Studies on Organomercury(II) Complexes of Isoniacinamide

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Organomercury(II) complexes involving isoniacinamide(I) of the type, RHgCl(L)(II) [R = phenyl, *o*-, *p*-hydroxyphenyl (*o*-, *p*- HOC_6H_4), *p*-acetoxyphenyl (*p*- AcOC_6H_4), 2-furyl ($2\text{-C}_4\text{H}_3\text{O}$); L = isoniacinamide] have been synthesized and characterized. Conductance measurements indicate that the complexes are non-electrolytes. From IR and UV spectral studies it is concluded that isoniacinamide is coordinated to the mercury(II) ion through the ring nitrogen atom. ^1H and ^{13}C NMR support the stoichiometry of the complexes. Fluorescence studies have been made for *o*-, *p*- $\text{HOC}_6\text{H}_4\text{HgCl(L)}$ complexes. For $\text{C}_6\text{H}_5\text{HgCl(L)}$, *p*- $\text{HOC}_6\text{H}_4\text{HgCl(L)}$ and *p*- $\text{AcOC}_6\text{H}_4\text{HgCl(L)}$ complexes, thermal studies (TG and DSC) have been carried out and relevant kinetic and thermodynamic parameters for thermal degradation have been enumerated. The fragmentation pattern of the complexes has been analysed on the basis of mass spectra. The $\text{C}_6\text{H}_5\text{HgCl(L)}$ and *p*- $\text{AcOC}_6\text{H}_4\text{HgCl(L)}$ complexes have been screened for antibacterial activity.

Introduction

Isoniacinamide functions are a constituent of the pyridine nucleotides, which occupy a central role as hydrogen transferring coenzymes. The pyridine ring in the coenzymes is attached in a N-glycosidic linkage to ribose [1]. The interest in the metal complexes of isoniacinamide has arisen because of the fact that although it is a polyfunctional ligand, its bonding mode to the metal ions remains the same as that in the biological system. In the present complexes, too, it is coordinated to mercury(II) ion through the pyridine nitrogen.

Further, isoniacinamide is an antibiotic substance and manifests significant therapeutic effects [2]. It is expected that the antibiotic action of a drug is enhanced in the presence of metal ions, since the introduction of metal complexes *in vivo* prolongs the metabolism of the drug and leads to a more pronounced biological effect. With this aim, we undertook the synthesis and characterization of some organomercury(II) complexes of isoniacinamide and screened some representative samples for antibacterial activity. This is a sequel to our investigation of metal ion-biomolecule interactions [3–6].

Experimental

The following instruments were used: Elico conductivity bridge, model CM-82 for conductance measurements; Shimadzu infrared spectrophotometer, IR-435 for IR spectra; Perkin-Elmer UV-VIS spectrometer, model 554 for UV spectra; Jeol FX-200 FT-NMR spectrometer for ^1H and ^{13}C NMR spectra; Jasco FP-500 spectrofluorometer for fluorescence studies; G-70, SETARAM (Lyon, France) for recording TG curves 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.* [7]. $\text{C}_6\text{H}_5\text{HgCl}$ [8], *o*-, *p*- $\text{HOC}_6\text{H}_4\text{HgCl}$ [9], *p*- $\text{AcOC}_6\text{H}_4\text{HgCl}$ [10] and $2\text{-C}_4\text{H}_3\text{OHgCl}$ [11] were synthesized by standard methods. Isoniacinamide was purchased from Aldrich Chemical Co., Inc., USA.

Preparation of complexes

A solution of isoniacinamide (0.01 mol) in 25 ml THF was added slowly to a solution of RHgCl

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(0.01 mol) in 25 ml THF. The contents were stirred for about 2 h at room temperature and filtered. The RHgCl(L) complexes were precipitated on addition of petroleum ether to the filtrate and recrystallized from acetone.

Results and Discussion

Satisfactory results of elemental analysis and spectral studies reveal that the complexes are of good purity. This is also supported by TLC. The complexes are white in colour and soluble in THF, DMSO, and acetone. Conductance measurements in 10^{-3} M solution are of the order of $0.50 \text{ ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$, indicating that the complexes are non-electrolytes. Some physical characteristics and elemental analysis data are presented in Table I.

Infrared spectra

Isoniacinamide has three bonding sites, *i.e.* heterocyclic nitrogen, amido nitrogen and carbonyl oxygen. The ligand may be coordinated to the metal by one or more of these.

In complexes of carbonyl donors a significant negative shift in carbonyl frequency takes place [12]. In the present study, the carbonyl stretching frequency absorbs at $\sim 1670 \text{ cm}^{-1}$, both in case of ligand and metal complexes. The same is true for $\nu(\text{NH})$ of the amido group which absorbs at $\sim 3325 \text{ cm}^{-1}$ in case of the ligand as well as the metal complexes. This rules out the possibility of bonding through the carbonyl oxygen or the amido nitrogen.

