Design and Evaluation of Inclusion Resolutions, Based on Readily Available Host Compounds

Simona Müller,[a] Marcel Cyrus Afraz,[a] René de Gelder,[b] Gerry J. A. Ariaans,[a] Bernard Kaptein,[c] Quirinus B. Broxterman,[c] and Alle Bruggink*[a,c]

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Resolution of enantiomers through selective crystallisation of diastereomeric inclusion compounds can extend the scope of traditional racemate resolution beyond salt forming compounds. To assess the practical value of this approach the literature was carefully screened and promising results were checked. Also an extensive range of new inclusion hosts suitable for resolution processes, derived from simple hydroxy- and amino acids were prepared and tested. Several techniques, including the Dutch Resolution approach utilizing mixtures of resolving agents, were applied. Over 70 potential resolving agents were tested in combinations with 34 racemates (over 100 racemates if literature results are included). Reproducibility of literature results was found to be problematic. Also the number of successful new resolutions found was very limited: only two efficient resolutions out of 1200 combinations of racemate and resolving agent tested in over 10.000 experiments! Crystal studies of representative combinations of resolving agents and inclusion compounds revealed some of the causes for the low rate of success in inclusion resolution. Compared to diastereomeric salts, the absence of strong electrostatic interactions substantially reduces the probability of forming crystals including both components. Molecular structure features allowing formation of intricate intramolecular and intermolecular H-bond networks were found to be responsible for inclusion crystal formation, and for the quality of the ensuing resolution through selective diastereomer crystallisation, in the successful cases. Whereas diastereomeric salt resolution continues to be of scientific and industrial interest, inclusion resolution should be viewed as of very limited scope; useful in specific instances, but lacking the wide applicability of classical resolution.

Introduction

Diastereomers take a prominent place in preparing optically pure compounds through resolution of racemates. In particular diastereomeric salts have a long history − well over 100 years − in mediating access to functional enantiopure molecules at any scale, ranging from milligrams for test purposes to multi-thousand tons production units for established fine chemical intermediates. Covalent diastereomers are far less frequently used, mainly because additional chemical operations are required before and after the resolution step. This disadvantage by far outweighs the main limitation of using diastereomeric salts, i.e. being restricted to the resolution of acids and bases. Within this context the development of resolutions through inclusion complexes by Toda[1] and other researchers[2] promised to be a new lead towards removal of this limitation. The ready availability of a variety of host compounds, required for formation of the enantioselective inclusion complexes, derived from simple and inexpensive enantiopure hydroxy acids such as tartaric acid and lactic acid, is an additional advantage.

From a more fundamental viewpoint, inclusion resolutions through selective crystallisation of diastereomeric molecular complexes would allow more in depth crystal studies aimed at a better understanding of chiral discrimination in crystal nucleation and crystal growth. In such complexes the stereoselective interactions can be more easily identified, as they are not overwhelmed by the strong electrostatic interactions present in diastereomeric salts. This in turn could lead to a more rational approach in the design and application of resolving agents. Thus far, our studies and related research by others have shown an ongoing synergistic development between increased fundamental understanding and rational design of resolutions through selective crystallisation on one hand, and additional insight through practical experience, i.e. trial and error, on the other side. The successful development of cyclic phosphoric acids as very useful resolving agents by Wynberg and ten Hoeve exemplifies the rational design.[3] Crystal studies by

[a] Department of Organic Chemistry, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands
[b] Department of Inorganic Chemistry, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands
[c] DSM Research, Life Sciences-Advanced Synthesis & Catalysis Department, P. O. Box 18, 6160 MD Geleen, The Netherlands
E-mail: alle.bruggink@dsm.com
Supporting information for this article is available on the WWW under http://www.eurjoc.com or from the author

Leusen[4] and by Vlieg and colleagues[5] show chiral discrimination to be the result of subtle differences in molecular interactions in solution, crystal nucleation, crystal growth and the resulting crystal lattice. Asking for predictions in organic multicomponent (and ionic) crystals is still beyond current scientific and computational capacity.

The discovery of Dutch Resolution, in which a racemate is resolved with a family of structurally related resolving agents, is an outstanding example of gaining further insight through practical experience. Most likely the effect is caused by certain family members acting as nucleation inhibitor for crystallisation of one of the diastereomeric salts.[6,7] Subsequently, proper practical experience has led to the development of a set of resolving agent mixtures, which allows fast and efficient resolution of a wide range of salt forming racemates. A similar success in resolution through inclusion complexes would greatly enlarge the scope of traditional as well as Dutch Resolution processes. Therefore, a wide range of potential host compounds for complex formation was prepared, and tested with a variety of racemates for formation of inclusion compounds and possible resolution properties. The scope of inclusion resolution was found to be more limited than initially expected based upon the results published so far in literature. Supporting spectral and crystal studies were performed, which led to a better understanding of the experienced limitations, and which may be useful for future applications of this method.

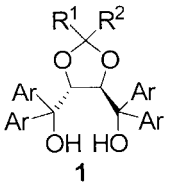
Results and Discussion

Selection and Preparation of Host Compounds

The easy access to enantiopure tartaric acid and lactic acid, together with the already known[1,2] successful results of their diol derivatives in inclusion resolutions, constituted a straightforward choice for the start of our studies. The range of diols, as published by Toda and Weber, could be easily extended by introducing a number of new substituents. This served to gain better insights in the importance of additional interactions in combination with the direct inclusion process, i.e. additional H-bonding, extra steric hindrance or reduced symmetry. To test the requirement of the diol moiety for success in inclusion resolutions several other derivatives were prepared. For similar reasons derivatives of malic acid and pantolactone were included. Scheme 1 gives an overview of the host molecules used in this study. The Taddols **1c**, **f**, **j**, **k**, **l** are new as well as the lactic acid derivatives **2b**, **e**–**g**, **i**–**n** and the potential hosts **3** and **4**.

As a potentially useful widening of the scope of inclusion resolutions also some readily available amino acids were chosen as starting materials for new host molecules. In order to cover a wide range of molecular diversity amino alcohols derived from alanine, phenylalanine, phenylglycine and proline were chosen; see Scheme 2. Also a number of

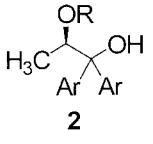
(*R*,*R*)-Tartaric acid derivatives (Taddols)



1

	R¹	R²	Ar
a	Me	Me	Ph
b	Me	Me	*o*-tolyl
c	Me	Me	*m*-tolyl
d	Me	Me	*p*-tolyl
e	Me	Me	*o*-anisyl
f	Me	Me	*m*-anisyl
g	Me	Me	*p*-anisyl
h	Me	Me	*p*-Cl-C_6H_4
i	cyclohexyl		Ph
j	cyclohexyl		*p*-tolyl
k	H	H	*p*-tolyl
l	H	Ph	*p*-tolyl
m	cyclopentyl		Ph

(*S*)-Lactic acid derivatives

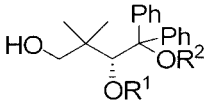


2

	R	Ar
a	H	Ph
b	H	*o*-tolyl
c	H	*m*-tolyl
d	H	*p*-tolyl
e	H	*o*-anisyl
f	H	*m*-anisyl
g	H	*p*-anisyl
h	H	*p*-Cl-C_6H_4I
i	H	*o*-CF_3-C_6H_4
j	H	*m*-CF_3-C_6H_4
k	H	*p*-CF_3-C_6H_4
l*	Ph	Ph
m*	*o*-anisyl	Ph
n	Me	Ph

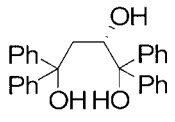
* inverted configuration (*R*)

D-Pantolactone derivatives



3 a: $R^1 = R^2 = H$
b: $R^1, R^2 = CMe_2$

L-Malic acid derivative



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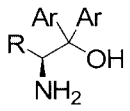
Scheme 1. Potential host compounds derived from enantiopure hydroxy acids.

