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The first organo-tungsten pyrylium salt and structural characterization of its pseudobase

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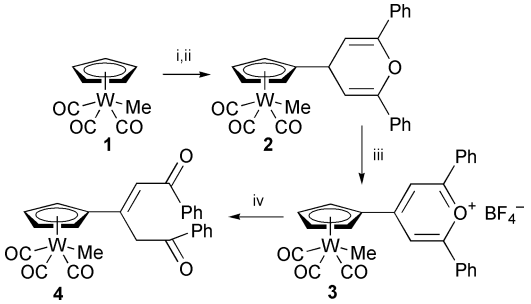
The first example of an organo-tungsten pyrylium complex (4-cyclopentadienyl-2,6-diphenylpyrylium)$W(CO)_3CH_3$ has been prepared, fully characterized and transformed in an aqueous basic medium to the corresponding pseudobase (3-cyclopentadienyl-1,5-diphenylpent-2-ene-1,5-dione)W-$(CO)_3CH_3$ which is the first X-ray structure analysed organometallic pseudobase.

It has been shown recently[1–3] that pyrylium salts bearing an organometallic fragment are very promising candidates for the labeling of biological molecules. Due to their electrophilicity, this family of compounds could be attractive for the selective introduction of heavy atoms into protein crystals by means of covalent bond formation with protein side chains carrying a primary amine. Since such heavy metal protein derivatives are required for crystallographic phase determination when using, for example, the multiple isomorphous replacement method (MIR),[4] organometallic pyrylium salts could potentially be of great use for three-dimensional protein structure determination by X-ray crystallography. Several synthetic approaches have been suggested for the preparation of organometallic pyrylium salts bearing benchrotrenyl,[1,5] ferrocenyl,[6] cyclopentadienyl-tricarbonyl-manganese[1,7] or -rhenium[1] fragments at the 4-position of the heterocyclic ring. Reactivity studies using benchrotrenyl pyrylium salts with primary amines, amino acids or proteins have shown that labeling was observed even using crystalline protein.[8] Nevertheless, X-ray diffraction experiments indicated the need for heavier atoms with larger electronic densities. We therefore sought to develop derivatives of the $CpW(CO)_3CH_3$ system which are both air and light stable and provide a heavy metal in a suitable organometallic environment.

We now report the synthesis of the first pyrylium salt containing a tungsten organometallic moiety and the X-ray structural analysis of the pseudobase obtained from its hydrolysis under basic conditions.

The tungsten pyrylium complex **3** was obtained by reaction of deprotonated starting material **1** with preformed 2,6-diphenylpyrylium salt followed by hydride abstraction from the resulting pyran derivative with trityl cation (Scheme 1).†



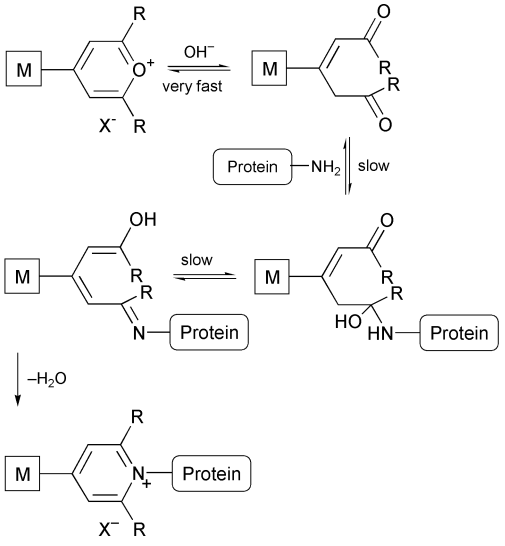
Scheme 1 *Reagents and conditions*: i, Bu^nLi, THF, −78 °C; ii, 2,6-diphenylpyrylium salt, THF, −78 °C to RT; iii, $Ph_3C^+BF_4^-$, CH_3CN, RT; iv, Na_2CO_3, acetone/H_2O/ether, RT.

Complex **3** was isolated as a deep purple air stable solid in 30% overall yield and characterized by elemental analysis, IR and ^1H and $^{13}C\{^1H\}$ NMR spectroscopies. In the ^1H NMR spectrum, a characteristic resonance at 8.79 (s) ppm was assigned to the two pyrylium protons. The $^{13}C\{^1H\}$ NMR spectrum exhibited three signals at 113.5, 164.1 and 171.2 ppm assignable to C^β, C^γ and C^α, respectively, of the heterocycle. These data are very similar to those of 2,4,6-triphenylpyrylium salt[9] and show no significant influence of the organometallic fragment on the heterocycle carbon chemical shifts.

