Assembling Organic Receptors around Transition Metal Templates: Functionalized Catechols and Dioxomolybdenum(VI) for the Recognition of Dicarboxylic Acids†

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The synthesis of two receptors for dicarboxylic acids **[12]**$^{2-}$ and **[13]**$^{2-}$, based on the self arrangement of two functionalized catechols **1** and **2** around a *cis*-$[MoO_2]^{2+}$ core, is described. Among the three pairs of enantiomers which may be produced during the complexation of two unsymmetrical catecholates around one molybdenum(VI) ion, only one is observed for each catechol derivative **1** or **2**. Depending on the base used during the complexation of catechols to the molybdenum atom, the dianionic receptors obtained display different solubility properties. These molybdenum-based receptors are chromogenic and, in methylene chloride, the affinities of the assembled receptors for dicarboxylic acids ranging from C_4 to C_8 have been assessed by UV-visible titrations after determining the stoichiometry of the complex formation using Job's method. While receptor **[12]**$^{2-}$ displays selectivity for C_4 and C_5 acids, the more flexible receptor **[13]**$^{2-}$ exhibits selectivity for C_7 and C_8. The binding mode of the diacids to the molybdenum receptor has been determined based on ^{1}H NMR titration. Due to the intrinsic chirality of the receptors, their binding properties versus chiral dicarboxylic acid have been examined. The enantioselective binding of *N*-carbobenzyloxy protected L and D-glutamic acid due to additional $\pi-\pi$ interactions of the protecting group with the receptor's framework is reported for **[12]**$^{2-}$ in methylene chloride. For comparison, the association constants of receptor **[12]**$^{2-}$ with a Boc protected L-glutamic acid and the racemic mixture of *N*-carbobenzyloxy protected glutamic acid have been determined.

Introduction

Architectural control on the directionality of specific interactions such as hydrogen bonds has received considerable attention in the field of molecular recognition. In particular, adequate spacing of 2-(acylamino)pyridine units[1b−3] has provided access to numerous receptors for dicarboxylic acids.[1] Since several synthetic steps are often required to achieve a topographical control on the orientation of multiple hydrogen bonds, the spontaneous assembly of smaller constituents to form receptors has been investigated.[4] As transition metals have demonstrated their ability to gather and orient organic fragments,[5] self assembly of half-receptors around metallic templates has been used to build specific receptors for neutral molecules.[6−9] More recently, a combinatorial approach based on orienting "half-receptors" around ruthenium(II) has been developed by Hamilton and illustrates the versatility of this approach.[10] So far, most of the coordinating fragments used for the orientation of fragments around transition metal atoms have been nitrogen-containing heterocycles, such as bipyridines, phenanthrolines, and terpyridines. The ability of catecholates to complex a large variety of transition metals[11] has prompted us to investigate the potential use of half-receptors containing this coordinating species. Results obtained using a *cis*-dioxomolybdenum(VI) template are presented.

Experimental Section

General. All commercial reagents were used without purification except $MoO_2(acac)_2$ which was purified by extraction from commercial material (5−10 g) and placed in a 60 mL glass filtering funnel (medium porosity) with three 30 mL aliquots of boiling acetylacetone. To the resulting yellow filtrate was added petroleum ether to yield a yellow precipitate which was collected by filtration and washed with several portions of petroleum ether. Spectroscopic characterization

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(1) (a) For a recent review on Molecular Recognition of Organic Acids, see: Seel, C.; Galan, A.; de Mendoza, J. *Top. Curr. Chem.* **1995**, *75*, 101−132 and also (b) Ballester, P.; Costa, A.; Deya, P. M.; Gonzalez, J. F.; Rotger, M. C.; Deslongchamps, G. *Tetrahedron Lett.* **1994**, *35*, 3813−3816.

(2) (a) Geib, S. J.; Vicent, C.; Fan, E.; Hamilton, A. D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 119−121. (b) Owens, L.; Thilgen, C.; Diederich, F.; Knobler, C. B. *Helv. Chim. Acta* **1993**, *76*, 2757−2774. (c) Vicent, C.; Fan, E.; Hamilton, A. D. *Tetrahedron Lett.* **1992**, *33*, 4269−4272. (d) Alcazar, V.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1521−1523. (e) Garcia-Tellado, F.; Albert, J.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1991**, 1761−1763. (f) Alcazar-Montero, V.; Tomlinson, L.; Houk, K. N.; Diederich, F. *Tetrahedron Lett.* **1991**, *32*, 5309−5312. (g) Garcia-Tellado, F.; Goswami, S.; Chang, S.-K.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7393−7394.

(3) (a) Tanaka, Y.; Kato, Y.; Aoyama, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2807−2808. (b) Rebek, J., Jr.; Nemeth, D.; Ballester, P.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 3474−3475.

(4) Schall, O.; Gokel, G. *J. Am. Chem. Soc.* **1994**, *116*, 6089−6100, and references cited therein.

(5) Chambron, J.-C.; Dietrich-Buchecker, C. O.; Sauvage, J.-P. *Top. Curr. Chem.* **1993**, *165*, 131−162.

(6) Schwabacher, A. W.; Lee, J.; Lei, H. *J. Am. Chem. Soc.* **1992**, *114*, 7595−7598.

(7) Fujimoto, K.; Shinkai, S. *Tetrahedron Lett.* **1994**, *35*, 1915−2918.

(8) Goodman, M. S.; Hamilton, A. D.; Weiss, J. *J. Am. Chem. Soc.* **1995**, *117*, 8447−8455.

(9) Goodman, M. S.; Jubian, V.; Hamilton, A. D. *Tetrahedron Lett.* **1995**, *36*, 2551−2554.

(10) Goodman, M. S.; Jubian, V.; Linton, B.; Hamilton, A. D. *J. Am. Chem. Soc.* **1995**, *117*, 11610−11611.

(11) Representative examples from (a) Albrecht, M.; Franklin, S. J.; Raymond, K. N. *Inorg. Chem.* **1994**, *33*, 5785−5793. (b) Nielson, A.; Griffith, W. P. *J. Chem. Soc., Dalton Trans.* **1978**, 1501−1506. (c) Pierpont, C. G.; Buchanan, R. M. *Coord. Chem. Rev.* **1981**, *38*, 45−87.