On the other hand, IR frequencies exhibit appreciable perturbation in the fundamental vibrations of the pyridine part of the molecule. Absorption bands at 1590 cm^{-1} due to $\nu(\text{C}\cdots\text{C})$ stretching frequency and at 1550 cm^{-1} due to $\nu(\text{C}\cdots\text{N})$ stretching frequency of the isoniacinamide molecule are shifted to ~ 1620 and $\sim 1600 \text{ cm}^{-1}$, respectively, on complexa-

tion [13]. Further, the pyridine ring vibrations of the ligand at 950 , 605 and 405 cm^{-1} also undergo significant positive shifts [14]. In case of metal complexes, these vibrations absorb at *ca.* 990 , 630 and 435 cm^{-1} indicating that coordination takes place *via* the pyridine nitrogen only. The $\nu(\text{Hg}-\text{Cl})$ frequency appears at $\sim 365 \text{ cm}^{-1}$.

UV spectra

In case of isoniacinamide, a very intense band appears at 256 nm ($\log \epsilon$ 7.1) which is attributed to the $\pi-\pi^*$ absorptions of the carbonyl group. In the metal complexes this band is shifted to *ca.* 234 nm ($\log \epsilon \sim 5.1$). In case of metal complexes involving isoniazid [5] which is structurally quite similar to isoniacinamide, but coordinates through the carbonyl group, a positive shift is observed in the absorption band due to the $\text{C}=\text{O}$ chromophore. In the present complexes, the negative shift in λ_{max} value rules out the possibility of bonding through the carbonyl group.

^1H NMR spectra

In ^1H NMR spectra, the following signals are attributed to the presence of an isoniacinamide moiety in the complexes: δ 7.70–7.92 (m, 2H, $\text{H}_{3,5}$) and δ 8.30–8.75 (m, 2H, $\text{H}_{2,6}$). The latter signal in pure isoniacinamide was observed at δ 8.10–8.30 (m, 2H). The downfield shift in case of metal complexes is due to the involvement of the ring nitrogen in complexation. In $p\text{-HOC}_6\text{H}_4\text{HgCl(L)}$ and $p\text{-AcOC}_6\text{H}_4\text{HgCl(L)}$ complexes, the resonance signals due to the C_6H_4 group and $\text{H}_{3,5}$ of isoniacinamide ligand overlap with each other and a multiplet is observed in the region δ 7.0–8.0. The furyl group in $2\text{-C}_4\text{H}_3\text{OHgCl(L)}$ analogue is identified by signals at δ 6.56 (d, 2H, J 9.8 Hz) and δ 7.48 (s, 1H).

Table I. Physical characteristics and elemental analyses.

Complex	Dec. temp. [°C]	Λ^a [$\text{C} = 1.5 \times 10^{-3} \text{ M}$]	Found (calcd) [%]		
			Hg	N	Cl
$\text{C}_6\text{H}_5\text{HgCl(L)}$	122	0.48	46.15 (46.20)	6.47 (6.44)	8.00 (8.05)
$o\text{-HOC}_6\text{H}_4\text{HgCl(L)}$	118	0.46	44.50 (44.57)	6.32 (6.21)	7.69 (7.76)
$p\text{-HOC}_6\text{H}_4\text{HgCl(L)}$	212	0.50	44.64 (44.57)	6.36 (6.21)	7.66 (7.76)
$p\text{-AcOC}_6\text{H}_4\text{HgCl(L)}$	185	0.50	41.04 (40.85)	5.50 (5.69)	7.10 (7.11)
$2\text{-C}_4\text{H}_3\text{OHgCl(L)}$	126	0.52	47.35 (47.29)	6.54 (6.59)	8.10 (8.35)

^a $\text{ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$.

¹³C NMR spectra

In pure isoniacinamide the signals due to C_{2,6} and C_{3,5} carbons appear at 146.9 and 123.4 ppm, respectively. On complexation, the former signal is shifted to *ca.* 151.5 ppm, while the latter remains unaffected. The shift is attributed to the involvement of the pyridine nitrogen in complexation. In isoniacinamide, the carbonyl group shows a signal at 168.6 ppm. This value remains unaltered in complexes. The signal due to the C₄ carbon appears at 135.4 ppm. Table II lists the position of resonance signals observed in the ¹³C NMR spectra.

Fluorescence studies

The *o*-, *p*-HOC₆H₄HgCl(L) complexes are fluorescent in nature. Hence their fluorescence spectra have been recorded. The absorption band is observed at 244 nm (log ϵ 4), while the emission band is at 488 nm. Thus, in accordance with the Franck-Condon principle and thermal relaxation of vibrational modes, the fluorescence spectra are observed on the red side of the absorption spectra approximately in a mirror image relationship [15]. A slight distortion in the mirror image pattern arises due to the appearance of a weak band at 312 nm (log ϵ 1.5) because of the forbidden transitions, Hg6(³p₁) → Hg6(¹s₀) and $J = 0 \rightarrow J = 0$ [5].

The spectrum is free from *anti*-Stokes effects. The pattern of the spectrum follows Levschin's rule, indicating that the geometry of the excited state is similar to that of the ground state [16]. The quantum yields of fluorescence, θ_f , calculated by the relative method [17], using anthracene as the reference, are as follows: *o*-HOC₆H₄HgCl(L), 0.65; *p*-HOC₆H₄HgCl(L), 0.62. Since the θ_f values show deviation from unity, it is inferred that fluorescence remains the dominant, but not the exclusive mode of emission. The non-radiative modes like inter-system crossing and internal conversion are likely to be contributing to the emission process.

