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Studies on Organomercury(II) Complexes of Maltol

Sangeeta BHATIA, Narender K. KAUSHIK,* and Gurvinder S. SODHI†
Department of Chemistry, University of Delhi, Delhi 110007, India
†Department of Chemistry, S. G. T. B. Khalsa College, University of Delhi, Delhi 110007, India
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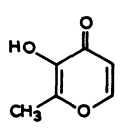
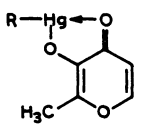
A number of organomercury(II) complexes involving maltol (**1**) of the type RHgL (**2**) [R=phenyl (C_6H_5), *o*-, *p*-hydroxyphenyl (*o*-, *p*-HOC_6H_4), *p*-acetoxyphenyl (*p*-$AcOC_6H_4$), 2-furyl (2-C_4H_3O); HL=maltol] have been synthesized and characterized. Conductance measurements indicate that the complexes are nonelectrolytes. From IR and UV studies, it is concluded that maltol acts as a bidentate ligand, coordinating to the mercury(II) ion through phenolic and carbonyl oxygen atoms. ^1H and ^{13}C NMR support the stoichiometry of the complexes. Fluorescence spectra have been recorded for *o*-, *p*-HOC_6H_4HgL complexes. For C_6H_4HgL, *p*-HOC_6H_4HgL, and *p*-$AcOC_6H_4HgL$ complexes, thermal studies (TG and DSC) have been carried out and relevant kinetic and thermodynamic parameters have been enumerated. In addition, the fragmentation pattern of the complexes has been analyzed on the basis of mass spectra.

During the course of our recent investigations on metal ion-biomolecule interactions, we have synthesized and characterized several organomercury(II) complexes and analyzed their biological activity.[1-6] The organomercury(II) purine complexes[3] were screened for C. N. S. activity; the isoniazid compounds[4] were tested for antitubercular activity; and the dithiocarbazate analogues[5] were examined for antifungal activity. To widen the scope of our investigations, we synthesized a few organomercury(II) complexes of maltol, an antibiotic substance and tested their antibacterial actvity.

Maltol (3-hydroxy-2-methyl-4*H*-pyran-4-one) (**1**) is found in the pine needles in the bark of larch. Since it is obtained as an alkaline degradation product of streptomycin salts,[7] its compounds exhibit considerable antibiotic activity. The interest in the metal complexes of maltol has arisen because of the following reasons. Firstly, since it is structurally related to flavones, the study of its complexes is expected to provide a model for the complexing properties of some naturally occurring keto-hydroxy systems. Secondly, the metal complexes of maltol possess relatively high stability owing to the formation of five membered chelate ring. Thirdly the metal complexes reveal a wide spectrum of antibacterial activity. It is expected that the antibiotic action of a drug is enhanced in the presence of metal ions, since the introduction of metal chelates in vivo prolongs the metabolism of the drug and leads to a more pronounced biological effect. In fact the present complexes have been found to be significantly active against *E. coli* and *P. pyocyanea* bacterial strains.



(1)



(2)

Experimental

The following instruments were used: Elico conductivity bridge, model CM-82 for conductivity measurements; Perkin-Elmer grating 621 spectrometer for IR spectra; Perkin-Elmer UV-visible spectrometer, model 554 for UV spectra; JEOL FX-200 spectrometer, for ^1H and ^{13}C NMR spectra; JASCO FP-550 spectrofluorometer for fluorescence studies; SETARAM G-70 thermoanalyzer for TG studies in air at a heating rate of 8° min^{-1}; Du Pont device for recording DSC curves up to 673 K at a heating rate of 8° min^{-1}. Mass spectra were recorded at Central Drug Research Institute, Lucknow (India).

Nitrobenzene was purified for conductance measurements by the method of Fay et al.[8] C_6H_5HgCl,[9] *o*-, *p*-HOC_6H_4HgCl,[10] *p*-$AcOC_6H_4HgCl$,[11] and 2-C_4H_3OHgCl[12] were prepared by standard methods. Maltol was purchased from Aldrich Chemical Co., Inc. USA.

Preparation of Complexes. A solution of RHgCl (0.05 mol) in 25 ml THF was added to a solution of maltol (0.05 mol) in 25 ml THF. The mixed solution was stirred for about 3 h at room temperature and filtered. The filtrate was evaporated under vacuum to one-fourth of its original volume and petroleum ether was added. The RHgL complexes separated out, which were filtered and dried. These were recrystallized from acetone solution by the addition of petroleum ether.