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of purified material was in excellent agreement with literature data.[12] When anhydrous conditions were required, all glassware was flame-dried under inert gas flow, experiments were run under argon, and all solvents were dried as follows. Toluene, ether, and tetrahydrofuran were distilled from sodium/benzophenone, and methylene chloride and acetonitrile were distilled from CaH_2. NMR spectra were recorded on a Bruker AM 300 spectrometer, and data were processed with Bruker-WINNMR for Windows. Chemical shifts were determined taking the solvent as an internal reference: $CHCl_3$ (7.26 ppm), $CHDCl_2$ (5.32 ppm), DMSO-d_5 (2.49 ppm). UV-visible experiments were run on a Hewlett-Packard HP8452A diode array spectrophotometer using a 2 nm resolution in quartz cells with an optical path length of 1 cm. FTIR spectra were recorded on a Bruker IFS 28 apparatus with KBr pellets as samples. Melting points were determined on a Kofler Heating Plate Type WME and are uncorrected. Elemental analyses were performed by the Service de Microanalyse of the Institut de Chimie de Strasbourg. Mass spectra (FAB) were obtained on a ZAB-HF mass spectrometer. Thin-layer chromatography (TLC) was performed using Macherey-Nagel Polygram Sil G/UV_{254} (0.25 mm) and Polygram Alox N/UV_{254} analytical polyethylene-coated plates. E. Merck silica gel 60 (70−230 mesh) and aluminum oxide 90 (70−230 mesh) were used for column chromatography.

Boronic Acid 4. To a solution of veratrole (**3**) (10.0 g, 72 mmol) in 50 mL of THF at 0 °C was added dropwise 40.5 mL of *n*-BuLi (1.6 M in hexane). After 2 h at 0 °C, the solution was transferred via cannula into 100 mL of THF containing 8.2 mL (72 mmol) of $B(OMe)_3$. The resulting solution was stirred for an additional 1 h at room temperature, and the solvents were evaporated. The crude boronate was taken into ether (250 mL), washed with 10% aqueous HCl, and then extracted with 10% aqueous NaOH. The aqueous phase was washed twice with ether and then acidified with concentrated HCl. The acidic (pH = 1) aqueous phase was extracted three times with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The crude boronic acid was then purified by chromatography over silica gel (7/3 hexane/ether) to afford an oil which crystallizes on standing, 7.0 g (44 mmol, 60%) of which was used without further purification. Mp: 72−73 °C. ^{1}H NMR ($CDCl_3$): 7.42 (dd, J_1 = 1.5 Hz, J_2 = 7.5 Hz, 1H), 7.11 (dd, J_1 = 7.5 Hz, J_2 = 8.0 Hz, 1H), 7.04 (dd, J_1 = 1.5 Hz, J_2 = 8.0 Hz, 1H), 3.94 (s, 3H), 3.47 (s, 3H).

Amides 8 and 9. The appropriate acid chloride, **5** or **6** (4.8 g, 20 mmol), was dissolved in 20 mL of THF, and 2.15 mL of DBU (0.03 mmol) was added. Dropwise addition of 2-amino-6-methylpyridine (**7**) (2.16 g, 20 mmol) with further stirring overnight and evaporation of the solvent afforded the crude amide which was purified over a silica gel column (CH_2Cl_2/hexane: 1/1) to yield the corresponding amide as a white solid. Compound **8**: 5.3 g (18 mmol, 90%). Anal. Calcd for $C_{13}H_{11}N_2BrO$ (291.14 g mol^{-1}): C(53.63), H(3.90), N(9.62). Found: C(53.40), H(3.85), N(9.42). Mp: 203 °C; ^{1}H NMR $CDCl_3$: 7.96 (d, J_1 = 6.5 Hz, 2H), 7.52 (d, J_2 = 6.5 Hz, 2H), 7.37 (dd, J_1 = 8.3 Hz, J_2 = 7.3 Hz, 1H), 6.46 (d, J_1 = 7.3 Hz, 1H), 6.35 (d, J_1 = 8.3 Hz, 1H), 5.81 (br s, 1H), 2.43 (s, 3H). Compound **9**: 5.3 g (18 mmol, 90%); Anal. Calcd for $C_{13}H_{11}N_2BrO$ (291.14g mol^{-1}): C(53.63), H(3.90), N(9.62). Found: C(53.68), H(4.05), N(9.53); Mp: 99 °C; ^{1}H NMR $CDCl_3$: 8.63 (br s, 1H), 8.14 (d, J = 8.5 Hz, 1H), 8.05 (dd, J_1 = 1.8 Hz, J_2 = 1.8 Hz, 1H), 7.81 (dm, J = 7.7 Hz, 1H), 7.65 (dm, J = 8.5 Hz, 2H), 7.62 (dd, J_1 = 7.7 Hz, J_2 = 8.5 Hz, 1H), 7.32 (dd, J_1 = 7.7 Hz, J_2 = 8.5 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 2.42 (s, 3H).

Protected Catechols 10 and 11. To a solution of the appropriate amide **8** or **9** (1.0 g, 3.5 mmol) and $Pd(PPh_3)_4$ (0.12g, 0.1 mmol) in 20 mL of toluene were added 3.5 mL of aqueous Na_2CO_3 (2 M) and **4** (0.63 g, 3.5 mmol) dissolved in 4 mL of EtOH. All solvents were carefully deoxygenated prior to use. After refluxing overnight, this mixture was washed three times with 2 M aqueous Na_2CO_3 and water. After removal of the solvents, the crude mixture was purified by chromatography (SiO_2/CH_2Cl_2) to afford **10** or **11**. Compound **10**: 1.15 g (3.3 mmol, 95%). Anal. Calcd for $C_{21}H_{20}N_2O_3$ (349.60 g mol^{-1}): C(72.39), H(5.78), N(8.04). Found: C(72.50), H(5.88), N(7.90). Mp: 96 °C. ^{1}H NMR $CDCl_3$: 8.81 (s, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.61 (m, 3H), 7.09 (dd, J_1 = 7.3 Hz, J_2 = 8.1 Hz, 1H), 6.92 (d, J = 8.1 Hz, 2H), 6.88 (d, J = 7.3 Hz, 1H), 3.88 (s, 3H), 3.57 (s, 3H), 2.39 (s, 3H). Compound **11**: 1.09 g (3.1 mmol, 90%). Anal. Calcd for $C_{21}H_{20}N_2O_3$ (349.60 g mol^{-1}): C(72.39), H(5.78), N(8.04). Found: C(72.60), H(5.99), N(8.07). Mp: 114 °C. ^{1}H NMR $CDCl_3$: 8.9 (s, 1H), 8.18 (d, J = 8.1 Hz, 1H), 8.05 (dd, J_1 = 1.5 Hz, J_2 = 1.1 Hz, 1H), 7.87 (ddd, J_1 = 1.1 Hz, J_2 = 1.5 Hz, J_3 = 7.7 Hz, 1H), 7.71 (ddd, J_1 = 1.5 Hz, J_2 = 1.5 Hz, J_3 = 7.7 Hz, 1H), 7.57 (dd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, 1H), 7.45 (dd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, 1H), 7.05 (dd, J_1 = 8.1 Hz, J_2 = 7.7 Hz, 1H), 6.88 (m, 3H), 3.86 (s, 3H), 3.57 (s, 3H), 2.34 (s, 3H).

