Journal of Organometallic Chemistry 817 (2016) 15–20

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Synthesis and anodic electrochemistry of cymanquine and related complexes

Kevin Lam [a, b, **], William E. Geiger [a, *]

[a] Department of Chemistry, University of Vermont, Burlington, VT 05405, USA
[b] Department of Chemistry, School of Science and Technology, Nazarbayev University, Astana 010000, Kazakhstan

ARTICLE INFO

Article history:
Received 12 April 2016
Received in revised form
5 May 2016
Accepted 8 May 2016
Available online 11 May 2016

Keywords:
Bioorganometallic
Cymantrene
Ferroquine
Chloroquinoline
Anodic oxidation
Weakly coordinating anion

ABSTRACT

Three compounds have been prepared in which a 4-aminochloroquinoline moiety is covalently linked to a cyclopentadienyl manganese tricarbonyl moiety. One of these ("cymanquine", **4**) is the analogue of the potent antimalarial drug ferroquine in which an FeCp group has been replaced by a $Mn(CO)_3$ group. The anodic electrochemistry of the new compounds was investigated in dichloromethane, using $[NBu_4][B(C_6F_5)_4]$ as the supporting electrolyte. Compared to ferroquine, oxidations of the new compounds occur at considerably more positive potentials and are highly irreversible, being located at their amine groups rather than at the organometallic center.

1. Introduction

A leading strategy in the expanding field of bioorganometallic chemistry [1–4] is the synthesis of hybrid compounds composed of covalently linked conjugate pairs of separately recognizable organic and organometallic (OM) moieties. The organic scaffold may have already identified medicinal properties. An OM bioconjugate is added with the goal of changing those properties in predictable ways or to provide the system with an electrochemical or spectroscopic analytical 'tag' [4,5].

Although a ferrocenyl group has been the most frequently-utilized OM conjugate [6], other moieties are being increasingly investigated, especially for the purpose of employing metal-carbonyl IR absorptions as analytical markers [7,8]. Among the most promising non-ferrocenyl OM bioconjugates are the strongly IR-active Group 7 'piano-stool' moieties $M(CO)_3(\eta^5\text{-}C_5H_4R)$, which have been termed cymantrene and cyrhetrene, when M = Mn and M = Re, respectively, and R = H [9–16].

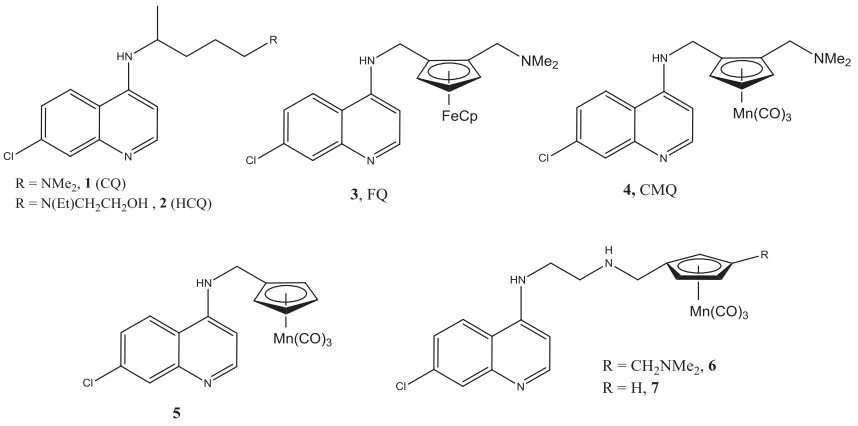
Described in the present paper are compounds in which the five-membered rings of cyclopentadienyl (Cp) manganese tricarbonyl moieties have been covalently linked to the endocyclic nitrogens of 4-aminoquinolines. The interests of ourselves and others [9,17] in conjugates of this general class has its origin in the fact that the organic scaffold is based on chloroquine (CQ, **1**) which, along with hydroxychloroquine (HCQ, **2**) finds use in the treatment of human diseases, including malaria [18,19] and rheumatoid arthritis [20,21]. However, the efficacy of CQ and HCQ as antimalarial drugs has been compromised by the fact that parasites such as *Plasmodium falciparum* have developed resistance to them [22–24]. One of the most promising new antimalarial agents to which *P. falciparum* strains are not resistant is the hybrid compound "ferroquine" (FQ, **3**), in which an alkylamine-substituted ferrocenyl group is linked to a CQ-like backbone [25–31]. Herein is reported the first preparation of the cymantrene analogue of FQ, which we term cymanquine (CMQ, **4**) by analogy with its ferrocenyl predecessor. Two other closely related new manganese tricarbonyl compounds (**5** and **6**) were also prepared.

