Chiral Recognition of Lactic Acid Derivatives with Chromenone−Benzoxazole Receptors

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The field of enantioselective complexation may be of great importance in the large scale resolution of racemic mixtures[1] and in the development of new asymmetric catalysts. Hydrogen-bonding receptors have been shown to be successful thanks to the influential work of Rebek,[2] Still,[3] Diederich,[4] Hamilton,[5] Mendoza,[6] and others.[7]

Receptor **1** can be easily prepared from the known aminochromenone **2**,[8] as shown in Figure 1 (overall yield 58%).

Titration of receptor **1** with acids can be readily followed in ^{1}H NMR because the aromatic *tert*-butylaniline residue in the receptor strongly shields the carboxylic α-hydrogens. In $CDCl_3$ decanoic acid shows a good association constant with this host[9] ($K_{assn} = 3.2 \times 10^4$ M^{-1}), its α-methylene groups being shifted 0.4 ppm upfield in the complex. The effect of the basic benzoxazole can be studied with the neutral decanamide, which only forms a weak associate, $K_{assn} = 2.7 \times 10^3$ M^{-1} while, owing to their higher acidity, monochloroacetic and dichloroacetic acid afford $K_{assn} = 1.3 \times 10^5$ M^{-1} and 8.7×10^5 M^{-1}, respectively.

Chiral recognition is an attractive challenge for these hosts. Conformationally α-hydroxy acids are relatively rigid compounds[10] and set the hydroxyl group in such a way that it eclipses the carbonyl group. For lactic acid carbamoyl derivative **3**, CPK models have shown that an additional hydrogen bond can be set with compounds in which an aminoethanol unit replaces the chromenone carboxylic acid (Figure 3). For asymmetric aminoethanols, chiral discrimination between both receptors is likely to occur.

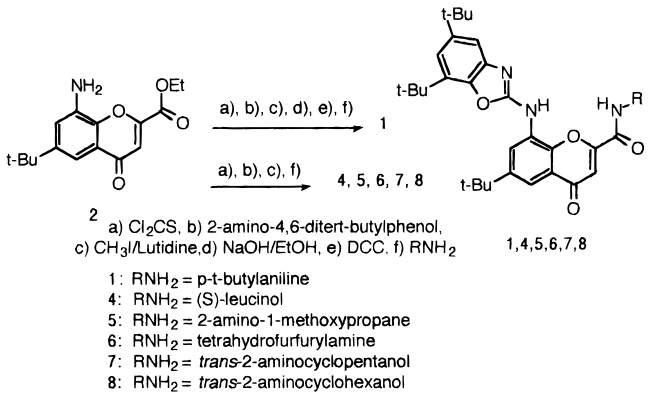

Figure 1. Preparation of receptors **1** and **4**−**8**.

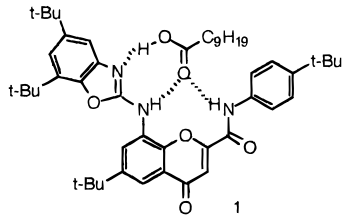

Figure 2. Proposed structure for receptor **2** associated with decanoic acid.

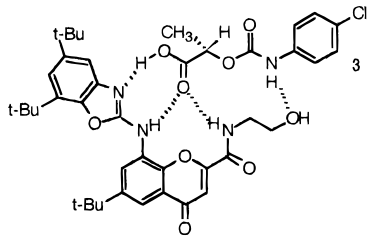

Figure 3. Complexes of carbamoyllactic acid (**3**) and a generic structure substituted with a aminoethanol unit.

To test this hypothesis, three new hosts **4**−**6** were prepared from the commercially available amines in a similar way to host **1** (Figure 1). Receptor (*S*)-**4** (57.7%, mp 224 °C, $[\alpha]_D = -36.8$ ($c = 0.6$, $CHCl_3$)) was prepared from optically pure (*S*)-leucinol. ^{1}H NMR titrations in $CDCl_3$ for the diastereomeric associates with both carbamoyllactic acids gave the following values: $K_{assn}(S,S) = 1.2 \times 10^5$ M^{-1} and $K_{assn}(R,S) = 2.3 \times 10^4$ M^{-1}. Good chiral recognition was obtained for the methoxypropane receptor **5** (58.4%, mp 198 °C). A competitive experiment[11] between **5** and optically pure (*S*)-carbamoyllactic acid (**3**) revealed a $K_{rel} = 4.3$. Conventional titration of racemic receptor **5** with the racemic guest **3** afforded an apparent constant of $K_{app} = 6.6 \times 10^4$ M^{-1}. From both of these values, it was possible to evaluate both diastereomeric constants for **5**[12] (Table 1). The similar geometries of compounds **4** and **5** provided similar results. On the other hand, separation of the chiral center from the chromenone in the tetrahydrofurane receptor **6** (52%, mp 186 °C) led to very poor chiral recognition. The same experiments as for **5** allowed the evaluation of both association constants (Table 1).

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(9) Titrations were carried out in $CDCl_3$ solutions at a constant 10^{-3} M host concentration. Data were evaluated with a homemade Monte Carlo-based curve-fitting program. Competitive experiments were performed with 3×10^{-3} M guests solutions to which pure host was added until saturation was reached. Proton shifts of guests were plotted against each other. A Monte Carlo nonlinear curve-fitting method provided the relative association constants.
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(12) Titration of racemic mixtures was carried out in the same manner as with optically pure host/guest to obtain an apparent constant K_{app}. The equation $2K_{app} = K_R + K_S$ combined with the K_R/K_S ratio obtained from the competitive experiment permitted the evaluation of both diastereomeric constants.

