Chiral Recognition of Diketopiperazines with Xanthone Receptors

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Good chiral recognition of diketopiperazines has been obtained with a receptor that combines a xanthone with a phosphonamide as an asymmetric group. Silicagel plates impregnated with an enantiomerically pure diketopiperazine provide an easy and effective way to resolve the receptor racemic mixture. The strong (*R,R. R*) complex yields a spot with a larger R_f, probably because the complex is less polar than the free receptor.

The chiral recognition of neutral compounds is still a challenging area.[1] Xanthene[2] and xanthone (Figure 1) receptors have shown promising properties in the association of amides,[3] phosphates,[4] carboxylic acids[5] or their salts.[6] This building block lacks asymmetric centers and therefore unable, alone, to discriminate between enantiomeric guests.

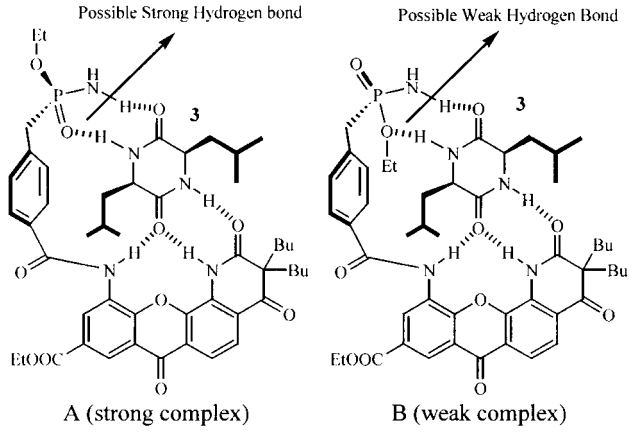

Figure 1. Proposed structures for the complexes of receptor **1** enantiomers and a diketopiperazine.

We have tried to combine a xanthone fragment with a phosphonamide ethyl ester to develop receptors capable of chiral recognition. As shown in Figure 1, this structure shows a clear-cut source for the chiral recognition. Only the phosphonamide with the right configuration (complex A) will be able to set the strong hydrogen bond with the phosphoryl oxygen, while the one with the wrong configuration is only able to set a weak hydrogen bond with the oxygen of the ethyl ester (complex B).

Receptor **1** can be easily prepared starting from the known amine **2**,[3] as shown in Figure 2.

Diketopiperazines have already been used as successful guests in chiral recognition.[7] We chose this kind of guest because of its rigidity and because inspection of CPK models revealed that, at first glance, it fits the cleft provided by receptor **1** well.

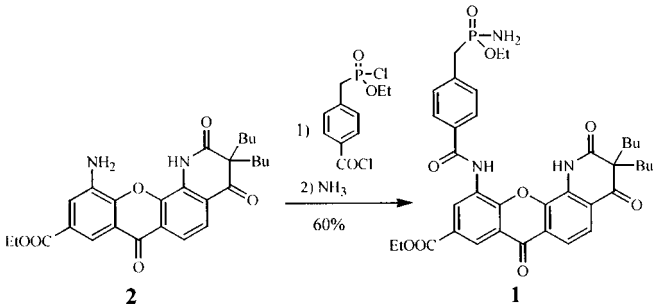

Figure 2. Preparation of receptor **1**.

Competitive titration[8] between an enantiomerically pure diketopiperazine **3** (Figure 1) and receptor **1** racemic mixture in $CDCl_3$ shows splitting of host **1** signals (H-3 proton shifts from 9.28 ppm to 9.36 ppm in one of the diastereomeric complexes and to 9.43 ppm in the other one). However, plotting these signals against each other only revealed a poor degree of chiral discrimination (K_{rel}=1.5) between these enantiomers. The most likely explanation for the low chiral recognition is the very weak collaboration between the phosphonamide and xanthone binding arms. A reappraisal of CPK models revealed that the toluic aromatic spacer in receptor **1** could be slightly too short for the best hydrogen bond geometry (Figure 1). Receptors **4, 5** and **6** (Figure 3) were prepared to overcome this possible drawback. In these compounds, the diphenylmethane and benzophenone spacers provide longer concave surfaces that should easily accommodate a diketopiperazine guest. Figure 4 shows the preparation of these compounds.