The mechanism of pyrylium to pyridinium conversion has been thoroughly studied.[10] Kinetic measurements using UV–visible spectroscopy performed on a series of 4-benchrotrenyl pyrylium salts indicated that in aqueous media, and especially at basic pH, the hydrolysis of the pyrylium salt is very fast and that the pseudobase form (open chain diketone form) resulting from the addition of OH^- to the pyrylium salt is in fact the reactive species that undergoes the nucleophilic addition by the protein amino group (Scheme 2).[3] Thus, knowledge of the structure and reactivity of the pseudobase form of pyrylium complex **3** is important for the understanding of the mechanism of protein labelling by these species.

Treatment of the tungsten pyrylium salt **3** with Na_2CO_3 in an acetone–water mixture and subsequent extraction with diethyl ether led to the corresponding pseudobase ((3-cyclopentadienyl-1,5-diphenylpent-2-ene-1,5-dione)$W(CO)_3CH_3$) **4** in 92% yield (Scheme 1) as a moderately air stable yellow solid.†

The structure of **4** was established by ^1H NMR analysis which revealed the presence of methylenic and vinylic protons at 4.51 and 7.24 ppm, respectively. The carbon atoms of the pent-2-ene-1,5-dione chain gave signals at 195.7 (C=O), 190.3 (conjugated C=O), 144.4 and 121.2 (C=C) and 41.7 (CH_2) ppm



Scheme 2 Reaction of a protein with a pyrylium salt in basic aqueous medium.

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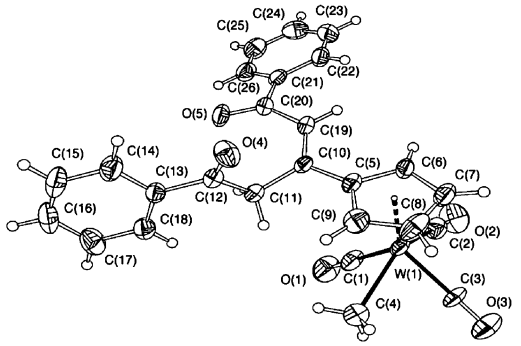

Fig. 1 The molecular structure of **4**. Selected bond lengths (Å) and angles (°); C(5)–C(10) 1.424(9), C(10)–C(19) 1.325(10), C(19)–C(20) 1.473(9), C(20)–O(5) 1.227(9), C(20)–C(21) 1.484(10); C(6)–C(5)–C(10) 126.5(7), C(5)–C(10)–C(19) 119.3(6), C(10)–C(19)–C(20) 124.7(6), C(19)–C(20)–O(5) 122.4(7), C(19)–C(20)–C(21) 118.1(6), C(5)–C(10)–C(11) 117.0(6), C(10)–C(11)–C(12) 112.6(6), C(11)–C(12)–O(4) 120.8(8), C(11)–C(12)–C(13) 118.4(6).

in the $^{13}C\{^{1}H\}$ NMR spectrum. These spectroscopic data are very similar to those of the corresponding compound bearing a phenyl group instead of the organo-tungsten fragment[11] except for the carbon C^3 signal which is shifted 8 ppm upfield.

The structure of pseudobase **4** was confirmed by X-ray crystallography (Fig. 1).‡ The complex exhibits a four-legged piano stool geometry with the methyl group on tungsten and the substituent on the Cp in perpendicular vertical planes. Bond distances within the diketone chain are in agreement with those reported for the only structurally characterized pseudobase $PhC(O)CH{=}C(CF_3)CH_2C(O)Ph$[12] which bears a CF_3 substituent in place of the Cp-tungsten fragment. The dihedral angles along the conjugated chain (C(6)–C(5)–C(10)–C(19) 18.6°; C(10)–C(19)–C(20)–O(5) 21.2°; O(5)–C(20)–C(21)–C(26) 18.7°) show significant deviation from planarity and the two phenyl end groups are almost perpendicular to each other.

The kinetics of reaction of complex **3** with *n*-butylamine in acetonitrile was studied spectrophotometrically. Conversion to the *N*-butylpyridinium salt followed a pseudo-first order reaction rate with $k_{obs} = 5.4 \times 10^{-4}$ s^{-1}. The structure of the final product was confirmed by ^{1}H NMR. For comparison, in the same experimental conditions, a k_{obs} of 0.58×10^{-4} s^{-1} and 0.32×10^{-4} s^{-1} was measured for 4-benchrotrenyl-2,6-diphenylpyrylium tetrafluoroborate and 2,4,6-triphenylpyrylium tetrafluoroborate, respectively.[3,13]

This synthesis may help provide a new approach in X-ray structural determination of proteins.