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Table 1. K_{app}, K_{rel}, and K_{assn} between Receptors and Lactic Derivative **3** in $CDCl_3$ at 20 °C

receptor	K_{app} (M^{-1})	K_{rel}	K_{SS} (M^{-1})	K_{RS} (M^{-1})
4		5.2	1.2×10^5	2.3×10^4
5	6.6×10^4	4.3	1.1×10^5	2.5×10^4
6	3.1×10^4	1.2	3.4×10^4	2.8×10^4
7	2.8×10^4	1.8	3.6×10^4	2.0×10^4
8		9.0	3.0×10^5	3.3×10^4

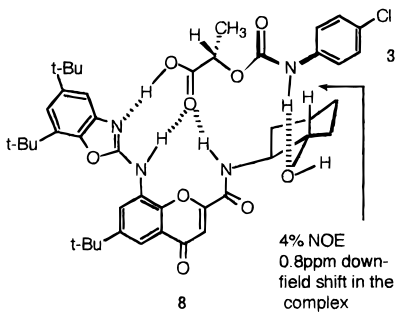

Figure 4. Proposed structures for the complex of receptors **8** with guest **3**.

One drawback of the above hosts is their many degrees of rotational freedom. Compounds in which the 2-aminoethanol unit is in a ring system could possibly lead to better results. Therefore, racemic receptors **7** (48.2%, mp 262 °C) and **8** (46%, mp 270 °C) were prepared in a similar way to the previous hosts (Figure 1). Competitive experiments with carbamoyllactic acid (**3**) revealed poor discrimination for **7** ($K_{rel} = 1.8$), but pointed to good chiral recognition for the cyclohexane host **8** ($K_{rel} = 9$) (Table 1), (Figure 4). This good chiral recognition suggested that its resolution could be accomplished using its binding capacities.[13] Preparative TLC plates of the yellow compound **8**, eluted with CH_2Cl_2/ether (8/2) to which 1% MeOH and 0.5% optically pure (*S*)-**3** had been added provided an easy way to separate both enantiomeric receptors[14] ((*SS*)-**8**), $[\alpha]_D = -4.8$ ($c = 0.6$, $CHCl_3$); ((*RR*)-**8**), $[\alpha]_D = +5.3$ ($c = 0.9$, $CDCl_3$).

Guest association produces a structure in which the hydrogen bonds are closed and is therefore easily eluted. Under the above conditions, the stronger the complex the larger the R_f (R_f ((*SS*)-**8**) = 0.85, R_f ((*RR*)-**8**) = 0.65; 5 elutions).

NOEs and ROESY experiments revealed a similar geometry for both the above diastereomeric associates, showing proximity between the methyl lactic group and the proton geminal to the hydroxyl group in the cyclohexane ring (6% and 4% NOE effects). This proton is strongly deshielded in the (*SS*,*S*) complex (0.8 ppm) due to the proximity of the nonbonding electrons of the carbamoyllactic acid oxygen. The structure proposed in Figure 4 shows a fourth hydrogen bond in this case. The presence of this H-bond is supported by a strong downfield shift of the carbamate-NH in the ^{1}H NMR spectrum of the (*SS*,*S*) complex (1.7 ppm). In the diastereomeric complex (*SS*,*R*), the methyl and the hydrogen of the guest exchange positions, leading to a situation with strong steric hindrance between the methyl and the carbamoyl lactic acid carbonyl group. This probably prevents the formation of the fourth hydrogen bond in the weaker complex (carbamate-NH is shifted only 0.9 ppm), leading to the observed chiral recognition.

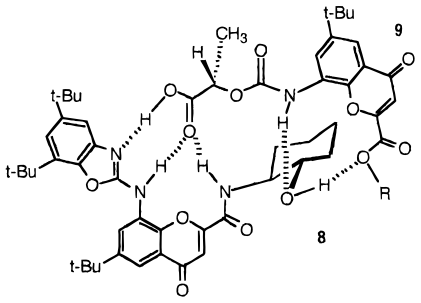

Figure 5. Structure of the complex between guest **9** and receptor **8**.

While the small association constant of the (*RR*,*S*) complex between guest **3** and receptor **8** can readily be measured by conventional NMR titration (Table 1), the stronger (*SS*,*S*) associate lies outside the limits of NMR. This constant was therefore evaluated from the previous competitive experiment.

Chromenones can also be introduced into the guests to obtain higher association constants, due to the formation of an additional hydrogen bond (Figure 5). The new (*S*)-lactic acid derivative **9** had a K_{assn} three times larger with (*RR*)-**8** than with (*S*)-**3**. The complex of (*S*)-**9** and (*SS*)-**8** was again too high to be measured directly in ^{1}H NMR. Competitive titration between (*S*)-**3** and (*S*)-**9** with (*SS*)-**8** showed that the effect of the chromenone was stronger in the case of the matching geometry, the association constant increasing 6-fold. From these values, a recognition of 18 can be deduced for racemic **8** and optically pure **9**. A final competitive titration with the previous compounds confirmed this chiral discrimination within the experimental error, with a relative association constant between both diastereomeric complexes of 16.

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Supporting Information Available: Table with ^{1}H NMR shifts of receptor **8**, its associates with carbamoyl lactic acid **3**, and its 400 MHz spectra and ROESY experiments of both complexes (6 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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