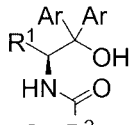
L-Amino acid derivatives



5

5	R	Ar
a	Me	Ph
b	Me	*p*-tolyl
c	Me	*p*-anisyl
d	Me	*p*-Cl-C_6H_4
e	Bz	Ph
f	Bz	*p*-tolyl
g	Bz	*p*-anisyl
h	Bz	*p*-Cl-C_6H_4
i	Ph	Ph
j	Ph	*p*-tolyl
k	Ph	*p*-anisyl
l	Ph	*p*-Cl-C_6H_4

Amides from L-amino acid derivatives

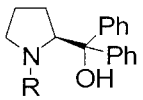


6

6	R^1	R^2	Ar
a	Me	Ph	Ph
b	Me	Ph	*p*-tolyl
c	Me	*p*-tolyl	Ph
d	Me	*p*-tolyl	*p*-tolyl
e	Me	*p*-anisyl	Ph
f	Me	*p*-anisyl	*p*-tolyl
g	Me	$(Ph)_2HC$	Ph
h	Me	$(Ph)_2HC$	*p*-tolyl
i	Bz	Ph	Ph
j	Bz	Ph	*p*-tolyl
k	Bz	*p*-tolyl	Ph
l	Bz	*p*-tolyl	*p*-tolyl

6	R^1	R^2	Ar
m	Bz	*p*-anisyl	Ph
n	Bz	*p*-anisyl	*p*-tolyl
o	Bz	$(Ph)_2HC$	Ph
p	Bz	$(Ph)_2HC$	*p*-tolyl
q	Ph	Ph	Ph
r	Ph	Ph	*p*-tolyl
s	Ph	*p*-tolyl	Ph
t	Ph	*p*-tolyl	*p*-tolyl
u	Ph	*p*-anisyl	Ph
v	Ph	*p*-anisyl	*p*-tolyl
w	Ph	$(Ph)_2HC$	Ph
x	Ph	$(Ph)_2HC$	*p*-tolyl

L-proline derivatives



7

a: R = H
b: R = PhCO
c: R = *p*-Tolyl-CO
d: R = *p*-Anisyl-CO

Scheme 2. Potential host compounds derived from amino acids.

N-acylated amino alcohols were included. Several of these compounds are new, i.e. **5c**, **f**, **g**, **h**, **j**, **k**, **l** and all representatives of **6** and **7** except **6a**, **6i** and **7a**, and none of them have been used in studies on inclusion resolutions. In total over 70 host compounds were prepared, many of them representing new examples of known types of derivatives. All compounds could be obtained employing known synthetic methods. Further details are available as Supporting Information.

Selection of the Racemic Guest Compounds

The racemates, i.e. the guests in the inclusion compounds to be formed, should represent a broad range of molecular diversity. All guests described in the literature so far, approximately 100, are relatively small compounds and most contain functional groups, suitable for hydrogen bonding with the host molecules. These two criteria have also played a major role in the selection of the guests used in the present research. Moreover, the guest molecules have been selected with respect to their industrial relevance and resistance to resolution by other known methods. Many of them constitute precursors for pharmaceuticals or other fine chemicals. Some of the selected racemates can be racemised under mild conditions and are therefore possible candidates for the application of asymmetric transformation. Table 1 gives an overview of all used guest compounds, divided into different categories. For comparative reasons also a small number of acids and bases, which can be resolved by other known methods, have been included; 34 racemates were tested in our studies. Together with the 100 examples already published but covering a smaller molecular diversity, a fair presentation of the scope and limitations of inclusion resolutions should be possible.

Resolution Experiments

Several standard methods for the execution of inclusion resolution experiments have been described. [8] The first, and most common is the combination of a host and a guest compound in a solvent, followed by crystallisation from solution. Since the optimal combination *ratio* is not known, the use of excess host as well as high excesses of guest is possible. The formation of the inclusion crystal in a well-defined host-guest *ratio* does not depend on the host-guest *ratio* in solution, but only on the stability of the inclusion crystal. The resolution process is simple to execute and the inclusion compound can be separated easily from the solution. Either liquid or solid guest compounds can be employed. However, the solvent itself may also be a suitable guest and might eventually become a competitor for the actual guest compound.

The second method uses a solvent in which host, guest or both are poorly soluble and a slurry is obtained. In this case the inclusion compound can both be formed by dissolution-recrystallisation or by direct absorption into the crys-

Table 1. List of potential guest compounds used in this study.

	Compound	Functionalities						
		Alcohol	Amine	Aromatic	Acid	Nitrile	Ether	Ketone/ester
G1	1-phenylethylamine		●	●				
G2	2-phenylglycinonitrile		●	●		●		
G3	2-amino-1-butanol	●	●					
G4	1-amino-2-propanol	●	●					
G5	2-amino-1-propanol	●	●					
G6	2-amino-3-methyl-1-butanol	●	●					
G7	3-pyrrolidinol	●	●					
G8	*trans*-2-methoxycyclohexanol	●					●	
G9	*trans*-2-methylcyclohexanol	●						
G10	*cis*-2-methylcyclohexanol	●						
G11	1-phenoxy-2-propanol	●		●			●	
G12	1-phenylethanol	●		●				
G13	tetrahydrofurfuryl alcohol	●					●	
G14	1-*tert*-butoxy-2-propanol	●					●	
G15	2-butanol	●						
G16	1,2-propanediol	●						
G17	5-hydroxy-3-methyl-2,5-dihydro-2-furanone	●						●
G18	3-nitro-2-pentanol	●						
G19	3-nitro-2-butanol	●						
G20	lactic acid	●			●			
G21	lactonitrile	●				●		
G22	mandelonitrile	●				●		
G23	solketal	●					●	
G24	1-phenyl-1,2-ethanediol	●		●				
G25	β-(chloro)isobutyric acid				●			
G26	ibuprofen			●	●			
G27	2-methoxycyclohexanone						●	●
G28	5-methoxy-5*H*-furan-2-one						●	●
G29	3,3a,4,8b-tetrahydro-2*H*-indeno[1,2*b*]furan-2-one			●				●
G30	propylene oxide						●	
G31	methyl phenyl sulfoxide			●				
G32	3-methylcyclohexanone							●
G33	3-aminopyrrolidine		●					
G34	*trans*-3-methylcyclohexanol	●						

tal lattice of a solid host. An advantage of this approach is that the solid material can act as a suitable template for nucleation, leading to easier preparation of a first batch of crystals.

The third method applied does not involve the use of any solvent. In this case either host or guest must be a liquid in which the other compound is dissolved or suspended. Simple grinding in a mortar sometimes works.[9] The separation of the solid inclusion compound from the excess of liquid guest can be more difficult. The major disadvantage of this technique is the restriction to the use of liquid hosts or guests.

Finally, the fourth method used in inclusion experiments is the sorption technique. In this method the gaseous guest compound is allowed to flow over the solid host compound and can be absorbed into the host's crystal lattice. Obviously, this technique is restricted to compounds, which are stable enough to be transferred into the gaseous phase. Thus, only small sized molecules with low boiling points are suitable for this approach. Also the need for special equipment makes the vapour sorption method the least favourable one.

Given the limited number of useful results in our elaborate experiments (see below) all methods were tested. Moreover, all known tricks and techniques to enhance crystallisation were applied, including slow evaporation of solvent, gradual temperature changes, the use of solvent mixtures (several host compounds do crystallise only as a solvate; also several inclusion complexes containing hydrates or solvates are known[10,11]), ultrasonic treatment after gel formation, high pressure (up to 15 kbar) and the application of mixtures of hosts (the Dutch Resolution approach).

Results of Inclusion Experiments

The number of successful resolutions was surprisingly low. Also reproduction of literature results was by no means a straightforward procedure. With 70 host compounds and 34 guest molecules in hand we performed several thousands of inclusion attempts using several of the methods summa-

rised above. Successful inclusion formations are given below together with an impression of the failed attempts.

Reproducibility: Experience in resolution through selective crystallisation teaches prudence in repeating literature results. Exact experimental conditions are often difficult to record. In particular crystal nucleation can be notorious in terms of reproducibility. Table 2 shows the poor reproducibility of literature procedures for inclusion resolutions in our hands.

Five attempts to repeat resolutions described by Toda (Entries 1–5), led in only one case to the documented inclusion complex (Entry 3). The resolution efficiency appears to be lower. In the other four batches pure crystals of the respective Taddols were obtained. Also results described by Weber using lactic acid derivative **2a** were only poorly reproducible. Resolutions of phenethylamine were unsuccessful in our hands as well as those with methyl cyclohexanol as guest racemate. Resolutions of methyl oxirane and methyl phenyl sulfoxide could be reproduced although with varying results. Summarizing, only 3 out of 10 literature examples could be reproduced and, moreover, with varying results.