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Notes and references

† *Synthetic procedure for* **3**: to a solution of the pyran complex **2** (232 mg, 0.4 mmol) in acetonitrile (10 mL) was added $Ph_3C^+BF_4^-$ (170 mg, 0.45 mmol). The solution was stirred for 0.5 h at RT. On addition of diethyl ether (30 ml), complex **3** precipitated as a deep purple solid (205 mg, 0.29 mmol, 72%). *Selected data for* **3**: $\nu(CH_2Cl_2)$/cm^{-1} 1936, 2026 (C≡O); δ_H(200 MHz, d_6-acetone): 0.54 (s, 3H, CH_3), 6.28 (t, 2H, J = 2.4 Hz, Cp), 6.93 (t, 2H, J = 2.4 Hz, Cp), 7.93–7.75 (m, 6H, Ph), 8.54 (m, 4H, Ph), 8.79 (s, 2H, $H^{3,5}$-pyr); δ_C(100 MHz, d^6-acetone) −30.8 (CH_3), 93.8 ($C^{2,2'}$-Cp), 98.3 (C^1-Cp), 99.6 ($C^{3,3'}$-Cp), 113.50 ($C^{3,5}$-pyr), 129.3 (C_{ortho}-Ph), 130.1 (C_{ipso}-Ph), 130.8 (C_{meta}-Ph), 135.9 (C_{para}-Ph), 164.1 (C^4-pyr), 171.2 ($C^{2,6}$-pyr), 214.5 (C≡O), 226.1 (C≡O); Elemental anal. Calc. for $C_{26}H_{19}BF_4O_4W$: C, 46.87; H, 2.85. Found: C, 46.76; H, 2.91%. *Synthetic procedure for* **4**: to a solution of the pyrylium complex **3** (143 mg, 0.2 mmol) in acetone (5 ml) and ether (5 ml) was added K_2CO_3 (70 mg, 2 mmol) in water (3 ml). The mixture was stirred for 10 min at RT during while the organic phase turned orange. After extraction with diethyl ether (10 ml), evaporation and addition of pentane to the resulting oil, the pseudobase **4** was obtained as a yellow powder (110 mg, 0.184 mmol, 92%). *Selected data for* **4**: $\nu(CH_2Cl_2)$/cm^{-1} 1922, 2017 (C≡O); δ_H(200 MHz, $CDCl_3$): 0.51 (s, 3H, CH_3), 4.51 (s, 2H, CH_2), 5.49 (t, 2H, J = 2.4 Hz, Cp), 5.59 (t, 2H, J = 2.4 Hz, Cp), 7.24 (s, 1H, –CH=), 7.67–7.43 (m, 6H, Ph), 7.91 (d, 2H, J = 8.5 Hz, Ph), 8.09 (d, 2H, J = 8.5 Hz, Ph); δ_C(100 MHz, $CDCl_3$): −30.9 (CH_3), 41.7 (C^4), 90.1 ($C^{2,2'}$-Cp), 92.5 ($C^{3,3'}$-Cp), 109.4 (C^1-Cp), 121.2 (C^2), 128.3, 128.4, 128.7, 128.9 ($C_{ortho,meta}$-Ph), 133.0, 133.6 (C_{para}-Ph), 136.5 (C_{ipso}-Ph), 138.8 (C_{ipso}-Ph), 144.4 (C^3), 190.3 (C^1), 195.7 (C^5), 215.1 (C≡O), 227.6 (C≡O); Elemental anal. Calc. for $C_{26}H_{20}O_5W$: C, 52.36; H, 3.36. Found: C, 52.84; H, 3.54%.

‡ *Crystal data for* $C_{26}H_{20}O_5W$ (**4**): The compound crystallises in the triclinic space group $P\bar{1}$; M_r = 596.27, a = 9.952(2), b = 10.753(3), c = 12.567(3) Å, α = 66.63(2), β = 71.183(19), γ = 63.35(2)°, U = 1086.2(4) Å^3, Z = 2, T = 293(2) K, μ = 5.353 mm^{-1}, D_c = 1.823 Mg m^{-3}, $F(000)$ = 580, Of a total of 6921 collected reflections, 6315 were unique (R(int) = 0.0325) and used in all calculations. The final wR_2 = 0.1622 (all data), R_1 [$I > 2\sigma(I)$] = 0.0755. The structure was solved by direct methods, SHELXS-97,[14] and refined by full matrix least squares using SHELXL-97.[15] SHELX operations were automated using ORTEX which was also used to obtain the drawings.[16] Data were corrected for Lorentz, polarization effects and for absorption by the method of Ψ scans. The minimum transmission was 74%.[17] Hydrogen atoms were included in calculated positions with thermal parameters 30% larger than the atom to which they are attached. The non-hydrogen atoms were refined anisotropically. All calculations were performed on a Pentium PC. CCDC reference number number 166487. See http://www.rsc.org/suppdata/cc/b1/b104419m/ for crystallographic data in CIF or other electronic format.

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