Half-Receptors 1 and 2. To a deoxygenated solution of CH_2Cl_2 (200 mL) containing the appropriate veratrole derivative **10** or **11** (2.0 g, 5.7 mmol) was added 1.5 mL (16 mmol) of BBr_3. After refluxing 2 h, the solution was carefully quenched with 200 mL of MeOH, and the solvents were removed under reduced pressure. The crude catechol derivatives were successively dissolved and evaporated three times with 100 mL of MeOH to remove the boronic acid as its methyl ester. The half-receptors were isolated in a pure form as white solids. **Compound 1**: 1.60 g (4.8 mmol, 85%). Anal. Calcd for $C_{19}H_{16}N_2O_3$, (CH_2Cl_2, $^3/_2H_2O$) (431.45 g mol^{-1}): C(55.52), H(4.85), N(6.47). Found: C(55.25), H(4.45), N(6.90). Mp: 295 °C dec. UV-visible λ_{max} nm (ϵ in M^{-1} cm^{-1}) in MeOH: 310 (22900); FTIR ν in cm^{-1} (bands): 3076 (νO−H), 1650 (νC=O), 1577 (δN−H); ^{1}H NMR in $(CD_3)_2CO$: 12.10 (s, 1H), 8.77 (d, J = 8.5 Hz, 1H), 8.65 (s, 1H), 8.48 (d, J = 8.1 Hz, 2H), 8.42 (dd, J_1 = 8.5 Hz, J_2 = 8.1 Hz, 1H), 7.85 (d, J = 8.1 Hz, 2H), 7.58 (s, 1H), 7.51 (d, J = 8.1 Hz, 1H), 6.93 (dd, J_1 = 8.1 Hz, J_2 = 7.3 Hz, 2H), 6.80 (dd, J_1 = 7.3 Hz, J_2 = 8.1 Hz, 1H), 2.81 (s, 3H). **Compound 2**: 1.68 g (5.1 mmol, 90%). Anal. Calcd for $C_{19}H_{16}N_2O_3$, (CH_2Cl_2, $^3/_2H_2O$) (431.45 g mol^{-1}): C(55.52), H(4.85), N(6.47). Found: C(55.21), H(4.81), N(6.44). Mp: 253 °C; UV-visible λ_{max} nm (ϵ in M^{-1} cm^{-1}) in MeOH: 218 (19,-300), 250 (16400), 304 (13100); FTIR ν in cm^{-1} (bands): 3070 (νO−H), 1641 (νC=O), 1565 (δN−H); ^{1}H NMR in $(CD_3)_2SO$: 11.34 (s, 1H, NH), 8.47 (s, 2H), 8.20 (s, 1H), 8.12 (dd, J_1 = 8.1 Hz, J_2 = 7.7 Hz, 1H), 7.98 (d, J_1 = 8.1 Hz, J_2 = 8.1 Hz, 2H) 7.83 (d, J = 7.7 Hz, 1H, H_9), 7.58 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 6.84 (d, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 2H) 6.74 (dd, J_1 = 7.5 Hz, J_2 = 8.1 Hz, 1H), 2.62 (s, 3H).

Assembled Receptors: $[MoO_2]^{2-}$ Complexes. The same typical procedure, under argon, was followed for the synthesis of each complex. A solution of half-receptor **1** or **2** (0.10 g, 0.31 mmol) in 100 mL of EtOH containing N(*n*-Bu)$_4$OH (0.65 mL 0.65 mmol) or KOH (0.035 g, 0.65 mmol) was added dropwise *via* cannula transfer into an ethanolic solution (300 mL) of $MoO_2(acac)_2$ (0.051 g, 0.15 mmol). After 2 h at room temperature, the solvents were removed under vacuum. The purification methods for the receptors were set up depending on their respective solubility properties. **Compound {12B}[N(*n*-Bu)$_4$]$_2$**: The crude mixture was taken in CH_2Cl_2 (200 mL) and washed twice with water. Drying over $MgSO_4$ and evaporation afforded **{12B}[N(*n*-Bu)$_4$]$_2$** as an orange solid, 0.190 g (0.15 mmol, 98%). Anal. Calcd for $C_{70}H_{100}N_6O_8Mo$ (1248.79 g mol^{-1}): C(67.32), H(8.06), N(6.72). Found: C(67.46), H(8.29), N(6.14). Mp: 115 °C. UV-visible in CH_2Cl_2 λ_{max} nm (ϵ in M^{-1} cm^{-1}): 304 (40400), 394 (10000). FTIR ν in cm^{-1} (bands): 1669 (νCO), 1602 (δNH), 892 and 843 (*cis*-νMo=O). Negative FAB Mass Spectrometry: Calculated for $\{M\}^-$ = $[C_{38}H_{28}N_4O_8Mo]^-$: 764.56; measured for I = 6.9 V: 765.10 (20%). ^{1}H NMR in $CDCl_3$: 8.38 (s, 2H), 8.26 (d, J = 8.8 Hz, 2H), 7.81 (broad m, 8H), 8.11 (d, J = 1.5 Hz, 2H), 7.60 (dd, J_1 = 8.8 Hz, J_2 = 1.5 Hz, 2H), 6.59 (m, 2H), 6.40 (m, 4H), 3.07 (m, 16H), 2.29 (s, 6H), 1.59 (m, 16H), 1.34 (m, 16H), 0.96 (t, J = 7.5 Hz, 24H). **Compound {12B}K$_2$·9H$_2$O**: The crude mixture was taken in MeOH and filtered over Sephadex

(12) (a) For IR see: Chakravorty, M. C.; Bandyoppadhyay, D.; Chisolm, M. H.; Hammond, C. E. *Inorg. Synth.* **1992**, *29*, 130−131. (b) for UV-vis see: Moore, F. W.; Rice, R. E. *Inorg. Chem.* **1968**, *7*, 2510−2514.

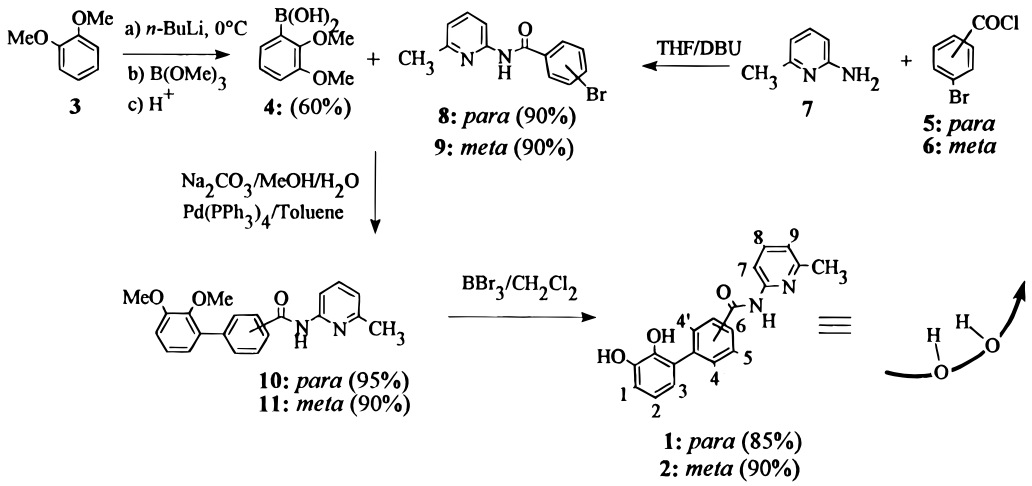


Figure 1. Synthesis of the half-receptors **1** and **2**.