Taddols as Hosts: Almost 200 successful inclusions have been described by Toda and co-workers, [18] involving close to 100 racemates, but using only 5 differently substituted Taddols (**1a**, **b**, **d** and **1i**, **m** with R^1, R^2 = $(CH_2)_4$ resp. $(CH_2)_5$ and Ar = phenyl) as resolving agents. In general the quality of these resolutions is excellent: Over 80% *ee* in 50% of all cases. Combined with yields of 80% (maximum yield of one enantiomer defined as 100%) or above the score drops to below 10%. All the latter results were obtained with Taddols bearing a phenyl group as aryl substituent; **1a** being the most successful resolving agent. Employing the solution method we performed 360 resolution attempts representing the 12 host Taddols **1a**–**l** and 34 of our guest racemates, **G1**–**34**. Inclusion crystals were obtained in 10% of all cases. Only 5 examples showed resolution of which a mere two with a quality of 0.8 (defined as $S = 2 \times ee \times$ yield), both using **1d** as resolving agent. One of the involved racemates, phenylethylamine, **G1**, has been resolved before through selective inclusion using **1a** as resolving host with a resolution quality of 0.58.[12] The successful resolution of *trans*-2-methoxycyclohexanol (**G8**), is new. The remaining 90% of our experiments gave − in equal numbers − formation of gels, or crystalline pure host compounds without guest included. See Table 3 for an overview of successful inclusion resolutions, and Table 4 for an overview of inclusions with inclusion of the racemic guest.

Table 3. Successful inclusion resolution experiments with Taddols.

Host	Guest	Ratio	Chirality guest	*ee*/ Method	Yield	*S*	Recovery method[a]
1b	**G20**	2:1	(*S*)	71% / I	11%	0.1	MeOH
1d	**G1**	1:1	L	95% / A	41%	0.8	MeOH
1d	**G8**	2:1	(*R*,*R*)	94% / D	39%	0.8	MeOH
1i	**G5**	1:1	n.d.	21% / A	24%	0.1	MeOH
1j	**G20**	2:1	(*S*)	66% / I	19%	0.2	MeOH

[a] MeOH: inclusion crystallisation of host with methanol, followed by standard isolation of guest.

Attempts to increase the score of positive results through the application of various other experimental set-ups were rather poor. We first attempted to induce crystallisations in solution at pressures up to 15 kbar. With this approach only the combination of **1d** with *trans*-2-methoxycyclohexanol (**G8**) produced inclusion crystals, furnishing the seeds for the positive result listed above. Repeating the successful resolution of phenylethylamine at pressures ranging from 3–15 kbar showed a small but consistent drop in *ee*.

Another 80 experiments using no solvent (using liquid guests in excess) did not give a single additional positive result, although the successful resolution of phenylethylamine could be reproduced albeit with an *ee* of 72% compared to 95% under solution conditions. Also vapour sorption techniques and grinding experiments gave no additional results, only showing that the good resolution of phenylethylamine with **1d** could be repeated, although with poorer efficiencies. We took our next resort to the Dutch Resolution approach using 10 different mixtures of the Taddols **1a**–**l**, each mixture consisting of 2 or 3 host molecules. In 300 experiments, using 30 guest racemates **G1**–**34**, 22 crystalline inclusion complexes were obtained. In 30% of our experiments gels were formed, whereas over 60% resulted in crystallisation of one or more host compounds containing no guest molecules. Compared to the 1:1 solution experiments the success rate is lower. Moreover, in all inclusion cases

Table 2.Reproducing literature results in inclusion resolutions.

			Literature result			This work		
Host	Guest	Ref.	Host-guest ratio	*ee* / Yield	Method	Host-guest ratio	*ee* / yield	Method
1a	**G1**	[12]	2:1	91/62%	cryst.	–	–	cryst.
1a	**G13**	[10]	n.d.[a]	21/n.d.	cryst.	–	–	cryst.
1i	**G5**	[13]	n.d.	69 (+)/n.d. and 100 (+)/n.d.	cryst. and fract. dist.	1:1	21 (n.d.)/24%	cryst.
1i	**G28**	[14]	n.d.	18(+)/91%	cryst.	–	–	cryst.
1i	**G30**	[15]	n.d.	52(+)/n.d.	cryst.	–	–	cryst.
2a	**G1**	[11,16]	1:1	8 (*R*) and 2.7 (*R*)/75%	cryst. and sorption	–	–	cryst.
2a	**G9**	[10,17]	1:1	35.3 (*S*)/64%	cryst.	–	–	cryst.
2a	**G10**	[17]	1:1	53 (*S*)/50%	cryst.	–	–	cryst.
2a	**G30**	[17]	2:1	9.3 (*R*) and 25(*R*)/90%	cryst. and sorption	2:1	10 (*R*)/25%	cryst.
2a	**G31**	[17]	1:1	32.8 (*S*)/72%	cryst.	1:1	87 (*S*)/30%	cryst.

[a] n.d.: not determined.

Table 4. Successful inclusion experiments without resolution using Taddols.

Host	Guest	Ratio	Yield	Recovery method[b]
1a	**G5**	1:1	42%	M
1a	**G7**	1:1	33%	M
1a	**G16**	1:1	12%	M
1b	**G6**	1:1	8%	M
1b	**G21**	3:2	22%	M
1b	**G23**	2:1	19%	M
1c	**G9**	2:1	23%	B/B
1c	**G25**	2:1	17%	B/B
1d	**G5**	1:1	13%	M
1d	**G7**	1:1	13%	M
1d	**G10**	1:1	18%	M
1d	**G16**	1:2	9%	M
1d	**G21**	1:1	18%	M
1d	**G25**	1:1	22%	M
1d	**G27**	1:1	23%	M
1e	**G23**	2:1	19%	B/B
1g	**G5**	1:1	9%	B/B
1g	**G7**	1:2	31%	B/B
1g	**G16**	1:2	22%	B/B
1i	**G3**	1:2	22%	M
1i	**G4**	1:2	24%	M
1i	**G6**	1:1	5%	M
1i	**G7**	1:1	11%	M
1i	**G16**	1:1	19%	M
1i	**G18**	1:2	22%	M
1j	**G4**	2:3	21%	B/B
1j	**G8**	1:1	34%	B/B
1j	**G9**	1:1	25%	B/B
1j	**G18**[a]	1:1	27%	B/B
1k	**G5**	1:2	33%	B/B
1k	**G6**	1:1	24%	B/B
1k	**G16**	1:1	27%	B/B
1k	**G20**	1:1	37%	B/B

[a] Resolution described in literature. [b] M: inclusion crystallisation of host with methanol, followed by standard isolation of guest. B/B: isolation of guest molecule by bulb-to-bulb distillation.

only a single resolving host was present, contrary to Dutch Resolutions employing diastereomeric salts. Furthermore, the quality of these resolutions lies below those of the 1:1 experiments, ranging from 0.2–0.6. The Dutch Resolution approach did, however, result in 4 new crystalline inclusion complexes not accessible through 1:1 batches: **1d·G19**; **1g·G3**; **1j·G21** and **1j·G23**. Disappointingly though, none of these complexes showed any optical activity, nor were these racemates resolvable in the 1:1 approach in which they formed inclusion crystals with some of the other host molecules (see Table 2).

Lactic Acid Derivatives As Hosts: A first series of solution experiments using **2a**–**e** as host and a selection of 11 guests (**G1**, **7**–**10**, **21**, **23**, **25**–**27** and **30**) gave only one example of crystalline inclusion: β-(Chloro)isobutyric acid (**G25**) with **2a** but showing no *ee*. In most cases the host compound crystallised (60%) or gels were formed (30%). A wider series using 7 hosts, **2a**–**f**,**k**, and 22 of our guest racemates (**G1**, **3**, **4**, **6**, **7**–**11**, **13**–**16**, **18**–**21**, **23**, **25**, **27**, **30** and **32**) in the solvent free fashion resulted in two hits: **2a·G25** as above and propylene oxide **G30** with **2a** as well. In both cases no resolution was observed. This solvent free approach gave mainly no crystallisations at all (50%) next to gels (20%) and host crystals (30%). Exploitation of solvent mixtures performed even worse, resulting exclusively in gel formation in 150 experiments. The Dutch Resolution approach was not any better producing only gels in the ca. 40 experiments employing **2a**–**d** and 12 selected guests: **G1**, **7**–**10**, **21**, **23**, **25**, **26**, **30**, **32**, **33**. To recheck the failure of this approach we repeated the resolution of **G31**, methyl phenyl sulfoxide, as described by Weber, [16,17] under various conditions. Single 1:1 experiments with **2a** gave successful resolutions in solution, as well as without additional solvent, with mediocre and varying efficiency from 0.2–0.4. However, application of host mixtures, composed from various combinations of **2a**, **b**, **d**, and **k**, completely destroyed these results: solutions remained clear for several months or stable gels were obtained resisting all attempts to induce crystal forming.

