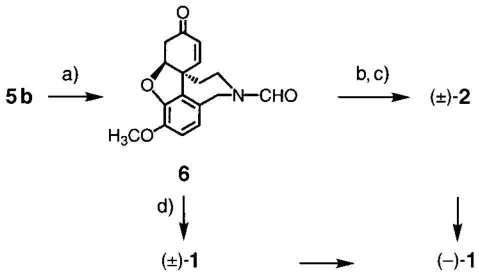

Scheme 2. a) 1) Tf_2O, pyridine, 99 %, 2) $Pd(OAc)_2$, PPh_3, Et_3N, HCO_2H, 97 %; b) ethylene glycol, PPTS, 92 %; c) 1) $LiAlH_4$, 2) HCl, 83 % (2 steps); d) 1) L-Selectride, 2) $LiAlH_4$, 61 % (2 steps). PPTS = pyridinium *p*-toluenesulfonate.

carbonyl group, as previously reported.[5g] (±)-Galanthamine has been optically resolved previously,[5g] and (±)-narwedine (**2**) has been converted into (−)-galanthamine (**1**).[5i,j, 8c] Therefore, the described efficient route to (±)-narwedine (**2**) and (±)-galanthamine implies a formal total synthesis of (−)-galanthamine (**1**).

In conclusion, we were able to improve the pivotal phenolic oxidative coupling reaction of norbelladine-type derivatives, which had been limited to moderate yields over 40 years, and have provided an efficient synthetic route for the industrial production of (−)-galanthamine (**1**).

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[9] The norbelladine-type derivatives **3a–h** were easily prepared from methyl gallate and tyramine in high yields, according to ref. [5d] and [5e].

[10] Typical procedure for the improved phenolic oxidative coupling: To a solution of **3d** (2.0 g, 4.0 mmol) in 2,2,2-trifluoroethanol (100 mL) was added a solution of PIFA (1.9 g, 4.4 mmol) in 2,2,2-trifluoroethanol (10 mL) at −40 °C under nitrogen, and the resulting mixture was stirred for 1 h. After the evaporation of the solvent under reduced pressure, the product **4d** (1.29 g, 65 %) was isolated by crystallization of the residue from ethyl acetate. The additional crop of **4d** (341.5 mg, 17 %) was obtained by column chromatography (chloroform/methanol 20:1) of the condensed mother liquor, followed by crystallization from ethyl acetate. **4d**: colorless needles; m.p. 187–189 °C (dec.) (ethyl acetate); ^1H NMR spectra of a mixture of two conformational isomers were measured. The signals for the minor isomer are shown in parentheses. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = (8.21) 8.19 (s, 1H; CHO), 7.47–7.22 (m, 10H), (7.05) 6.98 (d, J = 10.2 Hz, 2H), (6.76) 6.57 (s, 1H; Ar-H), 6.14 (d, J = 10.2 Hz, 2H), 5.15 (5.14) (s, 2H), 4.88 (4.84) (s, 2H), (4.69) 4.60 (s, 2H), 3.75 (3.74) (s, 3H), 3.71 (3.65) (t, J = 6.2 Hz, 2H), (2.29) 2.26 (t, J = 6.2 Hz, 2H); IR ($CHCl_3$): $\tilde{\nu}$ = 1663 (C=O, dienone), 1620 and 1593 (C=O, formyl), 1123 cm^{-1} (C–O); EI-MS (70 eV): m/z (%): 465 (7) [M^+], 404 (6), 91 (100), 65 (7); HRMS calcd for $C_{31}H_{29}NO_5$ [M^+]: 495.2045, found: 495.2052; elemental analysis: calcd (%) for $C_{31}H_{29}NO_5$: C 75.13, H 5.90, N 2.83; found: C 75.26, H 5.98, N 2.92.

