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(η^5-Cyclopentadienyl)Fe(CO)$_2$ complexes of barbiturate anions

Bogna Rudolf, Janusz Zakrzewski *

Department of Organic Chemistry, University of Łódź, 90-136 Łódź, Narutowicza 68, Poland

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Dedicated to Professor Stanisław Pasynkiewicz on the occasion of his 70th birthday.

Abstract

Visible-light irradiation of CpFe(CO)$_2$I with 5,5-diethyl-, 5-ethyl-5-phenyl- and 5-ethyl-5-(1-cyclohexenyl)barbiturate in the presence of diisopropylamine brings about formation of mono- and bis-CpFe(CO)$_2$ complexes of barbiturate anions in moderate yields.

Keywords: Barbiturate; Iron; Cyclopentadienyl; Photolysis

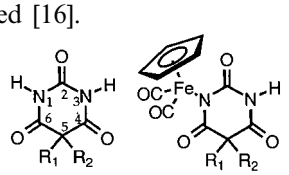
1. Introduction

The chemistry of organotransition-metal complexes of biologically important ligands constitutes a research field within a relatively new branch of organometallic chemistry, bioorganometallic chemistry [1–4]. In our laboratory we have been developing methods of introducing the CpFe(CO)$_2$ moiety (Cp = η^5-C_5H_5) to such ligands containing acidic N–H bonds, based on the photochemical substitution of iodide in CpFe(CO)$_2$I (Eq. (1), where X and/or Y are electron-withdrawing groups and B stands for diisopropylamine) [5–11].

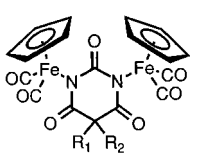
$$\mathrm{CpFe(CO)_2I} + \mathrm{HN(X)(Y)} + \mathrm{B} \xrightarrow{h\nu} \mathrm{CpFe(CO)_2N(X)(Y)} + \mathrm{BH^+I^-} \quad (1)$$

We have synthesized in this way CpFe(CO)$_2$ derivatives of pyrroles, indoles, cyclic imides, uracils, hydantoins and sulfonamides [5–11]. Some of these complexes proved versatile labeling reagents for proteins, enabling IR detection of bioconjugates (metal–carbonyl complexes display very intense infrared absorption bands in the region of $\sim$1900–2150 cm^{-1}, which is virtually free of any absorption of proteins) [11–14]. We have also found that the CpFe(CO)$_2$ derivative of 5,5-diphenylhydantoin can be used as an IR-detectable marker in carbonylmetalloimmunoassay (CMIA) of 5,5-diphenylhydantoin (antiepileptic drug known as phenytoin) [11].

In this paper we report on the synthesis of the CpFe(CO)$_2$ derivatives of barbiturates. Barbiturates of general formula **1** are central nervous system depressants that are frequently administered on a therapeutic basis as sedatives, hypnotics and anticonvulsants. They are also some of the most frequently abused drugs. The development of simple and sensitive immunoassays of these compounds is therefore of current interest [15] and their CpFe(CO)$_2$ complexes are potential tracers for CMIA. We also thought that preparation of the CpFe(CO)$_2$ complexes of barbiturates will shed light on the coordinating properties of these interesting N,O ligands as their transition-metal complexes are still rare and unexplored [16].



1 **2**



3

(a) $R_1 = R_2 = Et$
(b) $R_1 = Et$; $R_2 = Ph$
(c) $R_1 = Et$; R_2 = 1-cyclohexenyl

* Corresponding author. Fax: +48-42-6786583.
E-mail address: janzak@krysia.uni.lodz-pl (J. Zakrzewski)