Other Hydroxy Acid Derivatives: Lactic acid-derived hydroxy ethers **2l**–**n** and pantolactone derivatives **3a**, **b** as well as malic acid derivative **4** were tested in a limited experimental set-up. Out of 20 racemates only inclusion crystals with lactonitrile, **G21**, were obtained, but unfortunately no resolution. Gelation was once more the most prominent phenomenon in all experimental variations, in particular with **2l** and **2n** as host molecules.

Amino Acid Derivatives: The amide derivatives **6a**–**x** and **7b**–**d** were tested in a first series of experiments. Given their capability for intra- and intermolecular H-bond formation we hoped for inclusion results comparable to the successful Taddols. Nothing was farther from the truth, however. The very low solubility of these hosts limited our experimental space, as inclusion will only occur if the complex has an even lower solubility. Only DMSO, or in some cases chloroform, could be used, next to a solvent free version. Experiments with 24 of our guest racemates did not result in a single inclusion crystal. The benzhydryl-substituted hosts all gave gel formation, and the proline derivatives gave clear solutions, even after several months. The big majority of all other amide hosts precipitated from the solution as pure compounds, taking several weeks or months to the onset of crystallisation. NMR analysis of the precipitated material proved the absence of any inclusion, neither guest racemate, nor solvent or water. Finally, experiments combining the amino-alcohols **5a**–**k** with the non-acidic representatives of our guest collection resulted only in gels. These experiments were limited to the Dutch Resolution approach.

NMR Shift Experiments: Given the limited success in our resolution experiments we looked for a quick test indicating chances for formation of inclusion complexes and resolution. As taddols have been used as chiral shift reagents for *ee* determination by NMR spectroscopy,[19] we considered this as a useful Entry. A strong interaction in solution, as indicated by an NMR shift, could indicate a higher probability for the forming of an inclusion complex. For example phenethylamine, which was successfully resolved with Taddol **1a**, shows some clear shifting and splitting of NMR

signals in solutions of the racemate in the presence of this Taddol.[19a]

To test this hypothesis shift experiments were performed with racemic lactonitrile and 4 different Taddols. Taddols **1b** and **1d** were chosen because inclusion crystals (no resolution) were already obtained with lactonitrile in the crystallisation experiments (see Table 4), and Taddols **1a** and **1j** because these produced no inclusion crystals. The NMR signal of the methine proton of lactonitrile was split in the presence of Taddols **1a**, **1b** and **1d**. In the presence of Taddol **1j** no shift of the proton signal of lactonitrile was observed. Although the initial results were not conclusive the usefulness of NMR in predicting potential host-guest interactions was further explored by studying 4 of our lactic acid derived hosts, **2a**,**b**,**d**, and **e**, with a selection of 11 of our racemates. Results are collected in Table 5.

Comparing these results with the actually obtained inclusion crystals from hosts **2a**–**k**, as described previously, it becomes quite clear that useful predictions based on NMR cannot be made. Similar unsatisfactory results were obtained in shift experiments with hosts **2l**–**n** and **3a**, **b**. Also the application of host mixtures, to predict Dutch Resolution effects, produced no useful results.

Crystal Studies

We have found that in most cases of successful inclusion complex formation these can be rationalised in hindsight using information derived from an X-ray crystal structure determination. Also crystallisation of the pure host molecule can often be understood by inspecting the crystal structure. Contrary to resolutions through diastereomeric salts, where mainly strong ionic forces are directing crystal formation (and in which both ions must be present to maintain neutrality), participants in inclusion resolutions are involved in more subtle interactions allowing energy minima in crystals of various compositions: inclusion complexes of host and guests in various ratio's and enantiomeric excesses or crystals of hosts with or without inclusion of solvents. Thus, by studying a large number of crystal structures, both from the literature and this work, we could rationalize most of the observed results. However, studying crystal properties to predict resolutions is a highly risky approach as recently mentioned by Dunitz. [20]

Taddols as Hosts: A literature survey has shown that the Taddols tend to show characteristic behaviour in binding to their included guest molecules, independent of the final complex structure. Depending on the respective guest compound, the Taddols can form cavities, channels or layers, in which the guest molecule is embedded. Five of the inclusion complexes obtained in our studies were found to be suitable for analysis by X-ray: Taddol **1d** with (*R*,*S*) as well as racemic phenylethylamine (**G1**) and with *trans*-2-methoxycyclohexanol (**G8**), and Taddol **1j** with lactic acid (**G20**).

In the 1:1 inclusion complex of Taddol **1d** and (*R*)-phenylethylamine the two hydroxy groups of the Taddol molecule are hydrogen-bonded to each other, leaving one hydroxy hydrogen in a free position to form a hydrogen bond to an acceptor site of the guest molecule. Whereas suitable crystals of (*S*)-**G1** with **1d** could easily be obtained, usable crystals with (*S*)-**G1** could only be obtained containing 65% (*S*) only (*ee* = 30%). Also crystals containing 50% of both (*S*) and (*R*), i.e. the racemate, could be grown. The crystals with an equal amount of (*S*) and (*R*) clearly showed solid solution of the amine guest. A comparison of the (*S*) and (*R*) structures shows hardly any differences, which is consistent with the results of X-ray powder diffraction analyses, which were found to be nearly identical (see Figure 1).

In the 2:1 inclusion inclusion complex of Taddol **1d** and (*S,S*)-*trans*-2-methoxycyclohexanol (**G8**) the two hydroxy groups of both Taddol molecules are again internal hydrogen-bonded to each other, leaving one hydroxy hydrogen in a free position to form a hydrogen bond to the guest molecule or to the other Taddol molecule. In this inclusion complex both Taddols form a dimer, which is then hydrogen-bonded to the guest. The X-ray crystal structure of this inclusion compound is depicted below in Figure 2.

In the 2:1 inclusion complex of Taddol **1j** and (*S*)-lactic acid **G20** (Entry 34), the two hydroxy groups of both Taddol molecules are again internal hydrogen-bonded to each other, leaving one hydroxy hydrogen in a free position to form a hydrogen bond to the guest molecule. In this inclusion complex the two Taddols do not form a dimer, but

Table 5. H NMR-shift experiments with lactic acid derived diols.

Guests	Hosts ($\Delta\delta$ = shifting or splitting in ppm)			
	2a	**2b**	**2d**	**2e**
trans-2-methoxycyclohexanol (**G8**)	0[a]	0.023 (OCH_3)	0	0
cis-2-methylcyclohexanol (**G10**)	0	0	0	0
trans-2-methylcyclohexanol (**G9**)	0	0	0	0
3-pyrrolidinol (**G7**)	0	0	0	0
β-chloroisobutyric acid (**G25**)	0	0	0	0
ibuprofen (**G26**)	0	0	0	0
lactonitrile (**G21**)	0.020 (OC*H*)	0.024 (OC*H*)	0.023 (OC*H*)	0.034 (OC*H*)
1-phenylethylamine (**G1**)	0.028 (NC*H*)	0	0.021 (NC*H*)	0.038 (NC*H*)
solketal (**G23**)	0	0	0	0
propylene oxide (**G30**)	0	0	0	0
2-methoxycyclohexanone (**G27**)	0	0.021 (OCH_3)	0	0

[a] 0: no visible shifting or splitting of signals.

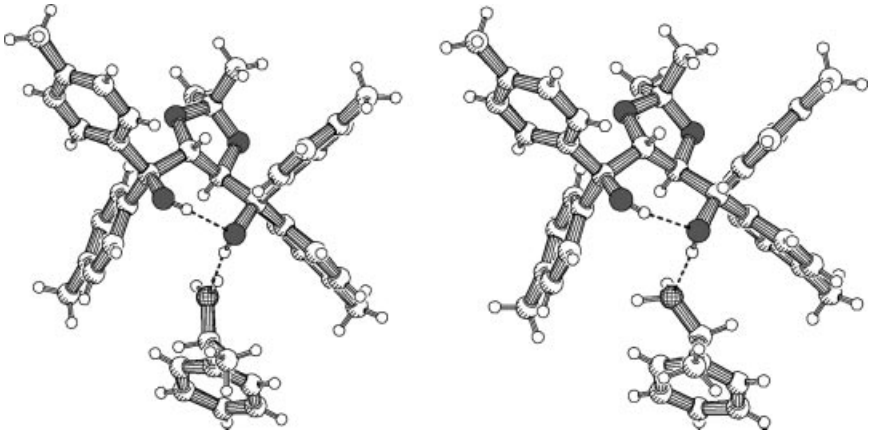


Figure 1. A PLUTON drawings of the 1:1 inclusion complexes of Taddol **1d** with (*R*)-phenylethylamine and with (*S*)-phenylethylamine (in crystals containing 65% *S*).