Results and Discussion

The complexes prepared are white in color and soluble in THF, DMSO, and acetone. The purity has been checked by elemental analyses, spectral studies and TLC. The conductance measured in 10^{-3} M (M=mol dm^{-3}) nitrobenzene solution (at 27 °C) was of the order of 0.5 Ω^{-1} cm^2 mol^{-1} for each of the complexes, indicating that they are nonelectrolytes. The results are summarised in Table 1.

Infrared Spectra. According to Katritzky and Jones[13] the absorption at 1660 cm^{-1} in maltol is assigned to ν(C=O) stretching frequency. This is lower than the conventional carbonyl stretching frequency partly because of the intramolecular hydrogen

Table 1. Analytical Data and Physical Characteristics

Complex	Decomp temp °C	$\Lambda/\Omega^{-1}cm^2mol^{-1}$	Found (Calcd)/% C	H	Hg
C_6H_5HgL	170	0.44	35.65 (35.73)	2.39 (2.43)	49.76 (49.80)
o-HOC_6H_4HgL	122	0.48	34.35 (34.37)	2.32 (2.39)	47.84 (47.97)
p-HOC_6H_4HgL	162	0.56	34.33 (34.37)	2.34 (2.39)	47.85 (47.97)
p-$AcOC_6H_4HgL$	116	0.50	36.57 (36.40)	2.49 (2.60)	43.51 (43.60)
2-C_4H_3OHgL	181	0.50	30.47 (30.53)	2.12 (2.04)	51.06 (51.15)

Table 2. ^{13}C NMR Data

Complex	R						Maltol					
	C_1	C_2	C_3	C_4	C_5	C_6	C'_2	C'_3	C'_4	C'_5	C'_6	CH_3
C_6H_5HgL	149.8	135.8	127.6	127.0	127.5	135.8	149.2	146.2	177.8	113.8	155.3	27.2
o-HOC_6H_4HgL	138.5	161.5	120.2	132.0	122.5	140.4	149.3	146.4	177.8	113.8	155.3	27.4
p-HOC_6H_4HgL	147.1	151.0	135.6	156.2	135.6	151.0	149.2	146.2	177.7	113.8	155.4	27.2
p-$AcOC_6H_4HgL$	148.6	138.1	122.2	150.7	122.2	138.1	149.1	146.2	177.8	113.9	155.2	27.2

bonding and partly due to the weakening of C=O bond by contributions from resonating structures. On complexation, this frequency is further lowered by ca. 45 cm^{-1}, indicating that C=O group is chelating. The ν(C=C) stretching frequency observed at 1580 cm^{-1} in case of the ligand is shifted to ca. 1560 cm^{-1} in complexes.[14]

In maltol, the band due to phenolic OH stretching occurs at 3200 cm^{-1} [15] and that due to δ(OH) at 1300 cm^{-1}.[14] These bands are absent in the spectra of the complexes, indicating the presence of metal-oxygen bond. A weak band at 450 cm^{-1} is attributed to ν(Hg-O) stretching vibrations.[16] The bands at 1290 and ca. 1220 cm^{-1} in case of ligand and complexes respectively are due to C-O-C stretching frequency.[15]

UV Spectra. The UV spectrum of maltol shows an intense band at 237 nm ($\log\varepsilon\approx6.7$) due to π-π^* absorption of chromophoric C=O group. This band is shifted to ca. 250 nm ($\log\varepsilon\approx6.1$) in case of the complexes. The shift in the absorption band due to carbonyl chromophore is attributed to the involvement of this group in complexation, thus supporting the conclusions drawn from IR studies.

^1H NMR Spectra. In ^1H NMR spectra, the following signals are attributed to the presence of maltol moiety in the complexes: δ 2.26 (s, 3H, CH_3 at C_2); δ 6.45 (d, 1H, H, J=6 Hz), 7.95 (d, 1H, H_6, J=6 Hz). The signal due to H_5 in free maltol absorbs at δ 6.30 (d, 1H, J=6 Hz). The downfield shift in case of metal complexes is due to involvement of carbonyl at C_4 in complexation. In the related kojic acid complexes,[6] the signals due to H_3 and H_6 absorb at ca. δ 6.93 and 8.05 respectively. In free kojic acid, the signal due to H_3 absorbs at δ 6.45 and that due to H_6 at δ 7.80. The downfield shift in these complexes is also attributed to the involvement of carbonyl at C_4 and hydroxyl at C_5 in complexation. The furyl group in the present complexes is identified by signals at δ 6.50 (d, 2H, J=10 Hz) and δ 7.52 (s, 1H).

