6c**	70	(−)-**51c**, 72

Note. Double co-crystallisation for substrates **51a**,**b**, single co-crystallisation for **51c**.
[a] Calculated based on its content in the racemate.



51a – c

R = Me (**a**), Ph (**b**), 3-$PhOC_6H_4$ (**c**).



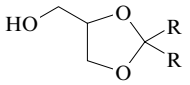
52a – e

Ar = Ph (**a**), 4-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-HOC_6H_4 (**d**), 3-HOC_6H_4 (**e**).

Similarly, good yields and high enantioselectivity were achieved [56] in the resolution of racemic cyanohydrins **52a – e** into optical isomers by co-crystallisation with brucine (**15**). For example, the CMC {**15**·(+)-**52a**} was isolated from a methanolic solution of equimolar amounts of brucine and the racemic cyanohydrin; the decomposition of the CMC with dilute HCl gave the enantiomer (+)-**52a** in a yield of 67% and *ee* 97%.

c. Alcohols containing heterocyclic fragments

Glycerol derivatives **53a – c**, which are multitarget synthons, are resolved into enantiomers with the use of chiral TADDOL-type SA.[19, 57]



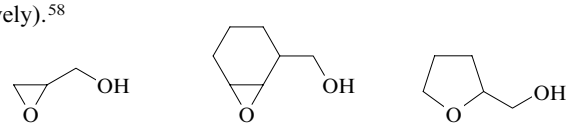
53a – c

R = Me (**a**); R – R = $(CH_2)_4$ (**b**), $(CH_2)_5$ (**c**).

Resolution of compound (±)-**53a** through the formation of the CMC {(*S*,*S*)-**6d**·(*R*)-(−)-**53a**} was performed with high efficiency using a two-step procedure:[57] the first step was suspension co-crystallisaton of diol **6d** with a racemic substrate in hexane at a 4 – 5-fold excess of the racemate with respect to the SA; the second step was crystallisation of the complex from a mixture Et_2O – hexane (1 : 5) with the same SA. After thermal dissociation of the CMC in vacuum, the optically active compound (*R*)-(−)-**53a** was obtained in a yield of 60% and *ee* 97%. The above CMC withstands heating at 50 °C in vacuum for 1 h, whereas heating to 80 °C for the same period leads to the complete dissociation of the complex. The crystalline residue represents pure diol (*S*,*S*)-**6d**, which can be repeatedly used for the resolution of the substrate (±)-**53a** without additional purification.

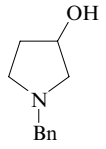
The separating agent (*S*,*S*)-**6d** forms CMC with glycidol (**54**). Single co-crystallisation (Et_2O – petroleum ether, 2 : 3) in the open system (slow solvent evaporation at room temperature) resulted in the enrichment of the substrate **54** with the (*S*)-enantiomer (to *ee* 34%).[48] Chiral SA **6a** gave the CMC with the composition of 1 : 1 with alcohols **55** and **56** from a mixture

benzene – hexane (4 : 1), but the efficiency of the resolution into optical isomers appeared to be low (*ee* 49 and 21%, respectively).[58]



54 **55** **56**

Diol (*R*,*R*)-**6d** binds selectively (*S*)-enantiomer of *N*-benzyl-3-hydroxypyrrolidine (**57**) into CMC.

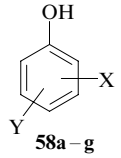


57

Enantiomerically pure amino alcohol (*S*)-**57** was obtained in a 44% yield by double co-crystallisation.[59] The X-ray diffraction data for the CMC {(*R*,*R*)-**6d**·(*S*)-(+)-**57**} indicate that not only hydrogen bonds, but also van der Waals interactions between the hydrophobic fragments of the SA and substrate take part in complexation.[59] In the ^{13}C NMR spectrum of amino alcohol **57** in the presence of the SA (*R*,*R*)-**6d**, splitting of the signals of some carbon atoms is observed. This indicates that the above SA can recognise enantiomers of the substrate **57** even in solution, which can be used for the determination of the enantiomeric composition of this hydroxypyrrolidine.

4. Phenols and biphenyldiols

Isolation of individual cresols **58a – c** from the products of coal distillation is a practically very important but difficult task. This particularly concerns the separation of *m*-cresol (**58b**) (b.p. 202.0 °C) and *p*-cresol (**58c**) (b.p. 201.8 °C).



58a – g

X = H: Y = 2-Me (**a**), 3-Me (**b**), 4-Me (**c**), 3-Et (**d**), 4-Et (**e**);
X = 2-Me: Y = 4-Me (**f**), 5-Me (**g**).