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Aqueous One-Pot Synthesis of Derivatized Cyclopentadienyl–Tricarbonyl Complexes of ^{99m}Tc with an In Situ CO Source: Application to a Serotonergic Receptor Ligand[**]

Joachim Wald, Roger Alberto,[*] Kirstin Ortner, and Lukas Candreia

The radionuclide ^{99m}Tc is among the most widely used isotopes in diagnostic nuclear medicine.[1] It is cheap, exhibits good decay characteristics, and typically burdens the patient with a low radiation dose. Whereas in the past ^{99m}Tc-complexes were preferentially applied as perfusion agents,[2] a challenge now lies in combining a ^{99m}Tc complex with a targeting molecule such as a tumor-specific peptide or a small

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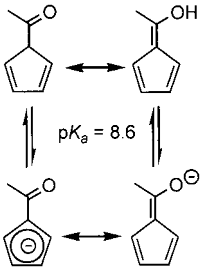
CNS receptor-binding molecule, as recently highlighted.[3] The numerous technetium or rhenium complexes that have been investigated in either case are essentially of the Werner type, comprising tetradentate N,S-ligands or polyamino polycarboxylates.[4] One such complex, which has become the most important myocardial imaging agent, is an organometallic compound.[5] Since any clinically useful diagnostic agent ultimately has to be prepared in water, the difficulty in using sensitive organometallic ligands such as cyclopentadienyl (Cp) is evident.

Apart from these feasibility considerations, the Cp ligand offers very attractive properties as a ligand for radiopharmaceutical purposes. Its inherent advantages are the small size, the low molecular weight, and the stability of half-sandwich complexes, $[CpM(CO)_3]$ (**1**; Me = Re and Tc). These highly crucial prerequisites minimize steric interference with the receptor binding part of a labeled biomolecule. Complexes **1** are highly lipophilic, which makes them particularly interesting as labeled, blood–brain barrier-crossing molecules.

The fact that **1** (M = Re) can be coupled to biomolecules by classical organometallic methods without affecting the bioactivity has been demonstrated by several groups.[6] The physiological stability of the complexes $[(R\text{-}Cp)Re(CO)_3]$ (**2**; R = steroid hormone,[7] antibody,[8] etc.) initiated investigations into the preparation of $[(R\text{-}Cp)^{99m}Tc(CO)_3]$ (**2a**). Wenzel reported a double ligand-transfer reaction, which ultimately led to the formation of **2a** starting from $[^{99m}TcO_4]^-$.[9] Based on this approach, further improvements towards a general synthesis of **2** and **2a** have recently been published[10] and octreotide was labeled in a five-step procedure.[11] Both approaches still suffer from unacceptable reaction conditions for routine use.

We recently reported the synthesis of *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$ (**3a**) directly from $[^{99m}TcO_4]^-$ in water.[12] Precursor **3a** is a very versatile source of the "*fac*-$[^{99m}Tc(CO)_3]^+$" moiety which accepts different chelators for the remaining three positions. Attempts to coordinate cyclopentadienyl or fulvene derivatives to **3a** failed or resulted in very low yields. This lack of reactivity is in agreement with the low tendency of neutral alkenes to compete with water in $[M(OH_2)_3(CO)_3]^+$ (M = ^{99m}Tc, Re). Alkyl η^1 coordination of deprotonated cyclopentadiene as the synthetic key step,[13] preceding ring slippage to η^5-coordination, is unlikely owing to its prohibitively high pK_a of about 14.

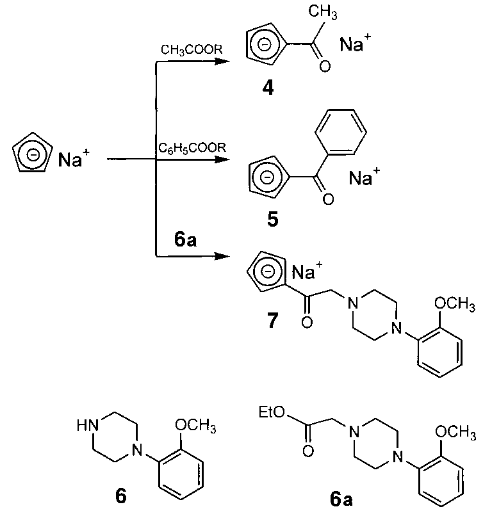


Scheme 1. Acidification of acetyl cyclopentadiene **4** by keto–enol tautomerism. Several isomers are possible.