One of the most important and widely studied properties of ferrocene derivatives is their anodic electrochemical behavior. Owing to the propensity of a ferrocenyl group to undergo a relatively facile one-electron oxidation, the question of possible involvement of ferrocene/ferrocenium redox chemistry in the

* Corresponding author.
** Corresponding author. Department of Chemistry, University of Vermont, Burlington, VT 05405, USA.
E-mail addresses: kevin.lam@nu.edu.kz (K. Lam), william.geiger@uvm.edu (W.E. Geiger).

http://dx.doi.org/10.1016/j.jorganchem.2016.05.009
0022-328X/

medicinal activity of FQ has arisen [32,33]. Cymantrene and Cp-substituted cymantrenes also exhibit one-electron oxidations, giving radical cations that are stable under controlled conditions [34]. Characterization of the anodic electrochemistry of compounds **4**–**6** is therefore relevant to both their general characterization and any mechanism of action in their possible biological activity [35]. Thus, information about the potentials and degrees of chemical reversibility of the anodic oxidations of these compounds are reported herein.



2. Experimental

2.1. Materials

Chemical reactions and electrochemical studies were conducted under a nitrogen atmosphere. The former were performed under standard Schlenk conditions and the latter were performed in a Vacuum Atmospheres drybox under oxygen levels of less than 5 ppm. Solvents were purified by sending them through an alumina column. Cymantrene was purchased from Molekula GmbH – Germany. Other reagents were purchased from Acros Organic or Sigma Aldrich and used as received. $[NBu_4][B(C_6F_5)_4]$ was prepared as previously described [36].