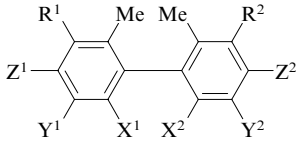
One of the components of the cresol mixture was isolated[60] through co-crystallysation with bisphenol **10**. The hydrocarbon framework of SA **10** ensures the 'bulkyness' of its crystal lattice, whereas two spatially fixed phenol hydroxyl groups selectively hold one of the isomers of the substrate inside the lattice. The selectivity of complexation of phenolic compounds with SA **10** grows in the series *o*-cresol < phenol < *p*-cresol < *m*-cresol.

The CMC {**10**·**58b**}was isolated from a solution of *m*- and *p*-cresols (1 : 1) in ethyl acetate. Crystallisation of the complex obtained from the same solvent and heating in vacuum gave *m*-cresol (**58b**) of 99.8% purity in a yield of 32%. According to X-ray diffraction data, the complex of SA **10** with *m*-cresol is characterised by less steric hindrance (as compared to *p*-cresol), which accounts for its prevailing formation. Similarly, the separation of *m*- and *p*-ethylphenols (**58d**,**e**) having the boiling points 214 and 219 °C, as well as 2,4- and 2,5-dimethylphenols **58f**,**g** (b. p. 211 and 212 °C, respectively) has been carried out through co-crystallisation with bisphenol **10**.[61]

Separation of *m*- and *p*-cresols was also performed[9] using bisamides **21** as the SA. Thus bisamide **21a** forms CMC predominantly with *m*-cresol, whereas bisamide **21b** gives a complex with the *p*-isomer. For example, the CMC {**21a**·2(**58b**)} was crystallised from an acetone solution of bisamide **21a** and a mixture of *m*- and *p*-cresols (2 : 3); heating of this complex in vacuum resulted in *m*-cresol in a yield of 75%. The CMC {**21b**·2(**58c**)}was crystallised for several hours after the addition of bisamide **21b** to the filtrate; from this CMC, *p*-cresol was isolated in a 73% yield. Both isolated isomers had 99% purity.

Phosphonium salts can be used for the separation of isomeric phenols. Thus the CMC {2(**25**)·(2-BrC_6H_4OH)} is crystallised from a solution of the salt $Ph_4P^+Br^-$ (**25**) and a mixture of 2- and 4-bromophenols (1 : 1) in mixture ethanol – ethyl acetate (1 : 10). Treatment of the complex with diethyl ether – water mixture gave an aqueous solution of SA **25**; 2-bromophenol with a purity >99% was isolated from the ethereal solution.[10]

Racemic biphenyldiol **59a** was resolved into enantiomers by co-crystallisation with diol (*R*,*R*)-**6c** from a mixture Bu^n_2O – hexane.[62] Crystallisation of the CMC {(*R*,*R*)-**6c**·(+)-**59a**} obtained, treatment of this CMC with 10% aqueous NaOH followed by neutralisation with dilute HCl resulted in biphenyldiol **59a** in a yield of 30% and *ee* > 99%.



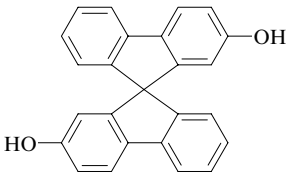
59a – d

$R^1 = R^2 = X^1 = Y^1 = H, X^2 = Y^2 = Me, Z^1 = Z^2 = OH$ (**a**);
$R^1 = R^2 = Y^1 = Y^2 = H, X^1 = X^2 = OH, Z^1 = Z^2 = Me$ (**b**);
$R^1 = R^2 = Cl, X^1 = X^2 = OH, Y^1 = Y^2 = H, Z^1 = Z^2 = Me$ (**c**);
$R^1 = R^2 = H, X^1 = X^2 = OH, Y^1 = Y^2 = Z^1 = Z^2 = Me$ (**d**).

Racemic biphenyldiol **59b** was resolved[62] into enantiomers through co-crystallisation with a derivative of cinchonidine (−)-**19a** from ethanol to give the enantiomer (+)-**59b** in a yield of 53% and *ee* > 99.9%.