The key step in the preparation of **2a** in water lies in the ability of a Cp-derivative to be deprotonated to a reasonable extent at physiological pH. This can be achieved by introducing electron-withdrawing substituents. The requirements of delocalizing the resulting negative charge over the Cp system prompted us to investigate the well-known acetyl cyclopentadiene (**4**; ACp),[14] in which the keto–enol tautomerism stabilizes the deprotonated form (Scheme 1).

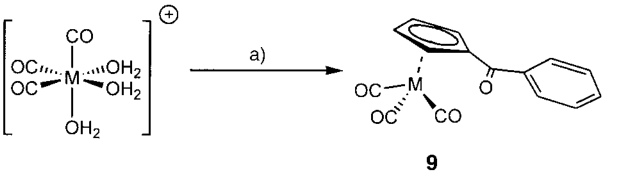
The pK_a value of formyl cyclopentadiene is about 8.[15] More accurately, we found that the pK_a value of **4** is 8.62(1) in 0.1M NaCl (potentiometric titration), which means an increase in acidity by about 5 orders of magnitude relative to cyclopentadiene. Thus, about 5% of **4** is dissociated at physiological pH. The enolate form of **4** should be able to coordinate efficiently to **3a** or its Re analogue, either through the alkoxide group, with subsequent intramolecular rearrangement, or directly to the negatively charged cyclopentadienyl ring, to afford the desired half-sandwich complex as the thermodynamic product.

The preparation of differently substituted carbonyl cyclopentadienyl compounds (Na[R-Cp]) by the reaction of NaCp with an ester functionality is straight forward and gives typically 50–60% yields. As a model for steroids, we introduced a phenyl group instead of the methyl group to get benzoyl-Cp (BCp) **5**. To assess the possibility of attaching Cp to more complicated (bio)molecules, we have chosen a lead structure of the class of aryl piperazines, 1-(2-methoxyphenyl)piperazine **6**, which are among the most thoroughly studied ligands for the 5-HT$_{1A}$ subclass of serotonergic receptors (Scheme 2).[16] Its Cp derivative **7** was prepared in the same way, after alkylation of the piperazine ring in **6** with ethyl bromoacetate to give **6a**. The pK_a values for **7** were found to be >12.5, 8.71(1), and 6.37(1). The dissociation constants pK_{a1} and pK_{a3} were assigned to the tertiary amine groups, and pK_{a2} represents the dissociation constant of cyclopentadiene. In contrast to NaCp, **4**, **5**, and **7** are reasonably soluble in water and are stable for hours, even when exposed to air.



Scheme 2. Derivatization of the cyclopentadienyl group with different organic (bio)molecules.

To demonstrate the possibility of preparing complexes with the general composition **2** (M = Tc or Re) directly in water, **3** was treated in phosphate buffer at pH 7.4 with **4**. Within 2 h at 85 °C, $[(ACp)M(CO)_3]$ (**8**) formed in about 15–25% yield for Re, and 40% for Tc. This is one of the first examples in which a Cp derivative reacts in water with an organometallic precursor to yield the corresponding half-sandwich complex. We anticipate that this convenient strategy can be extended to the preparation of other half-sandwich complexes, probably containing water ligands. As depicted in Scheme 3, the preparation of **2** directly in water is not restricted to **4**; compound **5** and the receptor binding molecule **7** also reacted comparably in water with **3** to yield the corresponding complexes $[(Cp')M(CO)_3]$ (**9**, Cp′ = **5**; **10**, Cp′ = **7**).



Scheme 3. Synthesis of cyclopentadienyl complexes $[(R\text{-}Cp)M(CO)_3]$ (M = Re) in water. Reagents and conditions: a) **5**, phosphate buffer, pH 7.4, 2 h, 85 °C.

The observed dimerization of the ligands at elevated temperatures and higher concentrations can be compensated by a slight ligand excess. The limitation of the yield essentially arose from the competing hydrolytic reaction of **3** with the very stable cluster compound $[M(\mu_3\text{-OH})(CO)_3]_4$, which represents the only rhenium-containing by-product.[17] The rhenium compounds of **9** and **10** were crystallized, and their structures were elucidated by X-ray studies. A SCHAKAL representation of **10** is given in Figure 1.[18, 19]

