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Synthesis and characterization of a potential bifunctional C_{60} - I_h fullerene-based catechol amide ligand

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The new C_{60} - I_h fullerene-based catechol amide derivatives C_{60} {C[COO(CH₂)_nCAM]₂} [n = 2, 3 or 4; CAM = 2,3-Ph(OH)₂CONH] were prepared using a modified Bingel-type reaction of C_{60} - I_h and characterized by variable-temperature ¹H NMR spectroscopy.

Radioactive elements can induce radiological and chemical intoxication.^{1–3} Internal radiation can produce harmful free radicals that activate apoptosis, which disables cell repair and leads to cell death.^{4–5} Thus, actinides should be eliminated from the body by chelating agent administration. Chelating agents form stable complexes with actinides so that the body can rapidly excrete a poison from blood and target organs. In addition, harmful free radicals should also be removed.

Sulfocatechol tiron (4,5-dihydroxy-1,3-benzenedisulfonic acid disodium salt) containing a catechol unit with two *meta*-sulfonate groups forms stable actinide complexes in a physiological pH range.⁶ Raymond *et al.*⁷ examined actinide-sequestering agents based on sulfocatecholamide (CAMS) ligands, which produced the low-toxicity ligand 5-LICAM(S). The latter has been identified as a suitable agent for the chelation of actinides *in vivo*. Leydier *et al.*⁸ described the synthesis and characterizaton of linear tetra-dentate ligands with various diamine backbones containing catecholamide (CAM). Among these ligands, 5-CYCAMS exhibited a great complexing ability under physiological conditions. The bifunctional CAM derivatives including calixarene-based CAM (1,3-CalixCAM),^{9,10} binol-based CAM (BINCAMS)¹¹ and EDTA-CAM¹² were synthesized. They have an efficient decorporation ability, but none possesses the capability to scavenge free radicals.

 C_{60} - I_h is the most studied fullerene. The spherical shape of C_{60} consists of 30 carbon–carbon double bonds, which determine its pseudo-aromatic structure due to the delocalization of π -electrons over its carbon core. Therefore, C_{60} can readily react with free radicals, ¹³ and this molecule was referred to as a free-radical sponge.¹⁴ However, C_{60} can be dissolved in toxic solvents, such as chlorobenzene, dichlorobenzene and toluene. The most versatile method to solve this limitation is the chemical modification of C_{60} that produces water-soluble fullerene derivatives as free-radical scavengers.^{15–19} Thus, the synthesis of C_{60} derivatives with good water solubility, high complexing ability and radical-scavenging activity is in great demand.

Therefore, a rational compound composed of C_{60} and CAM was designed in this study. We present here the synthesis of a 1,3-dicarbonyl biscatecholamide ligand and new C_{60} - I_h fullerene-based CAM ligands (Scheme 1).[†]

First, 2,3-dibenzyloxybenzoic acid 2 (80%) was prepared from commercially available 1.²⁰ Then, 3a-c and 2 were condensed

using HOBt/DCC to result in benzamides **4a–c** in 90% yields.²¹ The reaction between benzamides **4a–c** and malonyl dichloride in the presence of Et_3N in anhydrous CH_2Cl_2 afforded biscate-cholamide malonates **5a–c** in 90% yields. C₆₀-monoadducts



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[†] For detailed procedures and characteristics of the products obtained, see Online Supplementary Materials.

7a–c were synthesized using CBr_4 and DBU according to Hirsch *et al.*²²

The FTIR spectra of C₆₀-monoadducts **7a–c** were nearly superimposable with those of compounds **5a–c**, but they additionally had a characteristic C₆₀-monoadduct band at 526 cm⁻¹.²³ In the UV-VIS spectra of compounds **7a–c** three intense broad absorption bands at 228, 258 and 326 nm dominated. The characteristic absorption peak of the benzene ring was at 228 nm and those of fullerene at 258 and 326 nm.²⁴ In addition, a C₆₀-monoadduct absorption peak was observed at 430 nm.^{25,26}