(LH20) to afford {**12B**}$\mathbf{K_2 \cdot 9H_2O}$ as an orange solid, 0.125 g, (0.15 mmol, 99%). Anal. Calcd for $C_{38}H_{46}N_4O_{17}K_2Mo$ (1004.87 g mol^{-1}): C(45.42), H(4.61), N(5.57). Found: C(45.28), H(4.30), N(5.58). Mp: 123 °C. UV-visible in CH_3CN λ_{max} nm (ϵ in M^{-1} cm^{-1}): 298 (40400), 376 (10800). FTIR ν in cm^{-1} (bands): 1660 (νCO), 1598 (δNH), 892 and 841 (*cis*-νMo=O). Positive FAB Mass Spectrometry: Calculated for $\{M\}^+ = [C_{38}H_{28}N_4O_8MoK_2]^+$: 842.74; measured for I = 9.9 V: 843.90 (75%). ^{1}H NMR in CD_3CN: 8.82 (s, 2H), 8.16 (m, 4H), 7.75 (broad m, 8H), 7.59 (m, 2H), 6.63 (m, 2H), 6.45 (m, 4H), 2.28 (s, 6H). **Compound** {**13B**}$\mathbf{[N(n\text{-}Bu)_4]_2 \cdot H_2O}$: The crude mixture was taken in CH_2Cl_2 (200 mL) and washed twice with water. Drying over $MgSO_4$ and evaporation afforded {**13B**}$\mathbf{[N(n\text{-}Bu)_4]_2 \cdot H_2O}$ as an orange solid, 0.190 g (0.15 mmol, 98%). Anal. Calcd for $C_{70}H_{102}N_6O_9Mo$ (1266.79 g mol^{-1}): C(65.44), H(8.15), N(6.53). Found: C(65.25), H(8.06), N(6.26). Mp: 113 °C. UV-visible in CH_2Cl_2 λ_{max} nm (ϵ in M^{-1} cm^{-1}): 252 (41700), 286 (41000) 366 (6500). FTIR ν in cm^{-1} (bands): 1671 (νCO), 1577 (δNH), 892 and 849 (cis-νMo=O); Negative FAB Mass Spectrometry: Calculated for $\{M\}^- = [C_{38}H_{28}N_4O_8Mo]^-$: 764.56; measured for I = 6.0 V: 765.10 (10%). ^{1}H NMR in $CDCl_3$: 8.69 (s, 2H), 8.13 (d, J = 8.2 Hz, 2H), 8.10 (broad m, 4H), 7.60 (dd, J_1 = 8.2 Hz, J_2 = 7.35 Hz, 2H), 7.53 (broad m, 2H), 7.11 (m, 2H), 6.88 (d, J = 7.35 Hz, 2H), 6.67 (d, J = 9.0 Hz, 2H), 6.42 (d, J = 6.0 Hz, 2H), 6.37 (dd, J_1 = 9 Hz, J_2 = 6.0 Hz, 2H), 3.03 (m, 16H), 2.46 (s, 6H), 1.33 (m, 16H), 1.21 (m, 16H), 0.84 (t, J = 7.5 Hz, 24H).

Discussion

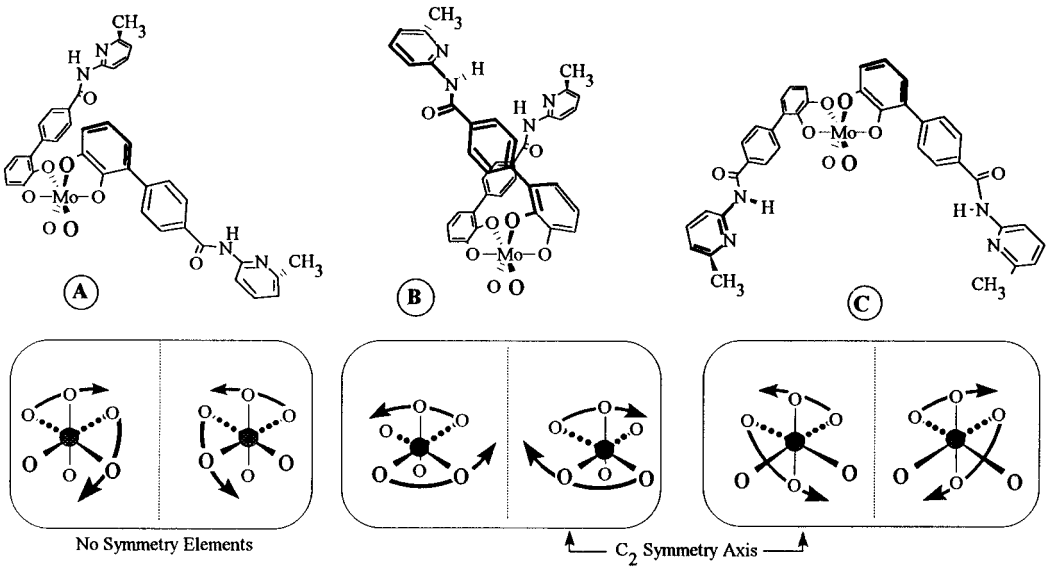
The syntheses of the half-receptors **1** and **2** were performed as depicted in Figure 1, starting from veratrole **3** and either *p*- or *m*-bromobenzoic acid. Low temperature lithiation of **3** followed by quenching with trimethyl borate and acidic workup afforded the boronic acid **4** (60% after chromatography over silica gel). The acid chlorides **5** and **6**, prepared from the appropriate bromobenzoic acid, were readily condensed with 2-amino-6-methylpyridine (**7**) in the presence of DBU to afford **8** or **9** in good yields after chromatography (SiO_2, CH_2Cl_2/traces of MeOH). The boronic acid **4** was coupled to the phenyl spacers bearing the amide **8** or **9** by "Suzuki" coupling reaction in excellent yields, using $Pd(PPh_3)_4$ in alkaline heterogeneous medium (MeOH/2 M aqueous Na_2CO_3/toluene, 1/1/5). Finally, deprotection of the catecholate chelating site was achieved using stoichiometric amounts of boron tribromide in CH_2Cl_2, affording the half-receptor **1** in 85% yield. Syntheses of the fully assembled receptors **[12]**$^{2-}$ and **[13]**$^{2-}$ were realized starting from *cis*-bis(acetylacetonato)dioxomolybdenum(VI) and by reaction in stoichiometric amounts of the half-receptor **1** or **2** in dilute conditions and in presence of a base: KOH or (n-Bu)$_4$NOH. Depending on the base used at this stage of the synthesis, the solubility of the targeted molybdenum complex in organic solvents can be controlled, and the use of (n-Bu)$_4$N$^+$ cation (*vs* K$^+$) considerably enhances the solubility of the receptor in halogenated organic solvents.