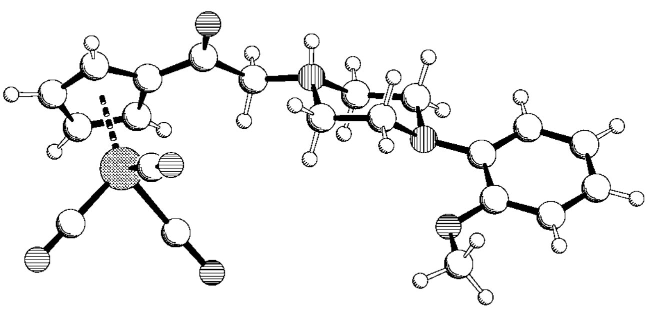


Figure 1. SCHAKAL representation of complex **10** (Re) with protonated piperazine shown without the counterion Cl⁻.[19]

Complex **9** (M = Re) has been prepared by Friedel–Crafts acylation of **1** by Fischer et al.[20] The crystal structures of **9** and **10** exhibit the typical piano-stool arrangements. The average bond lengths of Re–C(η^5) are 2.31 Å in both cases.

The preparation of $[(R\text{-}Cp)Re(CO)_3]$ directly in water offers a convenient alternative to the classical approach, which starts from $[ReBr(CO)_5]$ in benzene.[21] This is particularly important for the syntheses of half-sandwich complexes with a pendant biomolecule, since the latter are often insoluble in common organic solvents. The availability of a "cold" compound is essential for radiopharmaceutical application of the labeled "hot" biomolecules, as their characterization is only possible by chromatographic comparison.

To examine the potential of this novel approach for routine preparations of Cp-derivatized biomolecules such as **7** labeled with ^{99m}Tc, we transferred the reaction conditions to the no-carrier-added (n.c.a.) level. For kinetic reasons, cluster formation as the major competing reaction is not expected, since the concentration of ^{99m}Tc is very low (nM – µM range). The precursor **3a** was prepared as previously reported,[12] buffered (phosphate buffer, pH 7.4, 1 – 2 cm^3), and then mixed with an aqueous solution containing, for example, 0.1 – 1 µmol of **4**. The reaction was carried out for 15 min at 90 °C to afford the corresponding complex **8**(^{99m}Tc) in quantitative yield. Its identity was confirmed by coinjecting **8**(Re) and **8**(^{99m}Tc) into the HPLC (high-pressure liquid chromatrograph) (Figure 2), thus allowing the simultaneous detection by UV absorption and radiodetection (retention times 21.5 min for the Re-species and 21.9 min for the ^{99m}Tc-species; the delay is a result of the separation of the two detectors).

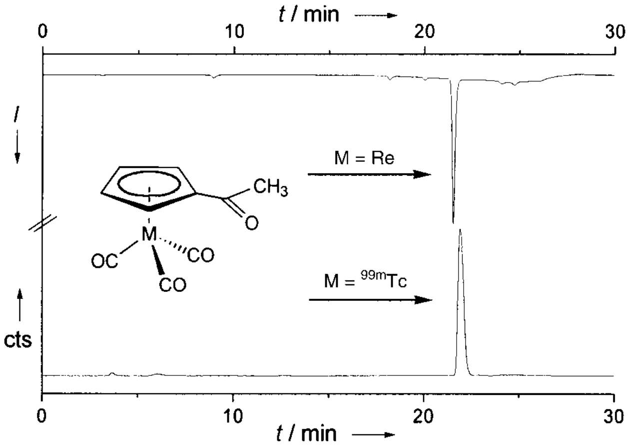
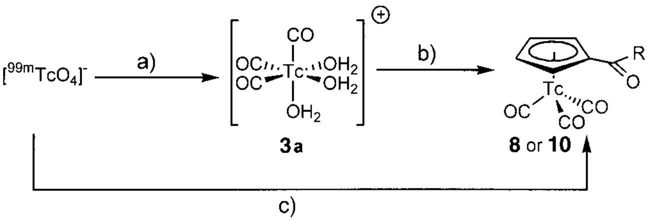


Figure 2. The upper trace shows the UV absorption at 250 nm for **8** (Re); the lower trace shows the radioactive trace for the corresponding ^{99m}Tc complex, proving their identity (delay due to detector separation).