The ¹H NMR-spectroscopic characterization of **7a–c** at room temperature was complicated by the presence of hindered rotations as a result of the sterically congested environment of hexa-substituted benzene rings and the strong electron-withdrawing effect of the C₆₀ unit. The broadening and complexity of the room temperature ¹H NMR spectra were caused by a large number of atropisomers.^{27–30}

Several methods were tried for the benzyl deprotection of **7a–c** to form target products **8a–c** under typical benzyl groupremoval catalytic hydrogenation conditions (room temperature, 200 ml min⁻¹ H₂, atmospheric pressure, Pd/C in THF). However, debenzylation was not observed by TLC. Thus, the deprotection conditions were altered: the temperature was raised from 25 to 40 °C; the catalyst amount was increased from 10 to 100% Pd/C of **7a–c** (w/w); and the reaction time was increased from 10 to 48 h. Nevertheless, the desired results were not reached. When TFA [10, 50 or 100% TFA/CH2Cl (v/v)] was used to deprotect the benzyl group, TLC showed that the malonate hydrolysis led to a complex result, and products **8a–c** were still not obtained. Therefore, another route was selected.

Recently, a new method for the effective cyclopropanation of C_{60} - I_h fullerene through a modified Bingel-type reaction without a basic catalyst was reported.³¹ This process provided an alternative route to methanofullerene using bromomalonates, which contain unprotected acidic or base labile groups. Thus, we synthesized **8a–c** through the deprotection of **5a–c** with the following cyclopropanation (see Scheme 1).[†] The deprotection of **5a–c** using Pd/C as a catalyst led to **6a–c** in 99% yields. Target products **8a–c** were obtained by the bromination of **6a–c** with NBS in ethyl acetate³² and subsequent cyclopropanation with C_{60} using glycine as a catalyst in a mixture of chlorobenzene and DMSO.

The FTIR spectra of C₆₀-monoadducts **8a–c** showed absorption bands at 3400, 1731, 1636 and 526 cm⁻¹, which could be attributed to the stretching vibrations of N–H, malonate carbonyl, benzamide carbonyl and characteristic C₆₀-monoadduct bonds, respectively.²³ The UV-VIS spectra of C₆₀-monoadducts **8a–c** measured at room temperature in CH₂Cl₂ (Figure 1) exhibited characteristic absorption bands at 258 and 329 nm due to ful-



Figure 1 UV-VIS spectra of (1) fullerene, (2) C_{60} - I_h fullerene-based CAM **8b** and (3) malonate **6b** in CH₂Cl₂.



Figure 2 ¹H NMR spectra (600 MHz, DMSO- d_6) of compound **8b** recorded at different temperatures: (1) 297.8 K, 16 scans; (2) 318.1 K, 16 scans; (3) 338.2 K, 16 scans; (4) 358.1 K, 16 scans and (5) 358.1 K, 64 scans.

lerene. 24 A $C_{60}\mbox{-}monoadduct$ absorption peak was also observed at 430 $nm.^{25,26}$

At room temperature, the ¹H NMR spectra of **8a–c** revealed unresolved broad signals caused by the rotational barrier of the N–CO bond.²⁸ The variable-temperature high-resolution ¹H NMR spectrum of compound **8b** is shown in Figure 2. Resonance signals of catechol protons were resolved at 358.1 K, δ : 7.2 (d, 2 H, H_{Ar}, *J* 7.2 Hz), 6.9 (d, 2 H, H_{Ar}, *J* 7.2 Hz) and 6.6 (t, 2 H, H_{Ar}, *J* 7.2 Hz). However, the ¹³C NMR spectrum (150 MHz, DMSO-*d*₆, 300.3 K, 11216 scans) was difficult to interpret. These results indicate that the rotation of **6b** was more hindered upon addition to C₆₀.

In conclusion, new C_{60} - I_h fullerene-based CAM derivatives were synthesized through a modified Bingel-type reaction and structurally characterized by FTIR, UV-VIS, ¹H, ¹³C NMR and mass spectra.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.05.015.

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