Regardless of the base used, only one pair of enantiomers out of the three possible was obtained. The reasons for ruling out the two other structures are briefly discussed hereafter. The receptors **[12B]**$^{2-}$ and **[13B]**$^{2-}$ have been characterized by standard techniques. FTIR clearly shows that the *cis*-MoO_2 geometry has been retained as two bands corresponding to the ν(Mo=O) are observed.[13] In addition to the correct molecular mass, mass spectrometry measurements confirmed in each case, the presence of the counter cations K$^+$ or (n-Bu)$_4$N$^+$. The use of potassium as counter cation induces the presence of nine water molecules detected in the elemental analyses of the receptors which should decrease its H-bonding ability toward dicarboxylic acids.

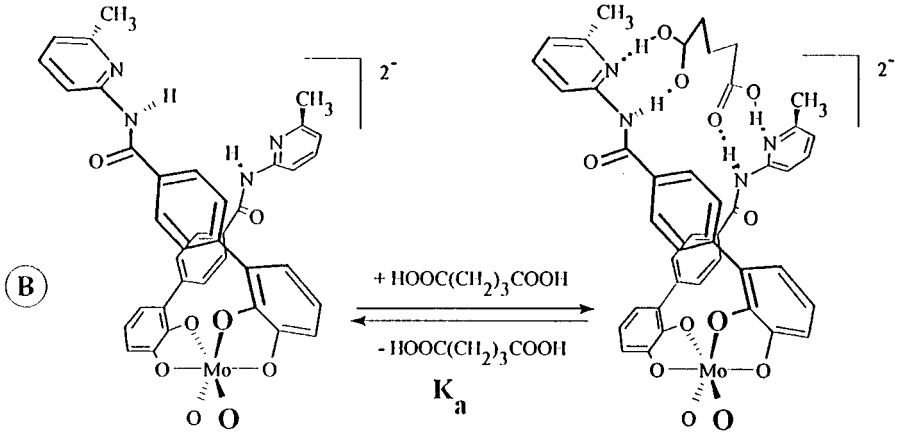
Due to the two possible orientations of each catecholate around the molybdenum atom, three pairs of enantiomers **A**, **B**, and **C** could theoretically be obtained. In Scheme 1, for receptor **[12]**$^{2-}$, are represented the possible complexes exhibiting different symmetries, which are a function of the position of the substituents of the catechol bidentates within the coordination sphere of the molybdenum. Form **B** is obtained from **A** by rotation (180°) of the front catecholate while form **C** is obtained from **A** by rotation (180°) of the back catecholate.

No symmetry axis is present in isomer **A** while both **B** and **C** exhibit a C_2 symmetry axis, and thus, will exist as pairs of enantiomers. Consequently, if **A** is formed during complexation, it should be easily identified by a more complicated ^{1}H NMR spectrum. Only signals corresponding to symmetrical species have been detected, and thus, data collected in the Experimental Section provide no evidence for the presence of form **A**. ^{1}H NMR characterization of the complexes obtained and NMR titration performed with chiral reagents (Pirkle's reagent) suggested that only one racemate had been isolated. Although isomers **B** and **C** afford the same spacing between the H-bonding sites, **C** is sterically disfavored due to the presence of the *cis*-dioxo ligands on the same side of the complex as the two (acylamino)pyridine functions. Complexation studies with glutaric acid af-

Scheme 1. Three Possible Arrangements of Substituted Catechols around MoO_2



Scheme 2. Probable Binding Mode for $[12B]^{2-}$ with Glutaric Acid



forded sufficient information to rule out structure **C**. If form **C** would be present, the proximity of the dioxo moiety should interfere with the binding occurring at the recognition site. However, monitoring glutaric acid complexation by ^1H NMR does not show significant displacement of chemical shifts for the protons located on the carbon chain of glutaric acid, which affords good evidence that the diacid binding occurs far from the *cis*-dioxo moiety.

In addition, previously reported crystal structures of MoO_2 species with substituted catecholates[13] have shown structures similar to **B**. Low temperature ^1H NMR experiments resulted in the broadening of the resonances corresponding to the phenyl spacers; no other signals were affected. Thus, no exchange occurs between forms **B** and **C**, which was expected considering the nonlability of the Mo−O bond. Thus, the complexation of dicarboxylic acids with the receptor **B** is likely to occur as depicted in Scheme 2.

UV-visible titrations were performed to assay the receptors' affinities for diacids ranging from C_4 to C_8. As it has been reported previously,[8] significant changes in the electronic absorption spectrum of receptors assembled around transition metal centers render UV-visible titrations more accurate than NMR for the determination of binding constants.

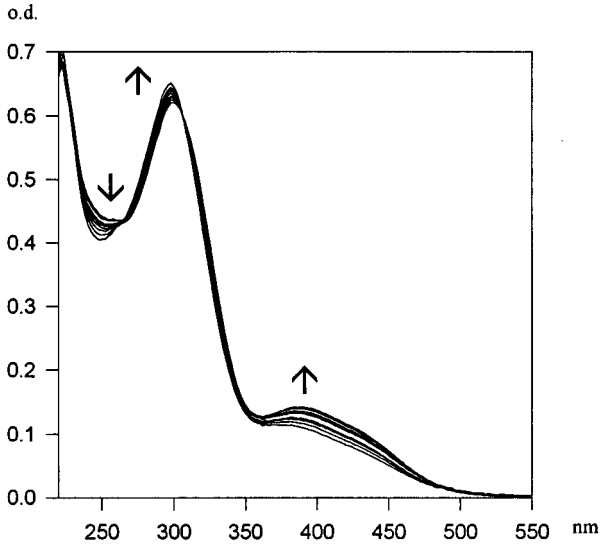


Figure 2. UV-vis titration of $[12B]^{2-}$ with adipic acid (C_6). $[12B]^{2-} = 5.0 \times 10^{-5}$ M and $[C_6] = 6.5 \times 10^{-4}$ M.

Titration curves, an example of which is given in Figure 2 for adipic acid with $[12B]^{2-}$, were analyzed using the Letagrop program (ver 2.4.93) and a 1/1 model. For each titration, the 1/1 stoichiometry of the complex

(13) See for example: Griffith, W. P.; Nogueira, H. S.; Parkin, B. C.; Sheppard, R. N.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Dalton Trans.* **1995**, 1775−1781.

