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# Guest dependent inversion of enantiomeric recognition in dehydrocholic acid host–guest enclathration

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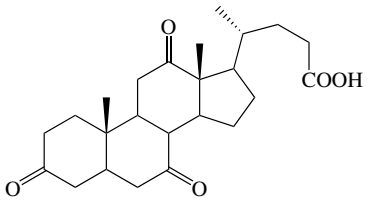
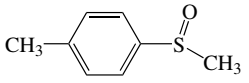
**Abstract**—A guest dependent inversion of enantiomeric recognition operated by the host dehydrocholic acid on a second guest is observed during host–guest dehydrocholic acid–sulfoxide assembly formation.


## 1. Introduction

One of the most important features of supramolecular chemistry is molecular recognition, by which molecules selectively bind to form well-defined structures held together by intermolecular forces largely composed of non-covalent interactions, such as hydrogen bonding.[1] The field directly derived from this area is host–guest chemistry, where a host compound spatially incorporates a guest molecule within its confines. An important application of host–guest chemistry is the separation of similar compounds by enclathration.[2] This involves the choice of a suitable host compound, which selectively combines with a particular guest forming crystalline inclusion compounds. In 2000, we reported the novel observation that dehydrocholic acid (3,7,12-triketo-5β-cholan-24-oic acid) **1**, a bile acid derivative lacking steroidal hydroxyl groups, can serve as a host molecule for host–guest optical resolution of several aryl methyl sulfoxides.[3] In particular, methyl tolyl sulfoxide (Tol) **2** is efficiently resolved in its (*R*)-form with an ee value of 99%, whereas methyl phenyl sulfoxide (Phe) **3** is obtained as an (*S*)-enantiomer with an ee value of 36%. Therefore, dehydrocholic acid represents the host of choice for this class of compounds.[4]




**1**

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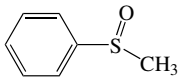


**3**

## 2. Results and discussion

Competition experiments among similar guests represent the most direct test for establishing the selectivity with respect to a given host and several examples have appeared in the recent literature.[5] For a two component system, three types of selectivities are usually observed: zero, modest or high, the three cases being well characterized by a specific selectivity curve.[2] The procedure for competition experiments consists of the preparation of mixtures of the two guests, in an appropriate solvent, such that the mole fraction of a given guest varies from 0 to 1. The host is added to each mixture and the resulting crystalline inclusion compound is analyzed by a suitable technique. The results of the competition experiment between methyl tolyl

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sulfoxide and methyl phenyl sulfoxide versus dehydrocholic acid are illustrated in Figure 1, where $X_{Tol}$ is the mole fraction of the guest Tol in the liquid solution and $Z_{Tol}$ is the mole fraction of the same guest, included in the host.

According to Ward,[6] the selectivity coefficient $K_{Tol/Phe}$ can be defined as

$$K_{Tol/Phe} = (K_{Phe/Tol})^{-1} = Z_{Tol}/Z_{Phe} * X_{Phe}/X_{Tol} \quad (X_{Tol} + X_{Phe} = 1)$$

and easily calculated from the data of Figure 1. The results of competition experiments between Tol and Phe, illustrated in Figure 1, showed that methyl tolyl sulfoxide is preferentially enclathrated over methyl phenyl sulfoxide by dehydrocholic acid for the hole concentration range and that the experimental points lie close to a selectivity coefficient of 5.1. It is noteworthy that $K_{Tol/Phe}$ reaches the highest value of 6.6 when the two guests are present in nearly equimolar amounts ($X_{Tol} = 0.48$).

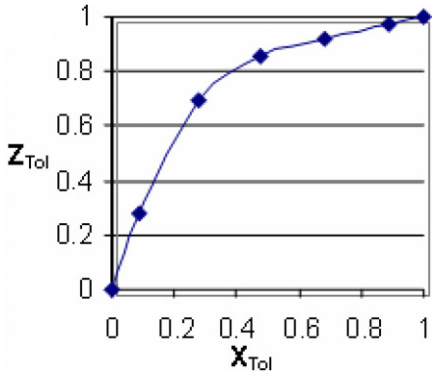


**Figure 1.** Selectivity of Tol with respect to Phe; the calculated selectivity coefficient is of 5.1.

Table 1 reports the enantiomeric excesses measured for the included methyl phenyl sulfoxide as a function of the molar fraction of Tol in liquid solution, in the competition experiments described above. In the absence of Tol, methyl phenyl sulfoxide is preferentially included within dehydrocholic acid as the (*S*)-enantiomer in 36% enantiomeric excess, confirming our previous reports.[3] The presence of racemic methyl tolyl sulfoxide in increasing amounts with respect to Phe, however, results in an inversion of the enantiomeric recognition, revealed as inclusion of the methyl phenyl sulfoxide (*R*)-enantiomer. It should be noted that also in this case the maximum effect in terms of enantiomeric excess is observed when the two guests are present in equimolar amounts ($X_{Tol} = 0.48$, entry 4 of Table 1).