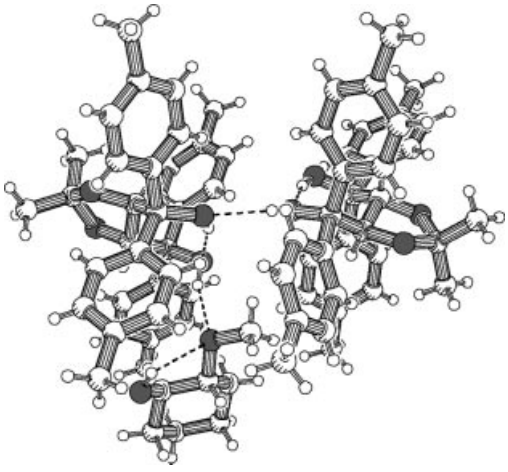


Figure 2. A PLUTON drawing of the inclusion complex of Taddol **1d** and (*R*,*R*)-*trans*-2-methoxycyclohexanol (G8).

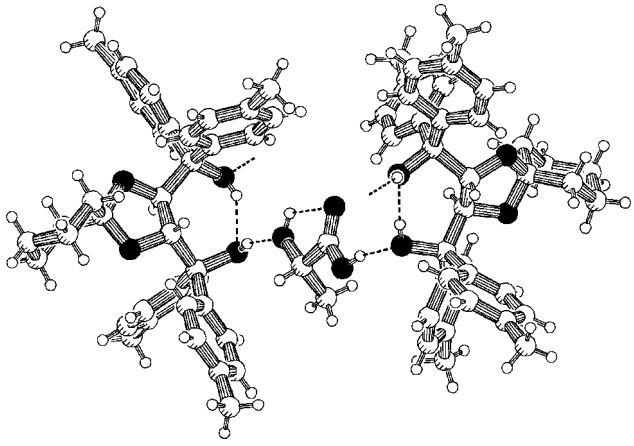


Figure 3. A PLUTON drawing of the inclusion complex of Taddol **1j** and (*S*)-lactic acid.

the guest molecule is hydrogen-bonded to one Taddol with its alcohol function and with its acid function to the other Taddol molecule. Additionally, the guest forms an internal hydrogen bond; see Figure 3.

Taken into account that these three guests already give three completely different binding motifs it is clear that any attempt at prediction a priory will be extremely difficult.

Lactic Acid Derivatives as Host: Also crystal structure data of lactic acid derived hosts were studied in some detail, combining newly generated data and literature results. Over 30 inclusion complexes with this type of hosts are known, including our work, but only for 12 structures crystal data are available (see Table 6). Several structure parameters were investigated, including molecular shape and rigidity, hydrogen bonding networks and crystal stabilities.

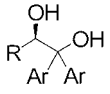
Conformations of hosts in pure form compared to those in inclusion complexes were found not to show very large differences indicating that the conformation of the host molecules remains similar in most cases despite the higher flexibility of these compounds when compared to the Taddols. In all molecules, with the exception of, **2r**, the alcohol groups are very close to each other. The predominance of the internal hydrogen bond, that forces the molecules into a specific shape, is also responsible for a high degree of dissymmetry, which could be related to enantioselectivity in resolutions. Thus, the presence of the strong internal H-bond should in fact be favourable for resolution processes. Due to the observed similarities in the conformation of the host structures it must be concluded that based on conformation alone the compounds cannot be discriminated as "bad" or "good" hosts.

A closer inspection of pure host structures with their inclusion structures delivers some interesting results. Host **2a**, for example, has in the inclusion crystals similar α torsion angles as in the pure host lattice, but shows substantial changes in torsion angles β_1 and slighter changes in β_2 (Table 7).

Obviously, the host molecule is flexible enough to adapt its structure somewhat to the included guest. The guest induces within the limits of the molecular folding a certain shape for the host structure (*Induced Fit*). Host **2o** (another good host with 6 reported inclusion complexes), which is

Table 6. Summary of known crystal structures of lactic acid related hosts

Host	2a	2o	2p	2q	2r	2s	2t	2u
Number of inclusion complexes	15	6	2	3	3	1	2	1
Complexes with crystal data available	4	1	0	0	3	1	2	1
Included guests	3-picoline, G25, G31, G32	3-picoline			MeOH, *N*-methylformamide, acetic acid	DMF, DMSO	DMF	EtOH



2

	R	Ar		R	Ar
a	CH_3	Ph	**r**	Ph	Ph
o	CH_3	4-*t*BuC_6H_4	**s**	Ph	4-*t*BuC_6H_4
p	CH_3	1-naphthyl	**t**	*p*-Tol	4-*t*BuC_6H_4
q	CH_3	4-biphenyl	**u**	$CH_2C(OH)Ph_2$	Ph

Table 7. Torsion angles of host **2a** and its inclusion compounds.

	Pure host **2a**	Inclusion complexes (mean value)	Standard deviation	Max. angle	Min. angle
α_1	–64.27°	–58.97°	4.01°	–64.1°	–54.9°
β_1	53.85°	34.48°	24.72°	60.11°	12.39°
β_2	–45.28°	–59.65°	12.34°	–71.61°	–47.66°

structurally very similar to **2a**, will have the same degree of flexibility. However, comparing the crystal structures of the pure host **2r**–**t** and its inclusion compounds it can be seen that in these cases the angles α, β_1 and β_2 remain almost the same which is expressed through the small deviation values (Table 8) compared to the values of host **2a** in Table 7. This indicates that these hosts have a much higher molecular rigidity with a diminished possibility to adapt their structure to a guest molecule.

Table 8. Torsion angles of inclusion compounds of the hosts **2r**–**t**.

	Inclusion complexes of hosts **2r**,**s** and **t** (mean value)	Standard deviation	Max. angle	Min. angle
α_1	–61.97°	2.44°	–64.18°	–57.51°
β_1	23.40°	5.89°	32.32°	15.47°
β_2	–66.03°	5.03°	–75.96°	–60.81°

If a guest is included in these hosts it must fit into a more rigid framework (*lock and key* principle). Small molecules, which hardly disturb the formation of the host lattice, can be included, confirmed by the successful inclusion of solvent type molecules only as shown in Table 6.

Hydrogen Bonds: The presence and direction of hydrogen bonds is of great importance for the stability and enantioselectivity of inclusion crystals. A strong hydrogen bond between host and guest, usually with the host acting as proton donor, appears to be essential in most cases. The presence of multiple strong intramolecular hydrogen bonds usually indicates a poor host, especially if all suitable substituents are involved. It is therefore unlikely that the compounds **2e**, **2i** and **2l**–**n** can act as efficient hosts, as their hydroxy functions are all tied up in intramolecular hydrogen bonds. This is apparent from the X-ray structures of these compounds, and an example of this is shown in Figure 4. In the case of compound **2e** a hydrogen bonded dimer is formed, a pattern which is observed in several of these compounds, pure hosts as well as in inclusion complexes. However, in this molecule the second hydroxy function forms a strong intramolecular hydrogen bond with the *o*-methoxy group of the aryl function, thus making it unsuitable for complexating guest compounds via intermolecular hydrogen bond donation. The *o*-CF_3-phenyl group of **2i** probably leads to the same disadvantage.