^{13}C NMR Spectra. The C_4 carbonyl in pure maltol shows a resonance signal at δ 173.2 while the C_3 carbon absorbs at δ 143.2.[17] In metal complexes these signals appear at δ ca. 177.84 and 146.20 respectively. Thus, it is concluded that the complexes are formed by deprotonation of C_3 hydroxyl and chelation through C_4 carbonyl. In the ^{13}C NMR spectra of kojic acid the signals due to C_4 and C_5 appear at δ 174.61 and 145.82 respectively.[6] In the case of the complexes, the former signal is shifted to δ about 179.52 and the latter to δ about 148.71, indicating also that complexation involves C_4 carbonyl and deprotonated C_5 hydroxyl. In the present complexes, the C_2, C_5, and C_6 carbons absorb at δ ca. 149.25, 113.85, and 155.28 respectively. The methyl group at C_2 shows a resonance signal at δ ca. 27.20. The data are recorded in Table 2.

Fluorescence Studies. The o-, p-HOC_6H_4HgL complexes are fluorescent in nature. Hence their fluorescence spectra have been recorded. The absorption band is observed at 250 nm, while the emission band is at 500 nm. Thus in accordance with Franck-Condon principle and thermal relaxation of vibrational modes, the fluorescence spectra are observed on the red side of the absorption spectra in approximately mirror image relationship.[18] A slight distortion in the mirror image pattern arises due to the appearance of a weak band at 310 nm ($\log\varepsilon\approx1.5$), which is attributed to the forbidden transitions, $Hg6(^3P_1)\rightarrow Hg6(^1S_0)$

and $J=0\rightarrow J=0$.[17]

The spectra are free from antistokes effects. The pattern of the spectra follows Levschin's rule, indicating that the geometry of the excited state is similar to that of the ground state.[20] The quantum yield of fluorescence, ϕ_f, calculated by a relative method,[19] using anthracene as the reference are: *o*-HOC_6H_4HgL, 0.73; *p*-HOC_6H_4HgL, 0.72. Since the ϕ_f values show deviation from unity, it is inferred that fluorescence remains the dominant but not the exclusive mode of emission. The nonradiative modes are likely to be contributing to the emission process.

Thermal Studies. Thermogravimetric (TG) studies have been carried out for C_6H_5HgL, *p*-HOC_6H_4HgL, and *p*-$AcOC_6H_4HgL$ complexes. The weight loss in each case corresponds to the formation of HgO, which slowly volatilizes beyond 773 K. The order (n) and activation energy (E_a) for thermal decomposition reaction have been elucidated by the methods of Coats and Redfern.[21] The linearization curves are shown in Fig. 1.

The order of reaction in each case is one. A comparison of the activation energy data reveals that *p*-$AcOC_6H_4HgL$ complex has the lowest value of E_a. This may be explained on the basis of electron withdrawing effect of the acetoxyl group which weakens the R-Hg bond, making thermal degradation relatively easy. In case of *p*-HOC_6H_4HgL complex, the phenolic hydroxyl group is electron donating and the R-Hg bond is strengthened. Therefore the E_a value in this case is higher than in the unsubstituted C_6H_5HgL complex. That R-Hg bond cleavage is involved in the pyrolysis of the complexes is also indicated by the mass spectra, where peaks for $C_6H_5^+$, $HOC_6H_4^+$, and $AcOC_6H_4^+$ fragments have been observed.

The activation energy values of the present complexes are lower than those of the corresponding theophylline and theobromine analogues.[3] In the latter cases, the ligands are bound to the mercury(II) ion through nitrogen, which according to HSAB theory, is softer than oxygen. The soft mercury(II) ion thus forms a stronger bond with nitrogen than with oxygen. This makes thermal degradation of maltol complexes relatively easy and the reaction involves a lower value of E_a.

The apparent activation entropy,[22] $\Delta S^{\neq}$ has a positive value for all the complexes. The *p*-HOC_6H_4HgL complex has the highest value of $\Delta S^{\neq}$, while the *p*-$AcOC_6H_4HgL$ has the lowest. Hence, the former decomposes with greatest degree of randomness, while the latter with the least.