This synthetic pathway was also applied to the Cp-derivatized serotonergic receptor ligand **7** with identical results. Excess **7** dimerizes during the reaction and the precipitate can be removed by filtration, thus increasing the specific activity efficiently, which may be of importance for preventing a saturation of in vivo receptors with a "cold" substrate. This unique reaction clearly reveals the high potential behind the chosen approach, which allows the preparation and use of half-sandwich ^{99m}Tc-complexes in physiological solutions for the first time, in quantitative yield and convenient for routine use.

At this stage, the reaction consisted of two steps, the initial preparation of **3a** and subsequent reaction with the respective Cp-derivatized (bio)molecule. To achieve a true one-pot synthesis for $[(R\text{-}Cp)^{99m}Tc(CO)_3]$, we introduced potassium boranocarbonate (**11**, $K_2H_3BCO_2$), the preparation and properties of which were recently reported by us.[22] Boranocarbonate **11** is an air-stable reducing agent, and acts as an in situ CO source in water at elevated temperatures. The simple addition of $[^{99m}TcO_4]^-$ in a saline solution to a vial that contained a small amount of **11**, is sufficient to give **3a** in quantitative yield. If, in addition to **11**, a small amount of the Cp-derivative **4** or **7** was present, 40 min at 90 °C was sufficiently long to produce the corresponding half-sandwich complexes **8** or **10** (^{99m}Tc) in a single step in > 95 % yield (Scheme 4).



Scheme 4. One- and two-step synthesis of complexes **8** and **10** (^{99m}Tc) directly in water and $[^{99m}TcO_4]^-$. Reagents and conditions: a) CO (1 atm), $NaBH_4$, pH 12 or $K_2[H_3BCO_2]$ only, >98%. b) **4** or **7** (0.1–1 μmol), 15 min 90°C, >98%. c) 0.1–1 μmol **4** or **7**, $K_2[H_3BCO_2]$ (**11**; 4 mg), $Na_2B_4O_7$, pH 10, 40 min 90°C, >95%.

Besides the major product, a second complex was formed in minor amounts, with a similar retention time. It is likely that **11** reduced the carbonyl group in **8** to a hydroxy group. We assume that the one-pot reaction is consecutive $[^{99m}TcO_4]^- \rightarrow$**3a**$\rightarrow$**8** or **10**. All the compounds labeled with ^{99m}Tc were stable in phosphate buffer for at least 24 h at 37°C without any significant decomposition, thus confirming the highly robust nature of $[(R\text{-}Cp)M(CO)_3]$.

We demonstrated herein that half-sandwich complexes $[(R\text{-}Cp)M(CO)_3]$ can easily be synthesized if the acid dissociation constant of the cyclopentadiene ring is increased. The reaction of acetyl cyclopentadiene and derivatives with $[^{99m}Tc(OH_2)_3(CO)_3]^+$ directly yielded the radiopharmaceutically relevant complexes $[(R\text{-}Cp)^{99m}Tc(CO)_3]$ in good yields. The major impact of this work emerges from the general possibility of introducing the very small and highly lipophilic $[Cp^{99m}Tc(CO)_3]$ moiety in a wide variety of small receptor-binding biomolecules. Furthermore, the direct reaction of acidic and water-soluble cyclopentadiene compounds with aqua ions could lead to interesting and novel species in aqueous organometallic chemistry.

Experimental Section

7: Alkylation of 1-(2-methoxyphenyl)piperazine (Fluka) with ethyl bromoacetate for 24 h at room temperature in the presence of Hünig's base, and purification on silica gel (CH_2Cl_2/ethylacetate 4:1 v/v) afforded **6a** in 65–70% yield. NaCp was freshly prepared in situ from Na (0.3 g, 12.7 mmol) and the corresponding amount of freshly distilled dicyclopentadiene. Compound **6a** in THF (1.8 g, 6.4 mmol) was added to the NaCp solution and heated at about 60°C for 6 h to afford a precipitate, which was isolated by filtration under N_2. The solid was washed several times with *n*-hexane to leave an almost colorless powder, which was recrystallized from hot THF to give analytically pure **7**. ^{1}H NMR (200 MHz, D_2O): $\delta = 7.0$ (m, 4H), 6.60 (brs, 2H), 6.15 (brs, 1H), 6.06 (brs, 1H), 3.74 (s, 3H), 3.50 (s, 2H), 2.95 (brs, 4H), 2.70 (brs, 4H); ^{13}C NMR (300 MHz, D_2O): $\delta = 182.4$, 150.4, 138.2, 122.5, 122.2, 119.1, 116.9, 116.5, 115.9, 114.2, 111.3, 109.7, 59.8, 53.0, 50.5, 48.1.