Further analysis of the available structures of inclusion crystals with preferential inclusion of one enantiomer of a racemate showed that in these cases always an intramolecular hydrogen bond directed from the tertiary alcohol to the secondary one is present. Figure 5 shows the X-ray structure of the 1:1 inclusion compound of host **2a** and (*S*)-methyl phenyl sulfoxide, **G31**, and Figure 6 shows the X-

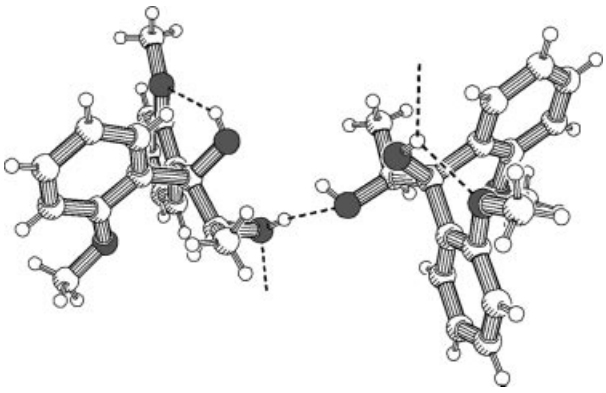


Figure 4. PLUTON drawing of the X-ray structure of host **2e** showing strong internal hydrogen bonds.

ray structure of the 2:1 inclusion compound of host **2a** and (*R*)-3-methylcyclohexanone (**G32**). In both complexes the tertiary alcohol donates its hydrogen to the secondary one, which in turn acts as donor to complex the guest molecule. This creates a more rigid system with lower symmetry compared to hosts without such a H-bond system. Without it, a more flexible host would result, with a lower probability of imposing enantioselectivity on the included guest. In effect it removes the pseudo-mirror plain which would otherwise be present in the host. Thus, the higher degree of rigidity and dissymmetry make it more likely that only one enantiomer of a racemate is included preferentially.

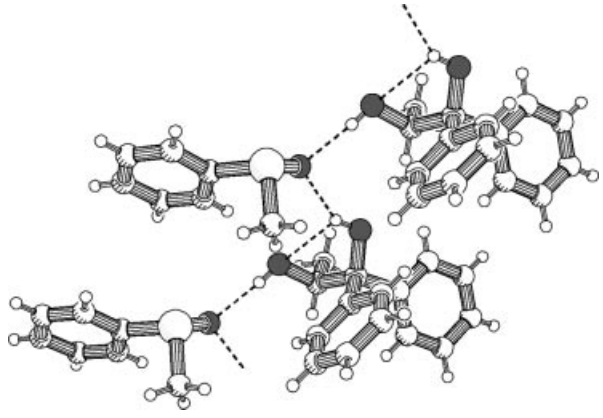


Figure 5. PLUTON drawing of the X-ray structure of the 1:1 inclusion compound of host **2a** and (*S*)-methyl phenyl sulfoxide (**G31**).

Crystal stability data, derived from DSC experiments, confirm these preliminary conclusions. For host **2a** and some of its inclusion complexes the stability of an inclusion crystal is higher than that of the pure host crystal. Also the inclusion crystal with an optically enriched guest is more stable than a crystal, which includes a racemic guest (see Table 9). All of these inclusion compounds show a similar H-bond system. Clearly, for a compound to be suitable as a host it should have a not too stable crystal structure. Crystal structure analysis of the pure host can provide useful insights to these aspects.

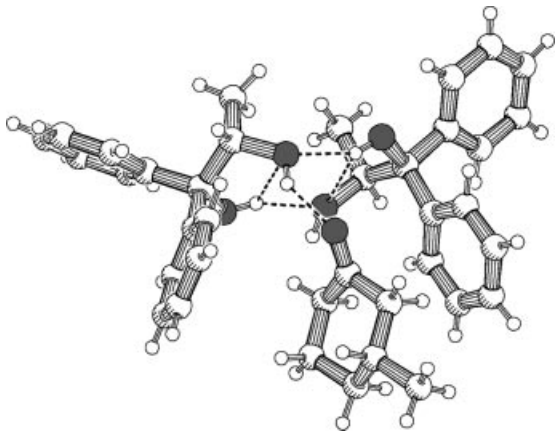
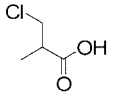


Figure 6. PLUTON drawing of the X-ray structure of the 2:1 inclusion compound of host **2a** and (*R*)-3-methylcyclohexanone (**G32**).[21]

Table 9. Available inclusion crystal structures of host **2a** and approximate stability data.

Chiral guests	Host-guest ratio	*ee* (%)	Heat of fusion ΔH (J/mol)	Free enthalpy ΔG_{KT} (J/mol)
	2:1	>99 (*R*)	73.63	11.27
	1:1	87 (*S*)	43.12	8.39
	1:1	0	39.39	6.00
None	N.A.	N.A.	22.6	4.43

Thus, taken into account the importance of hydrogen bonds, an analysis of the crystal structures of some potential hosts reveals why they are unlikely to give inclusion complexes. In **2f** the tertiary alcohol forms a hydrogen bond to the *m*-anisyl group of a neighbouring molecule (see Figure 7). The overall effect is the same as in **2e** (with the *o*-anisyl substituent): stabilisation of the crystal structure of the free host and no hydrogen bonding site available for external interaction. The methoxy, trifluoromethyl and chloro substituents in resp. **2g**, **h**, **j** and **k** might induce similar stabilisation effects.

The tolyl-substituted hosts **2b**–**d** have found other means to stabilize their structures and prevent formation of inclusions. In the case of host **2d** a fascinating crystal structure shows that four molecules form a tetramer (see Figure 8).

The hydrophilic alcohol groups are forming a complex with each other in the centre of the tetramer and the hydrophobic *p*-tolyl groups are directed outside. Host **2v**, where a *p*-tolyl group replaces the methyl substituent of **2d** and the aryl substituents are phenyls, shows a similar effect; now two molecules form a dimer (see Figure 9), leading to com-

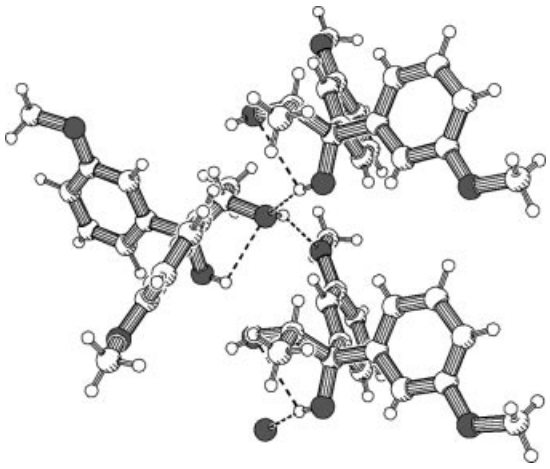


Figure 7. PLUTON drawing of the X-ray structure of host **2f**.

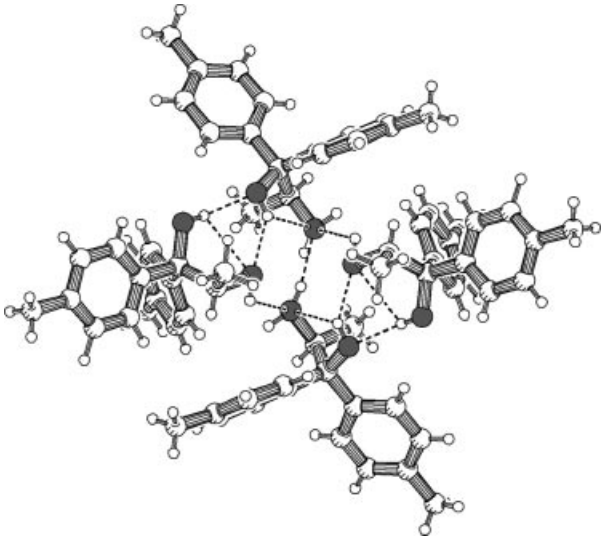


Figure 8. PLUTON drawing of the X-ray structure of host **2d**, forming a tetramer.[22]

parable barriers to formation of inclusion complexes. The hydrogen bonds are encapsulated in a polar region between two host molecules. Although there is still a hydroxy group available for hydrogen bonding to a guest, the formation of the dimer makes this site sterically less accessible.