α-(7-chloroquinolin-4-amino) –β–(N,N,-dimethylaminomethyl)cymantrene, cymanquine, CMQ, **4**. α-Formyl-(N,N,-dimethylaminomethyl)cymantrene **11** [37] (1.12 g, 3.87 mmol) was dissolved in 40 mL of dry methanol at 273 K. Sodium borohydride (0.322 g, 8.52 mmol) was added by portion over 15 min and the solution was allowed to come back to room temperature. After 2 h, most of the solvent was removed under reduced pressure and the mixture was dissolved in 30 mL dichloromethane. The solution was washed twice with 30 mL water, after which the organic layer was isolated, dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. α-hydroxymethyl-(N,N,-dimethylaminomethyl)cymantrene **12** was obtained in a 67% yield as a dark brown oil sufficiently pure to be used in the next step. To a solution of 50 mg (0.172 mmol) of this compound in 1 mL dry THF were added phthalimide (32.3 mg, 0.22 mmol) and triphenylphosphine (57.6 mg, 0.22 mmol). Then diisopropyl diazene-1,2-dicarboxylate (DIAD) (47 μL, 0.22 mmol) was added. After 1 h, the solvent was removed and replaced by 0.5 mL methanol. Hydrazine hydrate (24 μL, 0.32 mmol) was added to this solution, which was stirred at room temperature for 30 min. After addition of 10 mL of a 1 N solution of HCl, the solution was quickly extracted three times with 10 mL ethyl acetate. The pH of the aqueous layer was increased to 13 by addition of a solution of 1 N NaOH and thrice extracted with 10 mL dichloromethane. The organic layers were combined, dried over magnesium sulfate, and the solvent removed under reduced pressure to yield 26.2 mg of α-aminomethyl-(N,N,-dimethylaminomethyl)cymantrene **14**, which was used directly in the next step. This sample (0.090 mmol) was dissolved in a 2 mL dry propanol solution containing 7-chloro-4-fluoroquinoline (17.2 mg, 0.095 mmol) and refluxed overnight, after which the solvent was removed under reduced pressure and the compound purified by column chromatography over silica gel using AcOEt/Hexane (1:9) as the eluent. A light brown powder was obtained for CMQ **4** (12.4 mg, 16% yield over the three steps from the hydroxyl compound), m.p. 171.5°–172.5°. The solid did not seem to be overly air-sensitive. It was stored in the dark owing to the light sensitivity common among cymantrene derivatives. Calcd for $C_{21}H_{19}ClMnN_3O_3$: C, 55.83; H, 4.24; N, 9.30. Found: C, 56.25; H, 4.34; N 9.43. ^{1}H NMR (500 MHz, $CDCl_3$): 2.34 (s, 6H, $-NMe_2$), 2.79 (d, J = 12.9 Hz, 1H, $-CH_2-NMe_2$), 3.58 (d, J = 12.9 Hz, 1H, $-CH_2-NMe_2$), 4.08–4.16 (m, 2H, $-CH_2-NH-Ar$), 4.61 (t, J = 2.75 Hz, 1H, Cp), 4.76–4.77 (m, 1H, Cp), 4.88 (m, 1H, Cp), 6.40 (s, 1H, Ar), 7.35 (d, J = 8.9 Hz, 1H, Ar), 7.62 (d, J = 8.9 Hz, 1H, Ar), 7.66–7.68 (m, 1H, NH), 7.97 (s, 1H, Ar), 8.58 (s, 1H, Ar).^{13}C NMR (500 MHz, $CDCl_3$): 40.2 (NMe_2), 45.2 ($-CH_2NMe_2$), 56.0 ($-CH_2-NH-Ar$), 79.1 (Cp), 85.1 (Cp), 85.7 (Cp), 100.1 (Cp), 101.20 (Cp), 100.3 (Ar), 118.4 (Ar), 122.2 (Ar), 122.3 (Ar), 125.5 (Ar), 128.7 (Ar), 132.1 (Ar), 135.3 (Ar), 150.3 (Ar). MSCI+ *m/z* (%): 455.1 (8), 454.1 (30), 453.2 (24), 452.2 (100), 418.2 (2), 274.1 (2), 54.8 (3). IR (solid) υ(cm^{-1}): 632, 668, 807, 840, 1135, 1426, 1577, 1913, 1939 (strong, υ_{CO}), 2011 (strong, υ_{CO}), 2831, 2950. IR in CH_2Cl_2: υ_{CO} at 1934, 2022 cm^{-1}.

2.1.1. Compound *5*

Aminomethylcymantrene **15** [37] (100 mg, 0.430 mmol, 1 eq) was dissolved in 5 mL of dry, degassed, propanol and 7-chloro-4-fluoroquinoline (82 mg, 0.450 mmol, 1.05 eq). The solution was refluxed under nitrogen overnight, after which the solvent was removed under reduced pressure and the compound purified by column chromatography over silica gel using AcOEt/hexanes (1:9) as the eluent. A light brown powder was obtained (113 mg, 67%). Calcd for $C_{18}H_{12}ClMnN_2O_3$: C, 54.78; H, 3.06; N, 7.10. Found: C, 55.35; H, 3.11; N 7.11. ^{1}H NMR (500 MHz, $CDCl_3$): 4.23 (s, 2H, $-CH_2-NH-Ar$), 4.75 (s, 2H, Cp), 4.91 (s, 2H, Cp), 5.43 (s, 1H, -NH), 6.51–652 (m, 1H), Ar, 7.42 (d, J = 8.9 Hz, 1H, Ar), 7.77 (d, J = 8.9 Hz, 1H, Ar), 8.01 (s, 1H, Ar), 8.57–8.59 (m, 1H, Ar). ^{13}C NMR (500 MHz, $CDCl_3$): 40.6 ($-CH_2-NH-Ar$), 82.1 (Cp), 83.0 (Cp), 99.2 (Ar), 101.2 (Cp), 116.9 (Ar), 120.9 (Ar), 125.9 (Ar), 128.5 (Ar), 135.4 (Ar), 148.7