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Studies on Organomercury(II) Complexes of 5-Fluorouracil

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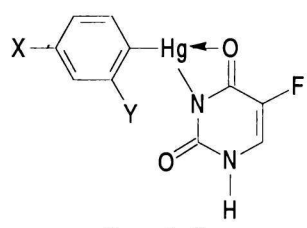
A number of organomercury(II) complexes involving 5-fluorouracil (HL) of the type RHgL (R = *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$, *p*-HOC_6H_4, *o*-HOC_6H_4) have been synthesized. Conductance measurements reveal that the compounds are nonelectrolytes. From IR and UV spectral studies the bonding modes of the ligand to the mercury(II) ion have been deduced. ^1H and ^{13}C NMR spectral studies confirm the stoichiometry of the complexes. The fragmentation pattern has been analyzed on the basis of mass spectral studies.

5-Fluorouracil is an anti-cancer drug [1]. For many decades, drugs used for cancer chemotherapy were predominantly derived from organic and biochemical preparations. When in 1969 *Rosenberg et al.* [2] discovered the strongly cell-mitosis-depressing, broad spectrum, inorganic anti-cancer agent, cisplatin, the use of metal coordination compounds in the search for new drugs for cancer treatment started to evolve. In the following years, numerous interesting results have attracted the attention of inorganic chemists [3—5]. There are possibilities for improving therapeutic activity and suppressing side effects of currently used anti-neoplastic drugs by using their metal complexes [6]. With this aim, we synthesized a few organomercury(II) complexes RHgL involving the ligand 5-fluorouracil (Formula 1).



Formula 1

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This is a continuation of our investigations on organomercury(II)—biomolecule interactions [7—10].

EXPERIMENTAL

The arylmercury(II) chlorides, RHgCl, were synthesized by the method of *Nesmeyanov et al.* [11]. 5-Fluorouracil was purchased from Aldrich Chemical Co., USA and used without further purification. Conductance measurements were carried out on an Elico conductivity bridge, model CM-82. The IR and UV spectra were recorded on Shimadzu model IR-435 and Perkin—Elmer UV VIS spectrometer, model 554, respectively. The ^{1}H and ^{13}C NMR spectra were recorded on Jeol FX-200 FT NMR spectrometer. Mass spectra were recorded on Jeol JMS DX-303 spectrometer.

Preparation of Complexes

The complexes were prepared by adding slowly a solution of RHgCl (0.01 mol) in 25 cm^3 of DMF to a stirred solution of 5-fluorouracil (0.01 mol) in 25 cm^3 of DMF at pH 8—9. The contents were stirred for 6 h at 50 °C and filtered. The filtrate was slowly poured over crushed ice and stirred vigorously. The precipitates so obtained were washed successively with hot water and benzene. The resulting product was dried and recrystallized from THF.

RESULTS AND DISCUSSION

The elemental analyses and spectral data revealed that the complexes were pure. This was also supported by TLC. The complexes were white in colour. The molar conductivity measurements in 10^{-3} M nitrobenzene solution were of the order of 0.50 S cm^2 mol^{-1}, indicating that the compounds were non-electrolytes. The analytical data of the complexes are presented in Table 1.

Table 1. Analytical Data of the Complexes

Compound	θ(decomp.)	w_i(calc.)/% w_i(found)/%	
	°C	Hg	N
p-MeC$_6$H$_4$HgL	196	47.68	6.65
		47.75	6.72
p-MeOC$_6$H$_4$HgL	206	45.99	6.41
		45.90	6.46
p-NO$_2$C$_6$H$_4$HgL	242	44.40	9.30
		44.32	9.25
p-HOC$_6$H$_4$HgL	210	47.45	6.62
		47.40	6.67
o-HOC$_6$H$_4$HgL	228	47.45	6.62
		47.52	6.66