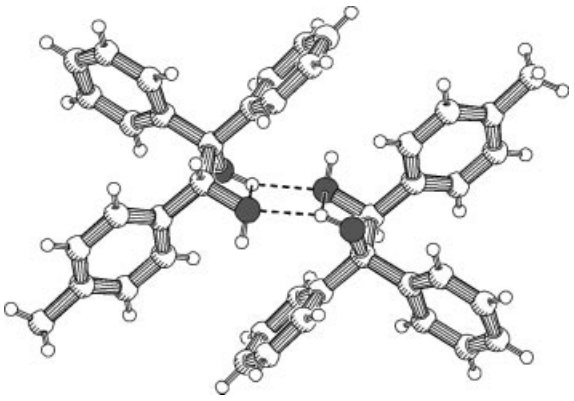


Figure 9. PLUTON drawing of the X-ray structure of host **2v** forming a dimer.[23]

As mentioned before, it may be expected that molecules with a crystal structure of low stability will be better hosts. The relative crystal stabilities at room temperature of a number of (potential) hosts were calculated from melting points and heats of melting determined by DSC. If the calculated ΔG values are lower or similar to the one of known *good* hosts − such as with **2a** − inclusion capabilities could be expected. However, if these values are relatively high it is less likely that a more stable crystal can be obtained through inclusion. The results in Table 10 confirm the relation between the absence of inclusions with compounds **2e**, **f**, **l**, and **m**, and their relatively high stability.

The pure compounds **2b** and **2c**, and to a lesser degree **2d**, however, are less stable than **2a**; consequently these compounds would be expected to be good hosts as well. The failure of compounds **2b** and **c** to give inclusion compounds remains puzzling. So far no satisfactory explanation could be found why these compounds do not give any inclusion, but in the over 80 attempts made, gel formation occurred in approximately one third of the cases. This might be preventing the forming of actual inclusion crystals.

Conclusions

The crystal studies of host and inclusion compounds proved to be very useful tools to understand the interactions between hosts and guests. Successful formation of inclusions and resolutions can usually be explained, and also the reasons for the lack of success in a great number of candidate host molecules could be determined by examina-

Table 10. Approximate heat of fusion and free heat of fusion values of some pure host compounds.

	Hosts							
	2a	**2b**	**2c**	**2d**	**2e**	**2f**	**2l**	**2m**
ΔH [kJ/mol]	22.6	20.6	22.4	21.9	25.4	33.4	25.9	30.3
M. p. [K]	364.9	348.9	353.9	365.1	371.1	357.6	409.5	384.4
ΔS [kJ/mol K]	0.062	0.059	0.063	0.060	0.068	0.093	0.063	0.079
$\Delta G_{(298)}$ [kJ/mol]	4.425	3.304	3.932	4.31	5.466	6.137	7.432	7.141

tion of their crystal structures. Although a number of conditions can be defined for enhancing successful inclusions (see below) it should be noted that in crystal formation there are always many ways for the molecules involved to find their own unique path to a stable crystal structure. These include the numerous possibilities for formation of polymorphic structures as recently discussed by Dunitz.[20] Formation of dimers, trimers or tetramers, inclusion of solvents, variation in stoichiometry and many other ways are acceptable to reach stable crystal configurations. Rational design and predictability are therefore perilous undertakings. Practice has shown how subtle differences in interactions in diastereomers can lead to completely different crystal structures and huge differences in solubility within a diastereomeric pair. An extreme example is the well known resolution of *dl*-phenylglycine with camphor sulphonic acid.[24] Nevertheless, the very few successful new inclusion resolutions found in our studies and the problems experienced in reproducing literature results leads to the conclusion that the scope of this type of racemate resolution is much more limited than initially expected. This is important from an industrial point of view as well as for more fundamental reasons. It is quite clear that the limitations of resolutions through diastereomeric salts cannot be eased through applying the inclusion approach. A quick testing of a range of resolving agents and swift formation of crystals as in Dutch Resolutions is not possible. Salt formation predominantly enhances chances for stable diastereomeric crystals (in which one or both enantiomers of the racemate to be resolved are present by definition), whereas in inclusion resolutions the partners are left with many choices to reach a stable end situation, either individually or in combinations. Given these limitations we can still see some communality in host structures with favourable properties for inclusions.

Taking literature results together with our work, over 125 successful inclusion resolutions using Taddols are currently known. Given our extensive experiments it is rather remarkable that only 5 resulted from our work. To a certain extent this might be explained by the sometimes structurally very closely related series of guest racemates used by Toda and colleagues. First of all hydrogen bonds are the key factor for success. Given the C_2 symmetry in most Taddols directional effects as with the lactic acid derived examples do not play a role. In the latter the direction of the hydrogen bonds is of special importance for inclusion resolution: internal H-bond from the tertiary to the secondary OH, external H-bond from the secondary OH to the guest molecule. Preferably the host molecules act as H-bond donors. A potential host must possess both a definite grade of rigidity, necessary for inclusion and inclusion resolution, but a certain degree of flexibility allowing an *induced fit* of a guest is beneficial. A low stability of the pure host crystals is probably necessary, as it enhances the possibility that including a guest will produce a more stable crystal. Inclusion of solvates or poor crystal habits of the host molecules can be good indicators for formation of inclusion complexes.

Racemic guest compounds should possess a hydrogen bond forming site (acceptor sites appear to be preferred). Analysing all literature examples of inclusion resolutions published by Toda et al. and Weber et al.it becomes clear that about 80% of the guests resolved in high enantiomeric excess, act as hydrogen-bond acceptors like ketones, sulfoxides or amines. A certain high degree of dissymmetry is required to allow the formation of two different inclusion structures with sufficient differences in stability and solubility, required for resolution. Experience showed that the use of liquid guests acting as solvent, increases the chance of inclusion crystallisation.

Our results show clearly a decrease in successful formation of inclusion compounds in every step moving away from the Taddol structures. The switch to lactic acid derivatives already results in a dramatic decrease in resolving abilities. Blocking the secondary alcohol function is not allowed (see results with **2l**–**n**) whereas adding extra hydrogen bonding hydroxy groups as in the pantolactones and the malic acid derivatives opens to many opportunities to reach stable solid phases (gels or crystals) without any inclusion. Replacing a hydroxy function by an amine or acylated amine moiety has a similar effect. The amine function allows for additional stabilizing hydrogen bonds between the host molecules itself resulting in tenacious gels (as in **5a**–**k**) or solids with very low solubility as in the amide series **6**.

All in all it has become clear that inclusion resolutions are of limited scope only and of little use in practical or industrial development of resolutions through selective crystallisation. The energetically favourable ionic interactions in separations through diastereomeric salts precludes many alternative crystallisation options compared to when this electrostatic factor is absent. In inclusion resolutions these other options too often frustrate successful enantiomer separations. Some scattered examples using completely different host molecules, such as the dipeptide derived from phenylglycine (resolving sulfoxides)[25], and *N*-octylglucamine (resolving Naproxen),[26] do not effect these statements.

Experimental Section

General Remarks: ^{1}H NMR spectra were recorded with a Bruker AC-100 or with a Bruker AC-300 (300 MHz, FT) spectrometer with tetramethylsilane as internal standard and the software WinNMR spectroscopy. IR spectra were run with a Perkin–Elmer 298, Perkin–Elmer FTIR 1720-X or ATI Mattson Genesis series FTIR spectrophotometer using Winfirst as software. Elemental analyses were performed with a Carlo–Erba instruments CHNSO 1108 elemental analyzer. For mass spectroscopy, a double focusing VG 7070E was used. For the chemical ionisation (CI) technique, methane was used as reacting gas. GC-separation was carried out on a fused silica-capillary column (DB-5, 30 m × 0.25 mm, film thickness 0.25 mm). Melting points were measured with a Reichert Thermopan microscope (uncorrected), a Büchi Melting Point B545 instrument or with a Perkin–Elmer DSC7 instrument. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at 589 nm, equipped with a quartz cell of 1.00-dm path length. The polarimeter was connected with a thermostat for exact temperature control and a recorder for continuous optical rotation measurements. GCwas performed with a Hewlett–Packard 5890 or 5890