The CMC {2(**14**)·(+)-**59c**} was obtained from a toluene solution of racemic biphenyldiol **59c** and a twofold molar excess of optically active *trans*-1,2-diaminocyclohexane (**14**); crystallisation of the CMC and treatment with a mixture ethyl acetate – dilute HCl (1 : 1) resulted in the enantiomer (+)-**59c** (Ref. 63) in a yield of 62% and *ee* 100%. Enantiomerically pure biphenyldiol (−)-**59c** was isolated from the filtrate in a yield of 52%. Similarly, crystallisation of the CMC {**14**·(+)-**59d**}gave enantiomerically pure biphenyldiol (+)-**59d** in a yield of 50%. Enantiomers of biphenyldiols **59c**,**d** are used as efficient ligands in asymmetric catalysis.[64, 65]

Resolution of racemic 9,9′-spiro-bifluorene-2,2′-diol (**60**) was carried out through the formation of the CMC {(*R*,*R*)-**22b**·(*R*)-**60**}, from which (after crystallisation from MeOH) the enantiomer (*R*)-**60** was isolated in a yield of 90% and *ee* 100%.[66]



60

5. Binaphthyldiols and biphenanthrenediol

Enantiomerically pure reagent **11a** (BINOL)[67] is widely used, for example, for the induction of chirality in catalytic asymmetric synthesis[68] and as a chiral solvating shift-reagent in NMR spectroscopy.[69–71] In this respect, different researchers have suggested original methods for resolution of the racemic compound **11a** and its analogues into enantiomers. Traditional method for the resolution of BINOL includes its transformation to cyclic phosphates, which are subject to hydrolysis after resolution.[72] However, a simpler method is the resolution of racemic BINOL through the formation of CMC with different chiral SA. Thus co-crystallisation of racemic compound **11a** with chiral ammonium salt **17** from EtOH gave[73] the CMC {(*S*)-**17**·(*S*)-(−)-**11a**}, which was treated with a mixture Et_2O-H_2O to isolate diol (*S*)-**11a** in a yield of 69% and *ee* 99.5%. Racemic BINOL (**11a**) can be resolved[10] into optical isomers through co-crystallisation with the salt (*S*)-(−)- or (*R*)-(+)-**26**. In turn, optically active phosphonium salts, which are important reagents in the Wittig reaction,[74] are prepared by the resolution of their racemates into enantiomers through co-crystallisation with (*S*)-BINOL.[10] As a result, the CMC {(*S*)-(−)-**11a**·(*S*)-(−)-**26**} is formed, the crystallisation of which from EtOH gives the phosphonium salt in a yield of 37% and *ee* 100%. Chiral alkyl aryl- and dialkyl sulfoxides (for example, compound **27**) form stereoselectively CMC with BINOL.[75,76] Thus the resolution of racemic BINOL through the formation of the CMC {(*S*)-(−)-**27**·(*S*)-(−)-**11a**}[76] crystallised from a mixture benzene–hexane (1 : 2) resulted in diol (*S*)-(−)-**11a**, which was isolated after two crystallisations of the complex in a yield of 83% and *ee* 100%. The enantiomer (*R*)-(+)-**11a** was isolated from the filtrate in a yield of 86% and *ee* 85%. The complexes have been studied by X-ray diffraction analysis.[75] Chiral SA, bisamides **22a**,**b** and **23**, which represent derivatives of natural L-tartaric acid,[66,77,78] have been successfully used for the resolution into enantiomers of substrates with molecules of the C_2 symmetry, BINOL among them. When equimolar amounts of bisamide (*R*,*R*)-**22a** and racemic compound **11a** were kept in a mixture benzene–hexane (1 : 4), the CMC {(*R*,*R*)-**22a**·(*S*)-**11a**}was formed, which was recrystallised and treated with an aqueous hydrazine solution to crystallise complex $\{NH_2NH_2\cdot$(*S*)-**11a**$\}$. After acidification with dilute HCl, pure enantiomer (*S*)-**11a** was isolated in a yield of 98% with 97% recovery of the SA (*R*,*R*)-**22a**.[66,77]

A convenient preparative method for the resolution of racemic diol **11a**[79,80] consists in co-crystallisation of this diol with quaternary ammonium salts **19a**,**b**, cinchonidine derivatives.[81] Thus the CMC {(−)-**19a**·(*R*)-**11a**} is formed from a methanolic solution of the salt (−)-**19a** and a twofold molar excess of racemic diol **11a**. Crystallisation and decomposition of the complex with dilute HCl resulted in the enantiomer (*R*)-**11a** in a yield of 75% and *ee* > 99%.[80]

Resolution of BINOL into enantiomers was also performed through co-crystallisation with (*S*)-proline in different solvents, however, the yield of the enantiomer (*S*)-**11a** did not exceed 56%, and *ee* did not exceed 78%.[82–84]

Resolution of binaphthyldiol **11b** (analogue of BINOL) into enantiomers through the formation of CMC **11b** with quinine (**18**) has been reported.[85] Crystallisation of the CMC gave the (*R*)-enantiomer in a yield of 76% and *ee* > 99%.