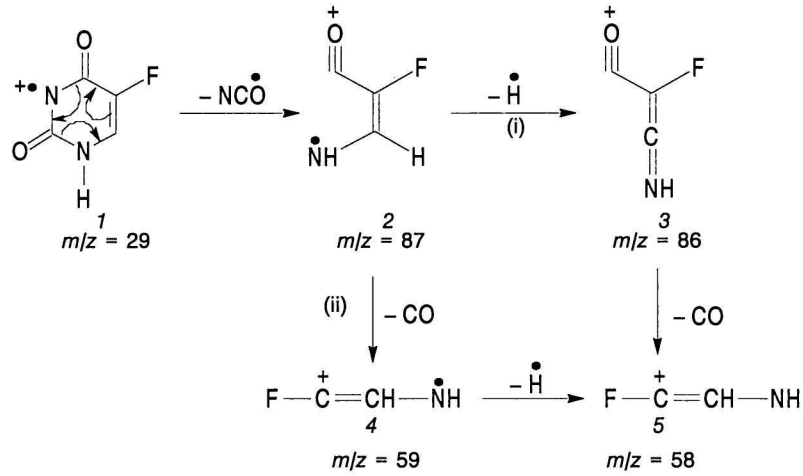
The complexing sites of 5-fluorouracil may be determined by the interpretation of 1500—1800 cm^{-1} $\tilde{\nu}$ region of the IR spectrum. *Susi* and *Ard* [12] have reported that the bands in this region may be attributed to ν(C-2=O), in plane ν(C-4=O) + ν(C=O) and out-of-plane ν(C-4=O) + ν(C=C). It has also been observed that due to the participation of carbonyl group in complexation, the bands in the 1500—1800 cm^{-1} $\tilde{\nu}$ region shift to lower energy [13]. Moreover, it has been reported that the carbonyl at C-4 has a greater affinity to get coordinated to the metal ion, especially mercury(II) ion [14, 15].

In the present study, the 5-fluorouracil ligand showed two medium intensity bands at $\tilde{\nu}$ = 1720 cm^{-1} and 1650 cm^{-1}. In the complexes, the former shifted to $\tilde{\nu} \approx 670$ cm^{-1}, whereas the latter absorbed at $\tilde{\nu}$ = 1600 cm^{-1}. The ν(C—N) stretching frequency shifted from $\tilde{\nu}$ = 1350 cm^{-1} in the ligand to $\tilde{\nu} \approx 1325$ cm^{-1} in the complexes. This indicated that the mercury(II) ion displaced the proton at N-3, similarly to other complexes reported earlier [16, 17]. Therefore, the 5-fluorouracil moiety acted as a bidentate group, being coordinated to the mercury(II) ion through C-4 carbonyl and deprotonated N-3.

The 5-fluorouracil ligand showed two absorption bands at λ = 260 nm (log {ε} = 5.2) and 218 nm (log {ε} = 1.7) in the UV spectrum. The former was attributed to the $\pi \rightarrow \pi^*$ transition of the carbonyl groups, while the latter was due to the corresponding transition of N⋯C⋯O chromophore [18]. On complexation the absorption due to the carbonyl group shifted to $\lambda \approx 268$ nm (log {ε} ≈ 6.2) indicating the involvement of one or both of the carbonyl oxygens in complexation. The N⋯C⋯O chromophore in metal complexes absorbed at $\lambda \approx$ 226 nm (log {ε} ≈ 6.0).

The ^{1}H NMR signal of 5-fluorouracil appeared as a broad singlet at δ = 8.40 (s, br, 1H, H-6) [19]. This signal remained unaffected on complexation. The C$_6$H$_4$ group absorbed as a multiplet in δ = 7.15—7.90 (m, 4H) region. The ^{13}C NMR signal of the free ligand showed resonance signals at δ = 110 (C-2), 118.1 (C-4), 140.2 (C-5), and 85.5 (C-6) [20]. In the metal complexes, the signal due to C-4 shifted to $\delta \approx$ 122.2. The downfield shift was attributed to the involvement of C-4 carbonyl in complexation. In addition, the resonance signal due to C-2 was observed at $\delta \approx$ 111.5 in the metal complexes.

The RHg$^+$, C$_6$H$_4$Hg$^+$, and Hg$^+$ ions dominated the mass spectra [21]. The carbonium ion, R$^+$, constituted the base peak in each case. The fragmentation of the ligand part of the complexes is shown in Scheme 1. The fragmentation resulted in ion *1* (*m*/*z* = 129). Loss of NCO$^\bullet$ from fragment *1* resulted in the formation of fragment *2* (*m*/*z* = 87). The latter cleaved through two pathways. In pathway (i), the fragment *2* successively eliminated H and CO giv-



Scheme 1

ing ions *3* (m/z = 86) and *4* (m/z = 58), respectively. In pathway (ii), the fragment *2* successively eliminated CO and H, giving ions *5* (m/z = 59) and *4* (m/z = 58), respectively [22].

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