Synthesis and characterization of ruthenium-phosphine derived complex containing the non-steroidal anti-inflammatory naproxen drug

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Ruthenium complexes containing non-steroidal anti-inflammatory drugs (NSAIDs) have been found by our research group to show interesting pharmacological properties, ranging from anti-inflammatory properties with reduced ulceration in the gastrointestinal tract to antiproliferative activity against cancer cells. These properties were shown in our previous studies for dinuclear carboxylates bearing the mixed-valence Ru_2(II,III) coordinated to four NSAIDs in a paddlewheel arrangement [1,2]. The antiproliferative effects of the naproxen complex of formula $[Ru_2(Npx)_4(H_2O)_2]PF_6$, Npx = naproxenate anion from naproxen, were investigated for C6 rat glioma cells [3] and also for the HT-29 and Caco-2 human colon carcinoma cells [4]. The objective of the present work was to prepare a complex of Ru(II) containing the naproxen drug. The reaction of the precursor $[RuCl_2(PPh_3)_3]$ with the deprotonated naproxen in the form of salt, under nitrogen atmosphere in the Schlenk line, gave the $[RuCl(Npx)(PPh_3)_2]$ mononuclear complex. The product composition seems to not depend on the temperature since both investigated conditions reflux and room temperature led to the same compound. The characterization of the complex was performed mainly by elemental analysis (% exp. C, 67,8; 5,4; calc. C, 67,5; 4,9); ^{1}H NMR, δ (ppm): 1.18 [d, 3H, H_2], 3.35 [q, 1H, H_1], 3.94 s, 3H, H_9], 7.73-6.96 [m, 36H, H (PPh_3 and Npx)]; ^{31}P NMR, δ (ppm): 31.45 [s, PPh_3 *trans*], 64.91 [s, PPh_3 *cis*]; IR-ATR, main bands at 1502 and 1482 cm^{-1} assigned to ν_a(COO) and ν_s(COO) stretching modes of the naproxenate ligand; and MALDI-TOF, m/z 891.065 ascribed to the molecular ion peak. The stability of the $[RuCl(Npx)(PPh_3)_2]$ mononuclear complex in methanol was followed by UV-VIS spectroscopy at 564 nm to estimate the period of time of its conversion into the corresponding μ-oxo complex which probably bears the naproxen and the phosphine ligands. The present studies showed that the naproxenate anion replaces the chloride ligand in the ruthenium-phosphine to give the derived drug-complex $[RuCl(Npx)(PPh_3)_2]$. The mononuclear complex may undergo transformation in solution to give the corresponding μ-oxo species which keeps the naproxen drug ligand. Both mononuclear and μ-oxo complexes have potential to be tested in future biological assays.

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