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2. Results and discussion

In contrast to all N–H acidic compounds studied by us earlier, barbiturates **1** contain two possible nitrogen donor atoms and obviously the question of the formation of mono- and bis-$CpFe(CO)_2$ derivatives arises. We have found that illumination with visible light of benzene solutions of **1a–c** [5,5-diethylbarbituric acid, 5-ethyl-5-phenylbarbituric acid and 5-(1-cyclohexenyl)-5-ethylbarbituric acid, respectively] with 1.15 equivalents of $CpFe(CO)_2I$ and an excess of diisopropylamine gives mono-$CpFe(CO)_2$ derivatives **2a–c** in 39–61% yield. When the threefold excess of $CpFe(CO)_2I$ was used, the bis-$CpFe(CO)_2$ derivatives **3a–c** were formed in 26–46% yield along with **2a–c** (24–33%). These products can easily be separated owing to their different solubilities (see Section 3). Interestingly, small amounts of **3a–c** were also detected in the experiments using 1.2 equivalents of $CpFe(CO)_2I$. This means that the introduction of the first $CpFe(CO)_2$ moiety does not substantially hamper the reactivity of the N(3)–H bond.

The structures of complexes **2a–c** and **3a–c** were confirmed by elemental analyses and by IR and NMR data. The IR spectra of barbiturates **1a–c** in chloroform solutions show two strong, partly overlapped bands at 1700–1720 cm^{-1}, in accord with the presence of two different CO groups: at C(4,6) and C(2). In the spectra of **2a–c**, three organic carbonyl bands were observed at $\sim$1720, 1680 and 1620 cm^{-1}, which can be assigned to carbonyls at C(4), C(6) and C(2), respectively. Finally, the IR spectra of **3a–c** display a broad, unresolved band at $\sim$1590 cm^{-1}.

The ^{13}C-NMR spectra of complexes **2a–c** display signals corresponding to three different carbonyl carbons in the coordinated barbiturate moiety, whereas those of **3a–c** display two such signals (in $\sim$2:1 ratio). These signals are shifted downfield in comparison with the same signals in corresponding barbiturates **1a–c**. Fig. 1 shows the changes of the ^{13}C chemical shifts of carbonyl carbons in **1b** caused by the replacement of one or two N–H hydrogens by the $CpFe(CO)_2$ moieties, compared with the analogous changes reported for phthalimide [7] and 5,5-diphenylhydantoin [11]. The structures of the latter two complexes have been determined by X-ray crystallography.

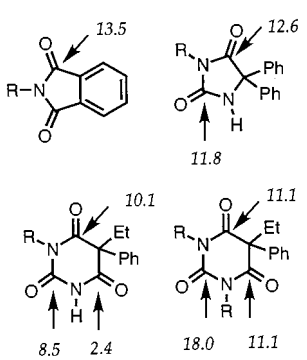

Fig. 1. Changes of the ^{13}C chemical shifts (in ppm) caused by the replacement of R = H by R = $CpFe(CO_2)$; δ(R = $CpFe(CO)_2$)–δ-(R = H).

These data reveal the same trend for all systems, although the changes observed for the barbiturate system are slightly weaker than those observed for phthalimide and 5,5-diphenylhydantoin. The effect of the replacement of one and two N–H hydrogens by the $CpFe(CO)_2$ moieties is roughly additive. The CO ligands in **2a** and **3a** give rise to one signal in the ^{13}C-NMR spectra, whereas in the spectra of other complexes two signals of CO ligands separated by 0.04–0.27 ppm are observed, in accordance with the diastereotopic character of these ligands brought about by the chirality center at C(5).

The absorption bands due to the stretching vibrations of the CO ligands in bis-$CpFe(CO)_2$ complexes **3a–c** appear at slightly lower wavelengths ($\sim$5 cm^{-1}) than the same bands in **2a–c**. This indicates that barbiturate anions bearing the $CpFe(CO)_2$ moiety are slightly stronger σ-donors and/or weaker π-acceptors than their N–H counterparts.