Resolution of racemic biphenanthrenediol **12** into enantiomers was performed through co-crystallisation with chiral SA (−)-**19b** from acetonitrile.[79] Decomposition of the CMC obtained with HCl afforded the optically active isomer (*R*)-**12** in a yield of 80% and *ee* 100%. According to the X-ray diffraction data for the complex {(−)-**19b**·(*R*)-**12**} (Fig. 3), in addition to hydrogen bonds between the OH groups of biphenanthrenediol and the nitrogen atom of the quinoline fragment (the distance OH···N is 2.77 Å), association between the cinchonidine derivative and biphenanthrenediol is supplemented by the π–π-interactions of conjugated systems of the closely located phenanthroline and quinoline rings (average distance 3.4 Å).

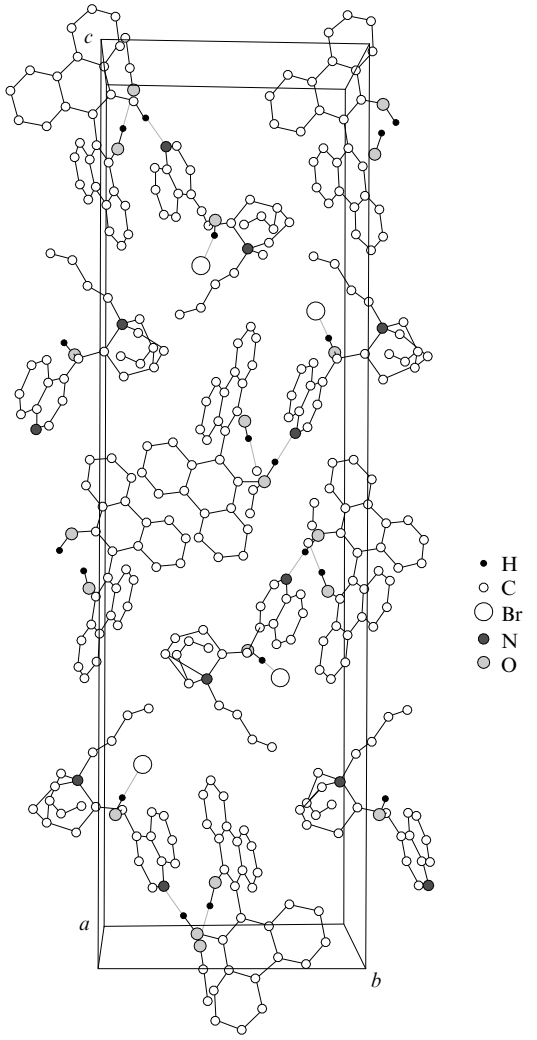


Figure 3. The crystal structure of the inclusion complex {(−)-**19b**·(*R*)-**12**} (only H atoms of the hydroxyl groups are shown).[79]

Racemic bisphenanthrenediol **12** was also resolved into enantiomers through co-crystallisation with chiral bisamide **23**. The CMC {2[(*R*,*R*)-**23**]·(*S*)-**12**}was formed in an ethanolic solution of (±)-**12** and a twofold excess of SA (*R*,*R*)-**23**. Crystallisation of the CMC and chromatographic purification on silica gel gave enantiomerically pure diol (*S*)-**12** in a yield of

74%, the CMC {2[(*R*,*R*)-**23**]·(*R*)-**12**} was isolated from the filtrate; the pure enantiomer (*R*)-**12** was obtained in a yield of 84% after decomposition of the CMC.[66, 77]

IV. Conclusion

The data discussed in this review allow a conclusion to be drawn that selective co-crystallisation of structurally related alcohols and phenols with chiral and achiral SA is an efficient method for their separation including resolution of racemic hydroxyl-containing compounds into enantiomers. Advantages of the method of selective co-crystallisation over other methods of the resolution of racemates consist, first of all, in the fact that they do not require transformation of hydroxyl-containing compounds into derivatives with acidic or basic groups. Moreover, chiral hydroxyl-containing compounds can, in turn, be used for resolution of other types of racemic substrates (for instance, amines, amides or sulfoxides) through the same CMC. Among novel promising approaches to the resolution of racemic substrates through CMC, there are processes combining the synthesis and resolution steps, which is possible to apply, for example, to the reduction of ketones involved into CMC with appropriate chiral SA. In this case, enantiomeric purity of the alcohol obtained in the reduction stage can be substantially increased as a result of its isolation in the form of a CMC with an appropriate chiral SA.

At the same time, a search for and studies of new systems separating agent – substrate for efficient separation of structurally related and racemic compounds into enantiomers remain actual.

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