Table 1.[a,c] **log K_a Values as a Function of Dicarboxylic Acids Length**[a]

receptor	counter cation	solvent	C_4	C_5	C_6	C_7	C_8
[12B]$^{2-}$	K^+	CH_3CN	*6.1 ± 0.6*	*4.3 ± 0.4*	2.9 ± 0.3	3.4 ± 0.3	3.1 ± 0.3
[12B]$^{2-}$	$(n\text{-Bu})_4N^+$	CH_3CN	*5.9 ± 0.6*	*4.5 ± 0.5*	3.5 ± 0.4	3.9 ± 0.4	2.6 ± 0.3
[12B]$^{2-}$	$(n\text{-Bu})_4N^+$	CH_2Cl_2	*b*	*7.1 ± 0.7*	5.2 ± 0.5	6.1 ± 0.6	6.2 ± 0.6
[13B]$^{2-}$	$(n\text{-Bu})_4N^+$	CH_2Cl_2	*b*	6.0 ± 0.6	*7.2 ± 0.7*	*8.9 ± 0.9*	6.5 ± 0.7

[a] $[\mathbf{12B}^{2-}] = [\mathbf{13B}^{2-}] = 5.0 \times 10^{-5}$ M. Data used for K_a calculation were collected every 2 nm from 240 to 260 nm, every 4 nm from 270 to 306 nm, and every 2 nm from 308 to 314 nm. Thus, 9 solutions were analyzed for 25 wavelengths. [b] Insoluble. [c] Italic corresponds to higher association constants. For comparison, the value of log K_a for propionic acid with the half-receptor **10** has been measured in CH_2Cl_2 to be 2.1 ± 0.2.

formation was confirmed by Job's method and the binding isotherm method.[18] Binding constants in acetonitrile (K^+ or $(n\text{-Bu})_4N^+$ as counter cation) and also in CH_2Cl_2 are collected in Table 1.

Subunits **10** and **11** by themselves exhibit poor affinity for mono- or dicarboxylic acids; however, binding of diacids is effective once the two H-bonding sites are maintained preorganized around the MoO_2 template. For comparison, association constants with propionic acid and the half-receptor **10** has been measured and is given in Table 1 caption. Alternative electrostatic binding occurring after proton transfers from the carboxylic acid to the pyridine has been ruled out for two reasons. As demonstrated by earlier studies of molecular recognition through H-bonds,[14−16] a proton transfer to the pyridine should give rise to a band at 332 nm in the UV region of the spectrum, which is not observed, neither with the half-receptors nor with the fully assembled receptors. Additionally, the release of two protons by the dicarboxylic acid would form a neutral receptor, and the electrostatic interaction would occur between the dicarboxylate and the counter cations (K^+ or NBu_4^+) present in solution. For the higher values of log K_a observed (from *ca.* 7 to 8), the corresponding ΔGs[17] are comprised between −8.5 and −9.5 kcal/mol, which is consistent with the formation of 4 H-bonds between the dianionic receptors and a neutral substrate.[16] Despite the relative rigidity of the **$[MoO_2(cat)_2]^{2-}$** framework, only a slight preference for C_4 and C_5 dicarboxylic acids is noticeable, which is, however, consistent with previous observations on [Cu(phenanthroline)$_2$]$^+$ based receptors.[8]

This could be explained by the free rotation of the CO−phenyl (spacer) bond enabling the receptor to adapt to the length of the diacid carbon chain. This free rotation is also responsible for the color changes observed during titrations. Adjustment of the distance between the two aminopyridine units to the length of each diacid leads to partial weakening of the conjugation between the amide bonds and the spacer, thus inducing a redistribution of the electronic density within the (catecholate)−MoO_2 moiety which is responsible for the visible absorption bands. Due to its less flexible structure, **[12B]**$^{2-}$ is the most chromogenic receptor. On the basis of the same number of free rotations, **[13B]**$^{2-}$ is more flexible. As depicted in Figure 3, free rotation of the same C−C bond between the catecholate moiety and the phenyl spacer allows large variations of the distance between the two aminopyridine units in the receptor **[13B]**$^{2-}$, while only

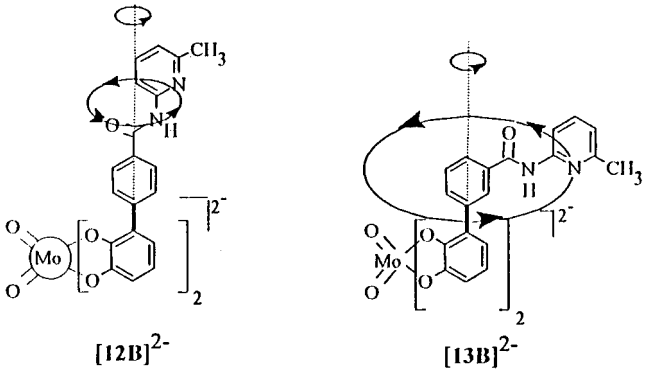


Figure 3. Topographical changes induced in **[12B]**$^{2-}$ and **[13B]**$^{2-}$ by free rotation around the axis of the spacer.

a small variation is obtained for receptor **[12B]**$^{2-}$. Thus, the adjustment to the length of the diacid for binding has a smaller effect on the electronic distribution of the chromophore in receptor **[13B]**$^{2-}$ than in receptor **[12B]**$^{2-}$. As a result of this enhanced flexibility of receptor **[13B]**$^{2-}$ in comparison to **[12B]**$^{2-}$, the difference in the binding constants as well as the selectivity regarding the length of the complexed diacid are significant. As observed in Table 1, the less chromogenic receptor **[13B]**$^{2-}$ exhibits a different selectivity, with a peak observed for C_7. The case of *N*-CBz-glutamic acid will be treated separately (*vide infra*).

The relative selectivity of the receptor **[12B]**$^{2-}$ for diacids C_4 and C_5 in CH_3CN and C_5 in CH_2Cl_2 may be expected from molecular models (CPK) and from literature reports[8,9] on copper(I) phenanthroline-based receptors. However, in the case of copper(I) receptors, the tetrahedral arrangement of substituted phenanthrolines around copper(I) seems to restrict the free rotation of the C−C bond between the phenyl spacer and the metal coordinating moiety, thus enhancing the stability of selectively formed C_5 complexes. The steric compression around the MoO_2 template in our case is apparently not sufficient for such restricted mobility which may explain the weak difference in C_4 and C_5 binding.

Considering the marked preference, in CH_2Cl_2, of receptor **[12B]**$^{2-}$ for C_5 dicarboxylic acids, and the intrinsic chirality of these receptors, the binding of chiral *N*-protected glutamic acid derivatives has been investigated. In a first analysis, for the binding of pure enantiomers, two log K_a have been calculated and are listed in Table 2. The first binding constant was obtained using a 1/1 model which corresponds to the lower limit of log K_a, and a second using a 2/1 model corresponding to the higher limit of the corresponding association constant.