3. Experimental

All photolyses were carried out under argon using a set-up of 4×150 W domestic tungsten lamps. The photolytes were magnetically stirred and externally cooled by immersion in a water–ice bath. All solvents were dried and distilled from appropriate drying agent prior to use. All reagents were commercially available (Aldrich, Fluka, Sigma) and were used as received. Chromatographic separations were carried out on Kieselgel 60 (Merck, 230–400 mesh ASTM) using chloroform as eluent. NMR spectra were run on a Varian Gemini 200BB spectrometer (200 MHz for ^{1}H) in $CDCl_3$ solutions and were referenced to internal TMS. IR spectra were recorded in $CHCl_3$ on a Biorad spectrometer. Elemental analyses were done by the analytical Services of the CBMiM PAN (Łodz).

3.1. Synthesis of 1-$CpFe(CO)_2$-barbituric acids **2a–c**

A mixture of $CpFe(CO)_2I$ (350 mg, 1.15 mmol), barbiturate **1** (1 mmol), diisopropylamine (2 ml) and benzene (15 ml) was photolyzed for 1.5–2 h. During the photolysis the initial black coloration turned yellow. The solid formed (diisopropylamine hydroiodide) was filtered off and the filtrate evaporated to dryness. The oily residue was dissolved in a small volume of chloroform and chromatographed. The yellow band which

followed the black band of unreacted $CpFe(CO)_2I$ was collected and evaporated to dryness. Analytical samples were prepared by crystallization from dichloromethane–ether.

2a: Yield: 39%. IR (cm^{-1}) 3290 (N–H); 2054, 2006 (Fe–CO); 1719, 1680, 1622 (barbiturate COs). ^{1}H-NMR (δ): 8.06, bs, 1H, N–H; 5.04, s, 5H, Cp; 1.92, q ($J = 7.1$ Hz), 4H, CH_2; 0.69, t ($J = 7.1$ Hz), 6H, CH_3. ^{13}C-NMR (δ): 212.47 (Fe–CO); 182.44 (C-4); 174.40 (C-6) 157.25 (C-2); 85.19 (Cp); 61.67 (C-5); 33.01 (CH_2); 9.74 (CH_3). Anal. Calc. (Found): C, 49.89 (49.72); H, 4.74 (4.60); N, 7.76 (7.42).

2b: Yield: 49%;. IR (cm^{-1}): 3300 (N–H); 2055, 2008 (Fe–CO); 1720, 1683, 1622 (barbiturate COs). ^{1}H-NMR (δ): 8.14, bs, 1H, N–H; 7.22, s, 5H, Ph; 4.93, s, 5H, Cp; 2.41, m, 2H, CH_2; 0.86 t ($J = 7.1$ Hz), 3H, CH_3. ^{13}C-NMR (δ): 212.36 and 212.29 (Fe–CO); 180.55 (C-4); 172.35 (C-6) 157.02 (C-2); 139.46, 128.85, 127.90, and 125.91, Ph; 85.22 (Cp); 60.92 (C-5); 30.18 CH_2); 10.26 (CH_3). Anal. Calc. (Found): C, 55.91 (55.63); H, 3.95 (4.19); N, 6.86 (6.76).

2c: Yield: 61%;. IR (cm^{-1}): 3290 (N–H); 2055, 2008 (Fe–CO); 1720, 1682, 1622 (barbiturate COs). ^{1}H-NMR (δ): 8.08, bs, 1H, N–H; 5.72, m, 1H, olefinic H; 5.03, s, 5H, Cp; 2.08, m, 2H, CH_2; 1.56, m, 8H, other cyclohexenyl and CH_2; 0.72 t ($J = 7.1$ Hz), 3H, CH_3. ^{13}C-NMR (δ): 212.39 and 212.35 (Fe–CO); 181.11 (C-4); 172.98 (C-6) 157.25 (C-2); 135.68 and 124.90 olefinic; 85.20 (Cp); 62.02 (C-5); 28.03, 25.78, 25.38, 22.77, 21.76, 9.70, others. Anal. Calc. for a hemihydrate (Found): C, 54.31 (54.69); H, 4.80 (4.82); N, 6.67 (6.68).