8: Compound **8** can be synthesized according to published routes, starting from $[ReBr(CO)_5]$ or directly from an aqueous buffer solution. $(NEt_4)_2[ReBr_3(CO)_3]$ (130 mg, 0.15 mmol) in phosphate buffer (15 mL) was added dropwise over a period of 2 h to compound **7** (70 mg, 0.18 mmol) dissolved in phosphate buffer (15 mL, pH 7.4). The mixture was heated for 3 h at 75°C, causing a brownish precipitate containing the product, as shown by using HPLC. The precipitate was filtered and dissolved in CH_2Cl_2. Separation of the product was performed by silica-gel column chromatography. Elution with CH_2Cl_2 gave nonpolar side products, whereas subsequent elution with CH_2Cl_2/2-propanol (80:1 v/v) gave compound **8** (20 mg, 23%). The product was recrystallized from an acidic mixture of EtOH/water by slow evaporation of ethanol. ^{1}H NMR (200 MHz, CD_3CN): $\delta = 6.9$ (m, 4H), 6.24 (t, 2H), 5.53 (t, 2H), 3.79 (s, 3H), 3.48 (s, 2H), 3.05 (t, $J = 4.8$ Hz, 2H), 2.65 (t, $J = 4.8$ Hz, 2H); ^{13}C NMR (300 MHz, CD_3CN): $\delta = 193.7$, 153.3, 142.4, 124.1, 121.9, 119.2, 112.0, 96.1, 90.2, 89.7, 87.4, 86.9, 65.6, 54.2, 50.9. FAB-MS (fast-atom bombardment mass spectrometry): $[M^+]$ 567.8 (567).

$[(R\text{-}Cp)^{99m}Tc(CO)_3]$: The starting material $[^{99m}Tc(OH_2)_3(CO)_3]^+$ (**3a**) was prepared as described elsewhere.[12, 22] An aqueous solution of **7**, for example, in phosphate buffer was added to **3a** (final concentration of **7** = 10^{-3}–10^{-4} M). Subsequent heating at 95°C for 15 min afforded $[(R\text{-}Cp)^{99m}Tc(CO)_3]$ in overall yields >95%. The HPLC retention times for **8** and **10** are 21.9 and 20.5 min, respectively.

For the one-pot synthesis of **8** or **10** (M = ^{99m}Tc), a vial was charged with **11** (4 mg, reducing agent and CO source) and $Na_2B_4O_7$ (5.5 mg), sealed and flushed with dry N_2. Generator eluate (2 cm^3) containing $[^{99m}TcO_4]^-$ was added, followed by an aqueous solution of **4**. Heating at 90°C for about 40 min gave **8** or **10** in high yields (≈80% and ≈20% reduced form). The yield and time course of the reaction were not influenced by the total amount of radioactivity (up to 20 GBq of ^{99m}Tc).

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[18] Crystallographic analysis: **10** ($C_{21}H_{22}ClN_2O_5Re$), colorless column, $0.19 \times 0.08 \times 0.03$ mm^3, monoclinic, space group $P2_1/c$, $a = 22.8795(14)$, $b = 14.0402(11)$, $c = 7.1351(4)$ Å, $\beta = 94.495(7)^\circ$, $V = 2285.0(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.756$ g cm^{-3}, R_1 ($I \geq 2\sigma(I)$) = 0.0325, wR_2 (F^2) = 0.1090 for 22230 data (5468 independent, 1263 observed