From data collected in Table 2, the binding activities of **[12B]**$^{2-}$ regarding the optically pure D- and L-*N*-CBz-glutamic acid are clearly enhanced, which has prompted us to examine this binding by the combination of UV-vis

(14) Hirst, S. C.; Tecilla, P.; Geib, S. J.; Fan, E.; Hamilton, A. D. *Isr. J. Chem.* **1992**, *32*, 105−111.
(15) Geib, S. J.; Hirst, S. C.; Vicent, C.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1991**, 1283−1285.
(16) Hamilton, A. D. *Adv. Supramol. Chem.* **1990**, *1*, 1−64.
(17) Cram, D. J. *Science* **1988**, *240*, 760−767.
(18) K. A. Connors in *Binding Constants: The Measurements of Molecular Complex Stability*; John Wiley and Sons Eds.: New York, 1987.

Table 2.[a,c] **log K_a Values for Receptors $[12B]^{2-}$ and $[13B]^{2-}$**

receptor	counter cation	solvent	L-*N*-Cbz-glutamic 1/1	L-*N*-Cbz-glutamic 2/1	D-*N*-Cbz-glutamic 1/1	D-*N*-Cbz-glutamic 2/1	D,L-*N*-Cbz-glutamic 1/1	D,L-*N*-Cbz-glutamic 2/1	L-*N*-Boc-glutamic
[12B]$^{2-}$	K^+	CH_3CN	5.5 ± 0.6	9.6 ± 1.0	6.0 ± 0.6	9.8 ± 1.0	6.3 ± 0.6	10.3 ± 1.0	5.8 ± 0.6
[12B]$^{2-}$	$(n\text{-Bu})_4N^+$	CH_3CN	6.6 ± 0.7	9.6 ± 1.0	7.0 ± 0.7	10.2 ± 1.0	6.7 ± 0.7	10.6 ± 1.1	6.1 ± 0.6
[12B]$^{2-}$	$(n\text{-Bu})_4N^+$	CH_2Cl_2	*8.0 ± 0.8*	*10.6 ± 1.0*	*8.0 ± 0.8*	*11.3 ± 1.1*	*b*	11.0 ± 1.1	7.0 ± 0.7

[a] $[\mathbf{[12B]}^{2-}] = 5.0 \times 10^{-5}$ M. Data used for K_a calculation were collected every 2 nm from 240 to 260 nm, every 4 nm from 270 to 306 nm, and every 2 nm from 308 to 314 nm. Thus, 9 solutions were analyzed for 25 wavelengths. [b] Calculations not converging toward a single K_4 value. [c] Italic corresponds to higher association constants.

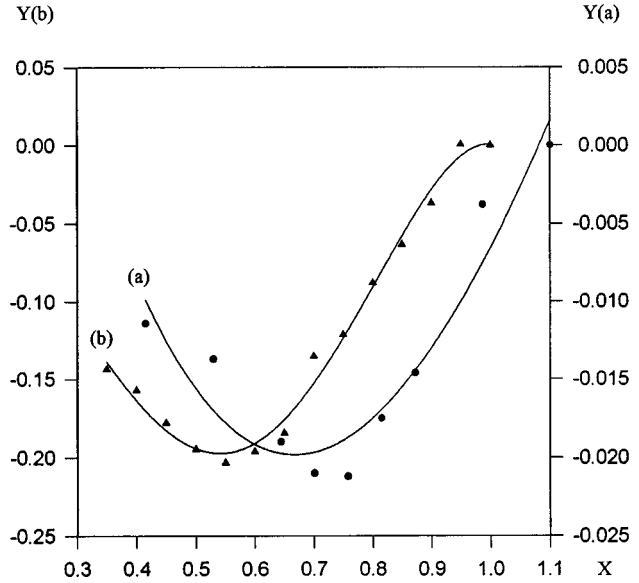


Figure 4. Job plot of the titration of **[12B]**$^{2-}$ with optically pure L-*N*-CBz-glutamic acid and with L-*N*-BOC-glutamic acid.

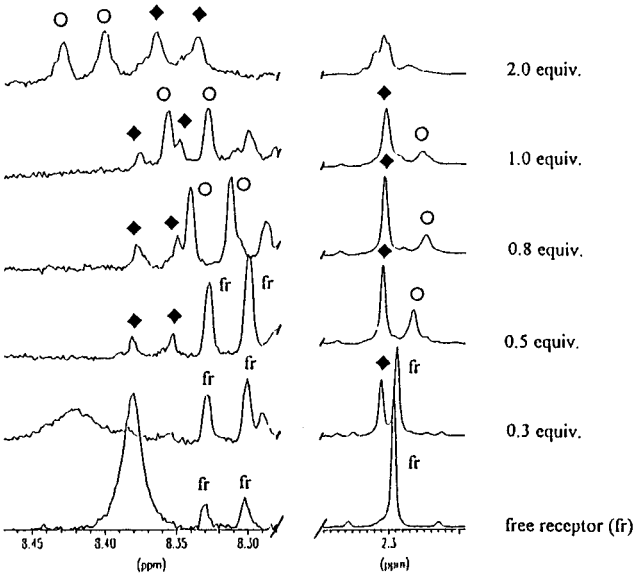


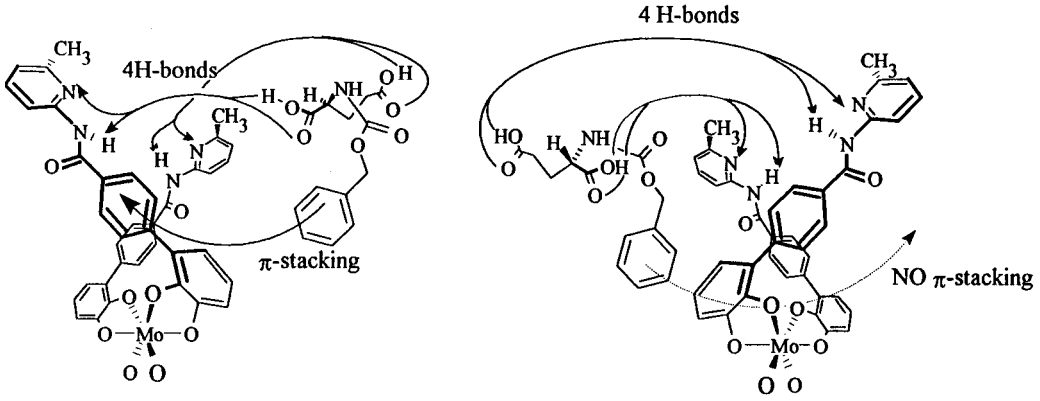
Figure 5. Evolution of ^{1}H NMR spectra during titration of **[12B]**$^{2-}$ with L-*N*-CBz-glutamic acid: (◆) first complex formed, (○) second complex formed.

methods (Job plot and K_a), and ^{1}H NMR. Attempts to determine the stoichiometry of the receptor-substrate complex formation using Job plots have resulted in graphs (Figure 4) in which, for both L and D *N*-CBz species, $Y = A_{exp} - A_R X_R - A_{acid} X_{acid}$ (X: molar fraction; A: absorbance at a given wavelength) reaches a minimum value for $X = \eta_R/(\eta_{acid} + \eta_R) = 0.66$ (η: molar amount; R: receptor; acid: dicarboxylic acid). This corresponds to a 2/1 receptor/substrate stoichiometry. The first explanation, which is less realistic, would be to consider the specific formation of a complex in which two receptors **[12B]**$^{2-}$ are bound to one substrate.