The TG data is supplemented by differential scanning calorimetry (DSC) studies. The thermal effects on DSC curves are endothermic in nature. The heat of reaction, ΔH has been enumerated from DSC curves. Thermal data are presented in Table 3.

Mass Spectra. The RHg^+, R^+, and Hg^+ ions dominate the mass spectra. The fragmentation pattern of

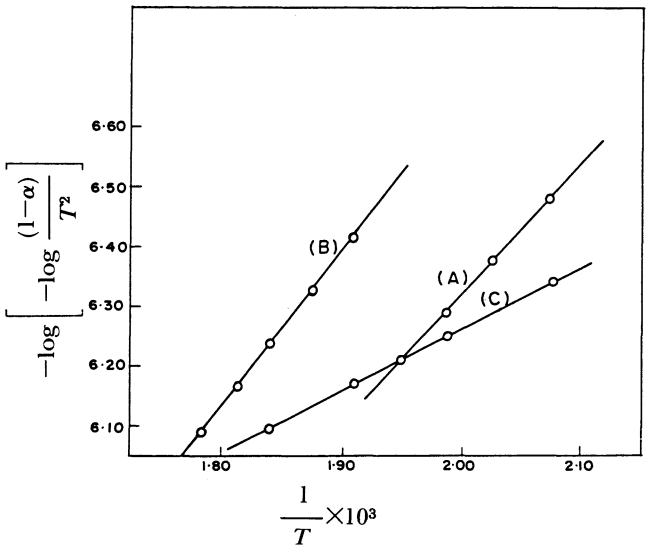
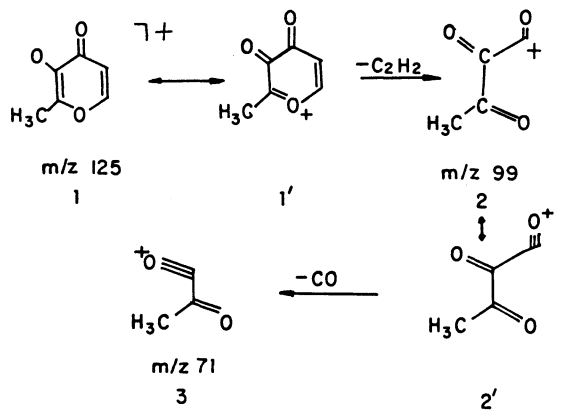


Fig. 1. Kinetic parameters from TG: (A) C_6H_5HgL, (B) *p*-HOC_6H_4HgL, (C) *p*-$AcOC_6H_4HgL$.



Scheme 1.

Table 3. Thermal Data

Complex	TG				DSC		
	Temp range / K	n	E_a / kJ mol^{-1}	$\Delta S^{\neq}$ / J deg^{-1} mol^{-1}	Thermal effect	T_{max} / K	ΔH / kJ mol^{-1}
C_6H_5HgL	453—523	1	42.46	29.59	Endothermic	495	108.92
p-HOC_6H_4HgL	453—573	1	50.99	38.99	Endothermic	518	128.92
p-$AcOC_6H_4HgL$	453—553	1	20.14	4.93	Endothermic	501	55.25

the RHg^+ portion is similar to that reported earlier.[4] The carbonium ion R^+ constitutes the base peak. The fragmentation of the ligand portion is shown in Scheme 1. The pattern is similar to that of 4-pyrone.[23] The molecular ion **1** (*m/z* 125) undergoes rearrangement to **1'** before losing C_2H_2. Fragment **2** (*m/z* 99) rearranges to **2'** and subsequently loses CO, resulting in fragment **3** (*m/z* 71).

Antibacterial Studies. The metal complexes have been tested against *E. coli* and *P. pyocyanea* bacterial strains using maltol as the standard for comparing the activity. The compounds were screened at two concentrations, 25 $\mu g\,ml^{-1}$ and 50 $\mu g\,ml^{-1}$. The inhibitory power of the complexes was greater than that of the control. The conpounds showed better inhibition at higher concentrations. At lower concentrations, the compounds were equally active against both bacterial strains. However, at higher concentrations, the order of activity against the two microorganisms was *P. pyocyanea*>*E. coli*. The C_6H_5HgL and *p*-$AcOC_6H_4HgL$ complexes were found to have higher activity than others.

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