Series II instrument, equipped with a capillary HP cross-linked methyl silicone (25 m × 0.31 mm) column, connected to a HP 5890 calculating integrator. Chiral GC was performed using a chiral B-DEX 120 capillary column (Supelco) or a WCOT Fused Silica 25 m × 0.25 mm, CP Chirasil-Dex CB DF 25 m, Varian with H_2 as carrier gas with a HP 6890 instrument. DSC thermograms were recorded with a Perkin–Elmer DSC7 instrument. Calibration was performed with In and Zn, Sn or Pb depending on the temperature range. Samples were prepared by the method described by Jaques, Collet and Wilen.[29] Samples were measured in stainless steel large volume pans (75 mL) or aluminium pans (30 μL) at a rate of 10 °C/min. HPLC was performed on a Shimadzu 10A VP liquid chromatograph equipped with a reverse phase column by Alltech (Econosphere, C8, 5u, 0.46 cm Ø × 25 cm), a chiral Daicel Chiralcel OD-H column (25 × 0.46 cm, particle size: 5 mm) or a chiral Daicel Chiralcel OB column (25 × 0.46 cm, particle size: 5 mm) with filtered hexane/2-propanol mixtures as mobile phase. Detection was at 254 nm and 222 nm and the flow rate was 0.5 mL/min at ambient temperature. Class VP 5.0 was the software used. Capillary Electrophoresis was performed on a HP 3D CE with the software HP 3D CE-Chemstation. For column chromatography, the flash technique was used with silica gel 60H (Merck) as stationary phase and a pressure of about 1.5 bar. Thin-layer chromatograms were run on glass-supported silica gel 60 plates (0.25-layer, F_{254}, Merck). Compounds were detected using UV and oxidizing reagents, i.e. 5% H_2SO_4 in ethanol or a mixture of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (21 g), $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (1.8 g), water (469 mL) and 97% H_2SO_4 (31 mL). Dry solvents were obtained as follows: Dichloromethane was distilled from phosphorus pentoxide. Diethyl ether was predried with calcium chloride and distilled from calcium hydride. Hexane and benzene were distilled from calcium hydride. Triethylamine and phenylethylamine were distilled from potassium hydroxide. Tetrahydrofuran was distilled from lithium aluminium hydride and ethyl acetate from potassium hydrogen carbonate. All other solvents and reagents were either p.a. or technical quality and used as obtained from the supplier.

Synthesis of Host Compounds: All host compounds were prepared according to known procedures. The starting hydroxy or amino acid was esterified using thionyl chloride in methanol, followed by arylations with a Grignard reagent or aryllithium derivative. Acylation of amino alcohols could efficiently be done using acid chlorides and standard Schotten–Baumann procedures. No *O*-acylation was observed. Most taddols, **1a**–**l**, were purified through chromatography followed by crystallisation. The host compounds derived from lactic acid, malic and amino acids could be purified by crystallisation only. Full details are available as Supporting Information (for Supporting Information see also the footnote on the first page of this article).

Guest Compounds: Racemic or optically pure guest compounds were obtained from regular commercial sources and purified and analysed were appropriate, using general methods shown below.

General Procedures for Inclusion Resolutions: Several experimental techniques were used to reach successful crystallisation in resolutions, including all common methods and tricks to induce nucleation and crystal formation. A representative selection is given below, using the Taddols as example.

General Procedure for Crystallisation Experiments with Individual Taddols in Solvent: The pure Taddols were dissolved together with the respective guest compound in hexane/toluene (1:1) or heptane and then filtered. Most experiments were executed in a host/guest ratio of 1:1 at room temperature. In those cases in which crystals were obtained, they were filtered off, washed with heptane and analysed for the presence of the respective guest compound by ^{1}H NMR analysis. If an inclusion complex was obtained, the *ee* of the guest included was determined. (see also below).

General Procedure for Crystallisation Experiments Under High Pressure: The pure Taddols were dissolved together with the respective guest compound in heptane and then filtered. The experiments were executed in a host/guest ratio of 1:1 at room temperature using 15 kbar of pressure for five hours.

General Procedure for Crystallisation Experiments with Individual Taddols: The Taddol was dissolved in the liquid racemic guest compounds while boiling. The mixtures were cooled to room temperature and filtered. In those cases in which crystals were obtained, they were filtered off, washed with heptane and analysed for the presence of the respective guest compound by ^{1}H NMR analysis. If an inclusion complex was obtained, the *ee* of the guest included was determined.

Procedure for Vapour Sorption Experiment: Racemic guest compound (i.e. phenylethylamine) was heated in a flask to 110 °C while powdered Taddol was kept in a small tube inside the flask, separated from the liquid amine. After 30 min the test tube was removed and analysed for the presence and the *ee* of included phenylethylamine.

Procedure for Grinding Experiment: Taddol and racemic guest (i.e. phenylethylamine) were mixed and ground in a mortar for 20 minutes. Solid host and liquid guest were combined in a ratio of 1:1 or 1:2. The solid was then washed with heptane and analysed. Inclusion complexes, when formed, were treated and analysed as above.

General Procedure for Crystallisation Experiments with Mixtures of Taddols: Various mixtures of the Taddols were dissolved with the respective guest compound in hexane/ toluene (1:1) or heptane and then filtered. They were used in a host/guest ratio of 1:1. Work-up and analysis of obtained crystals was as above.

General Procedures for *ee* Determination; Derivatisation with Benzoyl Chloride: Equal amounts of guest compound, benzoyl chloride and $NaHCO_3$ were mixed for 20 min. Then a few mL heptane were added and the reaction mixture was stirred for another 20 minutes. After filtration, the solvent was evaporated and the residue analysed for *ee* (see Table below).

Derivatisation with Camphonyl Chloride: Guest compound (5 mmol) was stirred in 25 mL of pyridine at 0 °C while 1.36 g (6 mmol) camphonyl chloride was added slowly. After stirring overnight, 2 mL MeOH were added and the solvents evaporated. After dissolving in 100 mL CH_2Cl_2, the product was washed with H_2O, 1 M $NaHCO_3$ and H_2O, dried and analysed for *ee* (see Table 11).

Supporting Information: Experimental details and properties of the tartaric acid, lactic acid, and amino acid derivatives are available as Supporting Information. Details of the crystal data and data collection of the complex **1d** with (*R*), (*S*), and racemic phenethylamine, the complex of **1d** with (*S,S*)-*trans*-2-methoxycyclohexanol, the complex of **1j** with (*S*)-lactic acid, the complex of **2a** with (*S*)-methyl phenyl sulfoxide, and the compounds **2e** and **2v** are also available.

X-ray Crystallographic Study: Crystallographic data for the structures described in this paper are available:

(4*R*,5*R*)-4,5-Bis[bis(4-methylphenyl)hydroxymethyl]-2,2-dimethyl-1,3-dioxolane (**1d**), complex with (*R*)-1-phenylethanamine (**G1**) (1:1); see Figure 1; CCDC-246184.

Table 11. Methods applied to determine the *ee*.

	ee Determination method	can be applied to
A	camphonyl chloride derivatisation, chiral GC, β-CD	R1,R3–5
B	optical rotation	R2,R6,R9–10,R15–R17,R21–R23,R25–R30
C	benzoyl chloride derivatisation, chiral HPLC, OD-H	R7,R11
D	camphonyl chloride derivatisation, ^{1}H NMR	R8
E	chiral HPLC, OD-H	R12
F	benzoyl chloride dervatisation, chiral HPLC, OB	R13
G	chiral GC, β-CD	R14,R18
H	benzoyl chloride derivatisation, chiral GC, β-CD	R19
I	diazomethane derivatisation, chiral GC, β-CD	R20
J	chiral HPLC, OB	R24

(4*R*,5*R*)-4,5-Bis[bis(4-methylphenyl)hydroxymethyl]-2,2-dimethyl-1,3-dioxolane (**1d**), complex with (*S*)-1-phenylethanamine (**G1**) (1:1); see Figure 1; CCDC-246185.

(4*R*,5*R*)-4,5-Bis[bis(4-methylphenyl)hydroxymethyl]-2,2-dimethyl-1,3-dioxolane (**1d**), complex with (*rac*)-1-phenylethanamine (**G1**) (1:1); CCDC-246186.

(4*R*,5*R*)-4,5-Bis[bis(4-methylphenyl)hydroxymethyl]-2,2-dimethyl-1,3-dioxolane (**1d**), complex with (1*R*,2*R*)-2-methoxycyclohexanol (**G8**) (2:1); see Figure 2; CCDC-246187.

(2*R*,3*R*)-2,3-Bis[bis(4-methylphenyl)hydroxymethyl]-1,4-dioxa-spiro[4.5]decane (**1j**), complex with (*S*)-2-hydroxypropanoic acid (**G20**) (2:1); see Figure 3; CCDC-246188.

(*S*)-1,1-Bis(2-methoxyphenyl)propane-1,2-diol (**2e**); see Figure 5; CCDC-246189.

(*S*)-1,1-Diphenylpropane-1,2-diol (**2a**), complex with *S*-methyl phenyl sulfoxide (**G31**) (1:1); see Figure 6; CCDC-246190.

(*S*)-1,1-Bis(3-methoxyphenyl)propane-1,2-diol (**2f**); see Figure 8; CCDC-246191.

CCDC-246184 to -246191 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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