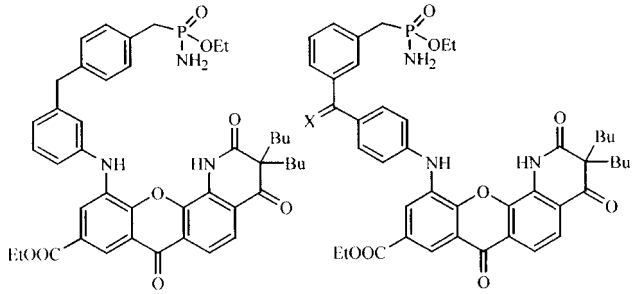

Figure 3. Structure of receptors **4**, **5** and **6**.

Again, competitive titrations in $CDCl_3$ using the optically pure diketopiperazine **3** and the hosts were carried out. Splitting of the guests signal in the NMR spectra was observed in all

cases. Plotting the H-3 signals of each diastereomeric receptor against each other revealed modest chiral recognitions for the diphenylmethane hosts **4** and **5** (K_{rel}= 2.2 and 2.7 respectively), but a reasonably good discrimination for the one with the benzophenone spacer (K_{rel}= 6.3).

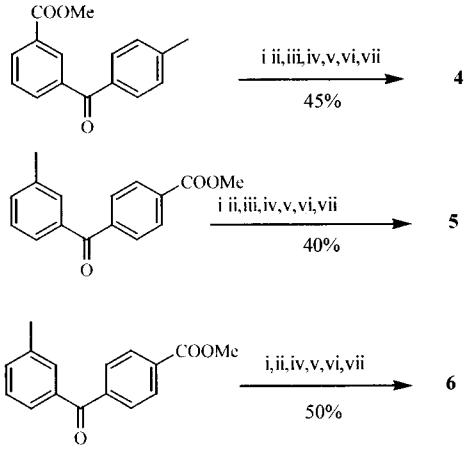

Figure 4. Preparation of receptors **4**, **5** and **6**.

The presence of chiral discrimination was confirmed with TLC experiments. When the previous racemic receptors were eluted with CH_2Cl_2/ether (1/1) on a TLC plate previously impregnated with a 1% solution of the diketopiperazine **3** in chloroform, separation of the yellow enantiomeric receptors took place. There was a good relationship between the measured chiral recognition and the R_f differences for each receptor. A single spot was obtained for receptor **1**, and two similar spots with R_f = 0.41 and R_f = 0.45 were detected for receptor **4**, which showed only a 2.2 ratio between the association constants of its enantiomers and the diketopiperazine **3**. Separation was clear for receptor **5**, which afforded two spots with R_f = 0.42 and 0.50, and was especially good for receptor **6**, in which its 6.3 chiral recognition provided a large separation with R_f = 0.31 and 0.52.

As in previous cases,[9,5b] complex formation explains the R_f differences well. The free receptor is able to establish strong hydrogen bonds with the silicagel and is therefore a highly polar species. In the complex, the hydrogen bonds are no longer available for the silicagel and the associate is easily eluted. This mechanism is only efficient in promoting elution if the association constant is large enough in comparison with that occurring on the silicagel.

The large R_f difference obtained for receptor **6** enantiomers provided an easy way to resolve the racemic mixture. Preparative silicagel TLC plates treated with the diketopiperazine **3** allowed us to separate around 100 mg of each enantiomeric receptor **6**. These compounds were initially obtained as the diketopiperazine complexes when extracted from the silicagel; a two-fold crystallization in ethyl acetate provided the pure receptors.

With the pure enantiomeric receptors **6** in hand, conventional titrations were carried out in order to confirm the chiral recognition as assessed from the competitive experiment. Titration was easily followed due to the movement of proton H-3 of the xanthone. This proton is deshielded in both complexes from 9.34 ppm to 9.51 ppm, suggesting that the geometry of both associates is very similar or at least close to that of the xanthone ring. The compound obtained from the less polar complex (*R,R. R*) ($[\alpha]_D$ = +83.0°, $CHCl_3$, *c* = 0.28) had K_{ass}= 3.6×10^3 M^{-1}, while the association constant is only 6.0×10^2 M^{-1} for the weak one (*R,R. S*) ($[\alpha]_D$ = –83.4, $CHCl_3$, *c* = 0.26). Within the experimental error, these values agree with those previously obtained and confirm the collaboration between the xanthone and phosphonamide binding arms (the three hydrogen bonds of the xanthone usually provide K_{ass} around the hundreds just with simple amides[3]).

We are now searching for applications for these new receptors.

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This paper is dedicated to the memory of Joaquín Pascual de Teresa.

References and Notes

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