Since equimolar amounts of the two guests in the liquid solution showed the highest influence both on selectivity and on the inversion of enantiomeric recognition, a Tol/Phe ratio of 1:1 has been used to study the influence of optically active Tol on included Phe. As shown in Table 2 the enantioselective enclathration of Phe is strongly influenced by the co-presence of Tol and especially by its enantiomeric enrichment in one of the two components, expressed as $X_{(R)\text{-Tol}}$ or $X_{(S)\text{-Tol}}$. When (*S*)-Tol is exclusively present in the liquid solution, in fact, Phe is included within

**Table 1.** Enantiomeric excesses and absolute configuration of included methyl phenyl sulfoxide as a function of the mole fraction of racemic Tol

| Entry | $X_{Tol}$ | ee % (absolute configuration) of included Phe[a] |
|---|---|---|
| 1 | 0 | 36 (*S*) |
| 2 | 0.09 | 0 |
| 3 | 0.28 | 45 (*R*) |
| 4 | 0.48 | 58 (*R*) |
| 5 | 0.68 | 56 (*R*) |
| 6 | 0.89 | 52 (*R*) |
| 7 | 1 | — |

[a] The absolute configuration of Phe recovered from the crystals was determined by comparison with pure samples, see Ref. 7.

dehydrocholic acid as (*S*)-enantiomer in 72% enantiomeric excess (entry 1 of Table 2), in almost two times the ee value of that found in the conditions reported in Table 1, entry 1.

Increasing the amounts of (*R*)-methyl tolyl sulfoxide, with respect to a constantly maintained 1:1 Tol/Phe ratio, however, overturned the enantiomeric recognition operated by the bile acid towards a progressive enclathration of Phe (*R*)-enantiomer, up to an ee value of 83%.

With these results in hand we turned our attention to a possible guest exchange between crystals of **1**·(*R*)-Tol[8] [or **1**·(*S*)-Tol[9]] and Phe dissolved in an appropriate solvent, which would reveal how strongly the host framework interacts with the guest molecule. Few reports were found in the literature dealing with guest exchange in inclusion crystals in solid-solution biphase.[10] The exchange experiments were performed on standing the inclusion compound, that is, **1**·(*R*)-Tol [or **1**·(*S*)-Tol], with racemic phenyl methyl sulfoxide guest, dissolved in ether/ethyl acetate 1:1 for 48 h. After this time the solid was filtered, washed, treated with aqueous $NaHCO_3$, extracted with ethyl acetate and analyzed by GC. The **1**·(*R*)-Tol complex exchanges the 15% of the included (*R*)-Tol with the guest Phe, which in turn is included within the dehydrocholic acid as (*R*)-Phe, with an enantiomeric excess of 65%. On the other hand, the **1**·(*S*)-Tol

**Table 2.** Enantiomeric excesses and absolute configuration of included methyl phenyl sulfoxide as a function of the mole fraction of optically active (*R*)-Tol and (*S*)-Tol

| Entry[a] | $X_{(R)\text{-Tol}}$ | $X_{(S)\text{-Tol}}$ | ee % (absolute configuration) of included Phe |
|---|---|---|---|
| 1 | 0 | 1 | 72 (*S*) |
| 2 | 0.1 | 0.9 | 72 (*S*) |
| 3 | 0.2 | 0.8 | 61 (*S*) |
| 4 | 0.3 | 0.7 | 19 (*S*) |
| 5 | 0.4 | 0.6 | 30 (*R*) |
| 6 | 0.5 | 0.5 | 72 (*R*) |
| 7 | 0.6 | 0.4 | 80 (*R*) |
| 8 | 0.7 | 0.3 | 81 (*R*) |
| 9 | 0.8 | 0.2 | 82 (*R*) |
| 10 | 0.9 | 0.1 | 83 (*R*) |
| 11 | 1 | 0 | 83 (*R*) |

[a] Ratio Tol/Phe 1:1 (Tol = (*S*)-Tol + (*R*)-Tol in different mole fractions); the absolute configuration of Phe recovered from the crystals was determined by comparison with pure samples, see Ref. 7; the amount of Tol and Phe included in **1** for each experiment is reported in Section 4.

complex exchanges the included (*S*)-Tol with the guest Phe (exchange yield 7%) that is included in **1** as (*S*)-Phe with an enantiomeric excess of 70%.

## 3. Conclusion

Both results are in agreement with the data reported in Table 2 and further support the occurring guest exchange in inclusion compounds, and even more importantly, the guest dependent inversion of enantiomeric recognition operated by the host. We were able to demonstrate the possibility of obtaining the control of the enantiomeric inclusion on (*R*)- or (*S*)-methyl phenyl sulfoxide in dehydrocholic acid assemblies via supramolecular chiral recognition induced by a second guest, that is (*R*)- or (*S*)-Tol. To the best of our knowledge, this is the first example of stereochemical information transfer controlled by a guest on a host, with respect to another guest.

## 4. Experimental

A typical procedure for competition experiments between Tol and Phe consists of the preparation of several mixtures of the two guests in different Tol/Phe molar fraction: 0:10, 1:9, 3:7, 5:5, 7:3, 9:1, 10:0, for a total amount of Tol/Fen of 2.7 mmols dissolved in ether/ethyl acetate 1:1 (2.8 mL). The solid host dehydrocholic acid **1** is added (0.124 mmol). The biphasic system is allowed to stand for 48 h. The solid inclusion compound is filtered, treated with aqueous $NaHCO_3$, extracted and the guest content, including enantiomeric excesses, analyzed by GC on a chiral column Megadex DETTBS. Absolute configurations of the sulfoxides recovered from the crystals were determined by comparison with pure samples: Phe, prepared according to the literature procedures;[7] Tol, commercially available. A typical procedure for competition experiments between optically active Tol and Phe consists of the preparation of mixtures of the two guests in equimolar concentration, but progressively increasing the percentages of the (*R*)-Tol over the (*S*)-enantiomer, dissolved in ether/ethyl acetate 7:3. Host **1** is added maintaining a ratio Tol/Phe/**1** of 3:3:1. The amounts of Tol and Phe included in **1** for each experiment of Table 2 are Tol/Phe entry #1 80:20, #2 82:18, #3 88:12, # 4 88:12, #5 86:14, #6 87:13, #7 90:10, #8 90:10, #9 90:10, #10 91:9, #11 91:9.

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