($I \geq 2\sigma(I)$)), 275 parameters, 6 restraints, numerical absorption correction, $\mu = 5.468\,\mathrm{mm}^{-1}$, $T_{\mathrm{min}} = 0.5802$, $T_{\mathrm{max}} = 0.8524$. Single crystals of **10** were obtained by dissolving the product in a slightly acidic EtOH/water mixture and slow evaporation of ethanol. Data were collected on a Stoe IPDS diffractometer using graphite-monochromated $\mathrm{Mo}_{K\alpha}$ ($\lambda = 0.71073$ Å) radiation, and were corrected for Lorentz, polarization, and absorption effects. The structure was solved by direct methods with SHELXS97 and refined with SHELXL97 on F^2 using all data with all non-hydrogen atoms anisotropically defined.[23] The hydrogen atoms were placed in calculated positions and isotropically refined with thermal parameters at $1.5 \times U$(eq) of the parent carbon atom, except for the piperazyl-N(H) which was found in the difference Fourier map and isotropically refined. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-160745 (**9**) and CCDC-160746 (**10**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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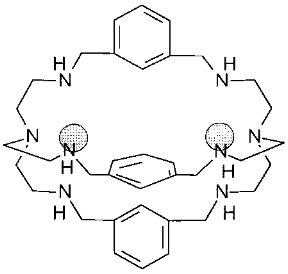
A Chemosensing Ensemble for Selective Carbonate Detection in Water Based on Metal–Ligand Interactions**

Luigi Fabbrizzi,* Antonella Leone, and Angelo Taglietti

The classical approach to the design of a fluorescent sensor involves the covalent linking of a fluorescent fragment (the "signaling unit") to a receptor, which displays specific binding tendencies towards a given analyte. In order to communicate the occurrence of the recognition event to the outside world, the receptor/analyte interaction must affect, to some extent, the emission properties of the signaling unit—either quenching the fluorescence through a defined mechanism (usually energy or electron transfer) or enhancing it by suppressing a pre-existing quenching process.[1]

Recently, Anslyn and co-workers[2] have taken inspiration from antibody-based biosensors in immunoessays and developed an efficient "competition" approach to the design of chemosensors: according to the so-called "chemosensing ensemble" approach, the plain receptor interacts in solution with a colorimetric or fluorescent indicator, namely, a highly colored or light-emitting substrate. Two main requirements have to be fulfilled: the receptor/indicator interaction must not be too strong and the indicator must show significantly different optical properties when bound to the receptor and when dispersed in solution. Thus, the indicator is displaced from the host cavity on titration with the desired analyte and released to the solution, where it displays drastically different optical features. Hence, the occurrence of the recognition event is communicated by either a substantial color change or a dramatic modification of the light emission. In their competition studies Anslyn and co-workers considered anion receptors capable of interacting with the analyte through formation of hydrogen bonds. Typical investigated analytes were citrate, tartrate, malate, and inositol triphosphate. The procedure of competitive spectrophotometry has been treated in detail by Connors.[3] Ueno and co-workers later extended the approach by covalently linking the dye to the receptor.[4]

We now extend the competition approach to the fluorescent sensing of anions by making use of a different type of receptor–analyte interaction: metal–ligand (coordinative) interactions. Coordinative interactions present some substantial advantages compared to hydrogen bonding and, in general, to electrostatic interactions.[5] In fact, they can be highly energetic as a result of the strong ligand-field stabilization energy effects that may be induced by coordination. Moreover, transition metal ions present definite stereochemical preferences which can be addressed to impart selective binding tendencies towards anions of a given shape. In order to benefit from these features, metal–ligand interactions have been utilized in the design of anion receptors operating in highly polar media, including pure water. In this connection, we have shown that the dicopper(II) cage complex **1** is capable of including polyatomic anions within its intermetallic cavity in an aqueous solution buffered at pH 8. The ion selectivity is determined by the bite length of the anion, that is, the distance between two consecutive donor atoms.[6] In particular, receptor **1** showed a definite preference towards the triangular $\mathrm{HCO_3^-}$ ion[7] and the two linear triatomic ions $\mathrm{N_3^-}$ and $\mathrm{NCO^-}$, whose bite length range between 2.28 and 2.42 Å. The intrinsic limit of receptor **1** as a proper molecular sensor is that only small changes in the absorption spectra and in the color are observed following anion recognition. For example, in the case of $\mathrm{HCO_3^-}$ ions, the color turns from the pale blue of the void receptor to the pale



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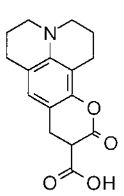

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