Such a possibility has been discarded on the basis that it has never been observed in any other case for regular dicarboxylic acids. The second option, which has been seriously considered, is based on the asymmetric nature of these receptors which have been considered as racemates. Compounds **[12B]**$^{2-}$ or **[13B]**$^{2-}$ are, respectively, mixtures of equivalent amounts of **(**λ**)-[12B]**$^{2-}$ and **(**δ**)-[12B]**$^{2-}$, or **(**λ**)-[13B]**$^{2-}$ and **(**δ**)-[13B]**$^{2-}$. Thus, during the complexation of pure L-*N*-CBz-glutamic acid, pairs of diastereomeric complexes will be formed. If the difference of stability between these two diastereomeric complexes is large enough, then the stoichiometry determined with the help of a Job plot will be different from 1/1. The 2/1 stoichiometry observed strongly supports the hypothesis that one diastereomeric complex is very stable and rapidly formed, while the other is not observed in the conditions of Job's method. In other words, one of the two enantiomers of the receptor is not involved in the complexation process until the most stable diastereomeric complex is completely formed. In these conditions, the first approximation made when calculating an upper limit for log K_a using a 2/1 model is adequate. No additional information could be obtained from UV-visible methods and attempts were made to confirm the stepwise formation of the diastereomeric complexes by ^{1}H NMR titrations. Due to the nature and the structure of the receptor and the substrate, only part of the proton NMR spectrum has been precisely assigned and considered as significant. The rest of the spectrum corresponded to the overlay of aromatic signals from the receptor and the *N*-CBz group of the substrate. In particular, the area between 1.5 and 2.5 ppm is useful and corresponds to the region in which the methyl groups of the aminopicoline function in both the free receptors and the resulting complexes are observed. The formation of one or several species could be distinguished in this region as well as at fields higher than 8.5 ppm. The evolution of the proton NMR spectra during titration in the areas defined above is represented in Figure 5.

This evolution indicates that upon addition of L-*N*-CBz-glutamic acid an initial type of complex forms immediately (peaks indexed ◆). This complex is stable and continues forming until 0.5 equiv of acid is added. When more than 0.5 equiv of acid is added, a second type of complex is formed (peaks labeled ○). As the first complex formed (◆) exhibits sharper signals than the second complex (○), to a first approximation, this demonstrates that the less favored complex is in fast exchange with its dissociated form, while the first complex produced preferentially is in slow exchange with its dissociated form. In presence of an excess of L-*N*-CBz-glutamic acid the uncompleted formation of the less favored complex still occurs as shown by the continuous shift of the peaks (○) corresponding to the complex. It is remarkable that

Scheme 3. Representation of (λ)-[12B]$^{2-}$ and (δ)-[12B]$^{2-}$ and Possible Interactions with L-*N*-CBz-Glutamic Acid



the peaks corresponding to the most favored complex are only slightly affected by the excess of chiral diacid added, most of the peaks assigned being only slightly broadened for 2.08 equiv added. The first complex formed is more stable than the second and corresponds to the preferential binding of one component of the racemic mixture of **[12B]**$^{2-}$ and thus, the preferential formation of a diastereomeric complex. When a large excess of acid is added, the equilibria leading to the formation of both enantiomeric complexes are displaced, no free ligand being observed and both complexes being formed in comparable amounts. A qualitative analysis confirms that in the presence of chiral substrate, two different complexes are formed, with different rates of formation and different stability constants. This is in agreement with the hypothesis of two forms (λ and δ) of the receptor complexing one form of a chiral substrate.

Such behavior may result from an additional interaction in the binding of one enantiomer. After duplication of the titration and repeating the exact same experiment with the pure D-enantiomer of the protected acid with the racemic receptor **[12B]**$^{2-}$, the examination of molecular models led to the schematic representation depicted in Scheme 3 and afforded a reasonable interpretation of the observed enantioselective binding.

As illustrated by the differences between log K_as for Cbz and BOC protected glutamic acids (even when the lower limit of log K_a is considered), the nature of the protecting group on the glutamic acid is essential in the selection of one enantiomer compared to the other, and the only additional interaction which may be developed between the receptor and the substrate is a π−π stacking between the aromatic spacers of the receptor and the protecting group of the acid. Scheme 3 summarizes the favored and disfavored formation of the diastereomeric complexes of the L-protected acid with **[12B]**$^{2-}$. This hypothesis is in agreement, for receptor **[12B]**$^{2-}$, with the results of binding experiments with the optically pure BOC protected L-glutamic acid. As expected, the Job plot from UV-visible data confirmed a 1/1 stoichiometry (Figure 4), and the formation of the receptor−substrate complex was less efficient. UV-visible titrations yielded a log K_a value of 6.1 in acetonitrile and 7.0 in methylene chloride similar to those obtained for glutaric acid (7.1 in methylene chloride). This selectivity is not in contradiction with the weak selectivity observed regarding the length of the diacid chains and illustrates the fact that strong interactions are not a prerequisite for selective recognition and that several weak interactions appropriately preorganized may be responsible for distinction between optical isomers. Such titrations have not been performed with receptor **[13B]**$^{2-}$ as this receptor exhibits a marked selectivity for C_7 dicarboxylic acids. The same type of experiments carried out with a racemic mixture of D,L-*N*-CBz-glutamic acid has given the same type of Job plot, binding isotherms, and the same value for the upper limit of log K_a. Using a 1/1 model for treating the titration data for the racemic mixture of *N*-CBz glutamic acid did not converge toward a single log K_a value. This would suggest that the titration of the racemic substrate should be considered as the simultaneous titration of two enantiomers of the substrate with the appropriate enantiomers of the receptors and that only one pair of diastereomers are formed with identical association constants. The specificity of this recognition is currently studied, mostly by 2D ^{1}H NMR and titrations with other chiral substrates. The detailed results and proofs of this interpretation will be published separately.

Conclusion

The concept of preorganizing multipoint H-bonds around transition metal complexes developed on copper and ruthenium with nitrogen-containing ligands may be extended to functionalized catechols and molybdenum. This approach offers the advantage of producing, under mild conditions, nonlabile transition metal complexes, such as receptors **[12B]**$^{2-}$ and **[13B]**$^{2-}$, which, respectively, display strong binding for glutaric and pimelic acids. In addition, the receptor racemic **[12B]**$^{2-}$ displays enhanced enantioselective recognition of optically pure L- or D-*N*-(carbobenzyloxy)glutamic acid, via directed multipoint hydrogen bonding and lipophillic interactions with a topographical control achieved via a *cis*-dioxomolybdenum core.

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