Thermal studies

Thermogravimetric (TG) studies have been carried out for C₆H₅HgCl(L), *p*-HOC₆H₄HgCl(L) and *p*-AcOC₆H₄HgCl(L) complexes. The weight loss in each case corresponds to the formation of HgO, which slowly volatilizes beyond 763 K. The order (*n*) and activation energy (*E_a*) for the thermal decomposition reaction have been elucidated by the method of Coats and Redfern [18]. The linearization curve is shown in Fig. 1.

Fig. 1. Kinetic parameters from TG for (A) C₆H₅HgCl(L); (B) *p*-HOC₆H₄HgCl(L); (C) *p*-AcOC₆H₄HgCl(L).

The order of reaction in each case is one. A comparison of the activation energy data reveals that *p*-AcOC₆H₄HgCl(L) complex has the lowest value of *E_a*. This may be explained on the basis of the electron withdrawing effect of the acetoxy group, which weakens the R–Hg bond, making thermal degradation relatively easy. In case of the *p*-HOC₆H₄HgCl(L) complex, the phenolic group is electron donating and the R–Hg bond is strengthened. Therefore, the activation energy value in this case is higher than in the unsubstituted C₆H₅HgCl(L) complex. That R–Hg

Table II. ¹³C NMR data.

Complex	R						Isoniacinamide (L)			
	C ₁	C ₂	C ₃	C ₄	C ₅	C ₆	C _{2,6}	C _{3,5}	C ₄	C=O
C ₆ H ₅ HgCl(L)	150	136	128	127.5	128	136	151.5	123.4	135.4	168.6
<i>o</i> -HOC ₆ H ₄ HgCl(L)	138.6	162	119.5	132	112.4	140.4	151.4	123.4	135.3	168.6
<i>p</i> -HOC ₆ H ₄ HgCl(L)	147.3	151	135.3	156.5	135.3	151	151.4	123.4	135.3	168.5
<i>p</i> -AcOC ₆ H ₄ HgCl(L)	148.8	138	122	151	122	138	151.6	123.5	135.4	168.6

Table III. Thermal data.

Complex	TG wt. loss Found (calcd) [%]	Temp. range [K]	<i>n</i>	<i>E</i> _a [Kcal/mol]	<i>S</i> [‡] [e. u.]	DSC Thermal effect	<i>T</i> _{max} [K]	Δ <i>H</i> [cal/g]
C ₆ H ₅ HgCl(L)	51.8 (50.2)	433–563	1	9.53	6.85	Endothermic	506	38.68
<i>p</i> -HOC ₆ H ₄ HgCl(L)	53.8 (51.9)	483–533	1	17.60	14.05	Endothermic	502	27.45
<i>p</i> -AcOC ₆ H ₄ HgCl(L)	54.1 (51.9)	463–573	1	6.54	2.86	Endothermic	523	46.95

bond cleavage is involved in the pyrolysis of the complexes is also indicated by the mass spectra, where peaks for C₆H₅⁺, HOC₆H₄⁺ and AcOC₆H₄⁺ fragments have been observed.

The apparent activation entropy [19], *S*[‡], has a positive value for all the complexes. The *p*-HOC₆H₄HgCl(L) complex has the highest value of *S*[‡], while *p*-AcOC₆H₄HgCl(L) has the lowest. Hence, the former decomposes with greatest degree of randomness while the latter with the least.

The TG data are supplemented by differential scanning calorimetry (DSC) studies. The thermal effects on DSC curves are endothermic in nature. The heat of reaction, Δ*H* has been enumerated for the thermal decomposition reaction from DSC studies. Thermal data are presented in Table III.

Mass spectra

The fragmentation pattern of the complexes shows that the RHg⁺, R⁺, HgCl⁺ and Hg⁺ ions dominate the mass spectra [20]. The fragmentation of the RHg⁺ portion is similar to that reported earlier [4]. The fragmentation pattern of the ligand portion is shown in Scheme 1. The isoniacinamide molecular ion 1 (*m/e* 122) is formed initially. It eliminates an NH₂ radical giving fragment 2 (*m/e* 106) which subsequently loses CO to give fragment 3 (*m/e* 78), fol-

Scheme 1

lowed by elimination of HCN, resulting in fragment 4 (*m/e* 51). The isoniacinamide molecular ion 1 (*m/e* 122) constitutes the base peak.

Antibacterial activity

The C₆H₅HgCl(L) and *p*-AcOC₆H₄HgCl(L) complexes were screened against *E. coli* and *P. pyocyanea* bacterial strains at concentrations of 25 and 50 μg ml⁻¹. The complexes showed greater inhibition at higher concentration. While both the samples were equally active against *E. coli*, the *p*-AcOC₆H₄HgCl(L) analogue showed greater inhibition against *P. pyocyanea*. The order of activity against two microorganisms is *P. pyocyanea* > *E. coli*.

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