*3.2. Synthesis of 1,3-bis[CpFe(CO)$_2$]-5,5-diethylbarbituric acid **3a***

A mixture of $CpFe(CO)_2I$ (921 mg, 3 mmol), 5,5-diethylbarbituric acid (185 mg, 1 mmol), diisopropylamine (2 ml) and benzene (20 ml) was photolyzed for 2 h. The solid formed was filtered off and the filtrate evaporated to dryness. Column chromatography of the residue gave a mixture of **3a** and **2a** as a yellow band followed by the black band of unreacted $CpFe(CO)_2I$; the binuclear complex **3a** crystallized from dichloromethane–ether whilst **2a** remained in the mother liquor and was crystallized from dichloromethane–heptane. Repeated crystallizations gave pure samples of **3a** (250 mg, 46%) and **2a** (120 mg, 33%).

3a: IR (cm^{-1}): 2051, 2002 (Fe–CO); 1590 (barbiturate COs). ^{1}H-NMR (δ): 4.99, s, 10H, Cp; 1.82, q ($J = 7.3$ Hz), 4H, CH_2; 0.52, t ($J = 7.3$ Hz), 6H, CH_3. ^{13}C-NMR (δ): 213.49 (Fe–CO); 183.64 (C-4,6); 166.60 (C-2); 85.32 (Cp); 57.60 (C-5); 33.90 (CH_2); 9.91 (CH_3). Anal. Calc. (Found): C, 49.29 (49.52); H, 3.76 (3.30); N, 5.23 (5.33).

*3.3. Synthesis of 1,3-bis[CpFe(CO)$_2$]-5-ethyl-5-phenylbarbituric acid **3b** and 1,3-bis[CpFe(CO)$_2$]-5-(1-cyclohexenyl)-5-ethyldiethylbarbituric acid **3c***

A mixture of $CpFe(CO)_2I$ (921 mg, 3 mmol), barbiturate **1b** or **1c** (1 mmol), diisopropylamine (2 ml) and benzene (20 ml) was photolyzed for 2 h. A yellow solid was filtered off and washed with benzene. The filtrate was evaporated to dryness and chromatographed to give **2b** or **2c** (26 and 24%, respectively). The solid was triturated with water to remove diisopropylamine hydroiodide, dried and chromatographed. A yellow fraction was collected to afford **3b** or **3c**. Analytical samples were crystallized from dichloromethane–heptane.

3b: Yield: 31%. IR (cm^{-1}): 2051, 2002 (Fe–CO); 1587 (barbiturate COs). ^{1}H-NMR (δ): 7.18, m, 5H, Ph; 4.88, s, 10H, Cp; 2.29, q ($J = 7.3$ Hz), 2H, CH_2; 0.72, t ($J = 7.3$ Hz), 3H, CH_3. ^{13}C-NMR (δ): 213.53 and 213.28 (Fe–CO); 181.57(C-4,6); 166.50 (C-2); 141.94, 128.50, 127.01 and 125.56 (Ph) 85.38 (Cp); 60.99 (C-5); 31.25 (CH_2); 10.53 (CH_3). Anal. Calc. (Found): C, 53.46 (53.13); H, 3.45 (3.34); N, 4.80 (4.92).

3c: Yield: 26%. IR (cm^{-1}): 2050, 2002 (Fe–CO); 1590 (barbiturate COs). ^{1}H-NMR (δ): 5.63, m, 1H, olefinic H; 4.98, s, 10H, Cp; 2.04, m, 1H, CH_2; 1.59, m, 8H, cyclohexenyl; 0.55, t ($J = 7.3$ Hz), 6H, CH_3. ^{13}C-NMR (δ): 213.45 and 213.28 (Fe–CO); 182.27 (C-4,6); 166.40 (C-2); 137.52 and 122.27 (olefinic); 85.20 (Cp); 29.17, 25.38, 25.31, 22.94, 22.03 and 9.86 (others). Anal. Calc. for a hemihydrate (Found): C, 52.29 (52.19); H, 4.24 (4.04); N, 4.69 (4.86).

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