

A ^1H NMR Study of the Factors affecting the Intramolecular Interaction between the Phenyl Rings and the Mercury(II) Ion of several Methylmercury(II) Complexes containing Substituted Phenyl Groups

PAUL A. LAMPE and PETER MOORE*

Department of Chemistry and Molecular Sciences, University of Warwick, Coventry CV4 7AL, U.K.

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Complexes of methylmercury(II) ion have been prepared with several homologous series of ligands which contain phenyl rings: (1) $\text{C}_6\text{H}_5(\text{CH}_2)_n\text{X}$ ($\text{X} = \text{NH}_2$, S^- , $n = 1, 2, 3$; and $\text{X} = \text{CO}_2^-$, $n = 0, 1, 2$) and (2) $p\text{-R-C}_6\text{H}_4(\text{CH}_2)_{n-1}\text{CH}(\text{NH}_2)\text{CO}_2^-$ ($\text{R} = \text{H}$, $n = 2, 3$; $\text{R} = \text{OH}$, $n = 2$). The observation of a high field shift of the $[\text{MeHg}]^+ ^1\text{H}$ nmr resonance is interpreted as an anisotropic shielding effect due to an intramolecular interaction between the mercury(II) ion and the phenyl ring. Such an interaction is only observed for series (1) when $\text{X} = \text{NH}_2$ or S^- and $n = 1$ or 2. In the case of the N-bound methyl(L-tyrosinato)mercury(II), there is fairly good agreement between the crystal structure and that observed in solution, as estimated from the anisotropic shift and conformational analysis based on the backbone vicinal coupling constants. A similar conformational analysis is reported for the complex formed with L-3-phenylalanine.

Introduction

Methylmercury(II) ion is known to favour a linear two-co-ordinate structure in most of its complexes and, with flexible multidentate ligands such as amino acids or peptides, it usually forms a strong bond to only one of the donor atoms and only weaker interactions occur with some of the other donor atoms or groups in the molecule [1-3]. Even with a rigid bidentate ligand like 1,10-phenanthroline, this tendency to stay linear is apparent with a very distorted structure resulting from the strong, almost linear, interaction with one N-atom and a weaker angled co-ordination to the other N-atom [2]. We have also observed similar behaviour in a crystal structure of a complex formed between methylmercury(II) ion and the potentially bidentate ligand *trans*-(1,2-dithiol)cyclohexane [4].

This tendency of $[\text{MeHg}]^+$ ion to form linear complexes and to co-ordinate primarily with unidentate

donor molecules makes it difficult to enhance the affinity of ligands for this very toxic species, and accordingly we have been investigating other factors which might increase the stability of the complexes it forms [5-7]. We have observed, for example, that methylmercury(II) binds much more strongly (by a factor of $10^{3.2}$) to the single cysteinyl thiol-group in the active site of the enzyme papain than to the thiol group of cysteine itself [6]. One factor which might account for this enhanced affinity for the thiol group of papain is the known intramolecular interaction which occurs between the aromatic rings of some amine-bound amino-acids such as phenylalanine, tyrosine and *l*-dopa [3, 5-8]. This interaction arises from an edge-on 'co-ordination' (at ca. 3.2 Å) between the mercury(II) ion and the 1,2-carbon atoms of the phenyl ring, as shown by the recent crystal structure (Fig. 1) of the complex

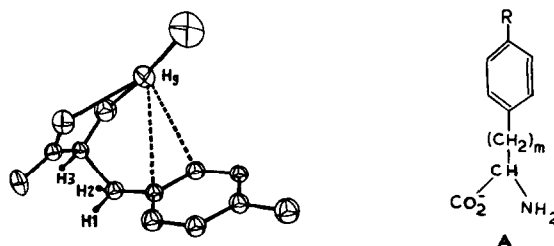


Fig. 1. Structure of the tyrosinato complex.

formed with tyrosinate ion (A; $\text{R} = \text{OH}$, $m = 1$) [7]. It was demonstrated that the presence of this type of interaction depends on the length of the carbon chain between the donor amino-group and the phenyl-ring, since the interaction is absent in the complex formed with the longer *L*-2-amino-4-phenyl-butanate ion (A; $\text{R} = \text{H}$, $m = 2$) [7].

In the present work, we have searched for the presence of other phenyl ring-mercury(II) interactions, and the importance of the donor atom (X), using as models the ligands $\text{C}_6\text{H}_5(\text{CH}_2)_n\text{X}$ ($\text{X} = \text{NH}_2$, S^- , $n = 1, 2, 3$; $\text{X} = \text{CO}_2^-$, $n = 0, 1, 2$) and $p\text{-R-C}_6\text{H}_4\text{-(CH}_2\text{)}_{n-1}\text{CH}(\text{NH}_2)\text{CO}_2^-$ ($\text{R} = \text{H}$, $n = 2, 3$; $\text{R} = \text{OH}$, $n = 2$). It has been established that when a phenyl ring

*Author to whom correspondence should be addressed.

interaction is present, there is an upfield shift in the ^1H nmr resonance of $[\text{MeHg}]^+$ ion arising from the anisotropic shielding produced by the close proximity of the ring current of the arene ring [3, 7–9]. We have used the upfield shift in the position of the methyl group resonance as an indicator of the presence of an aromatic ring interaction in the present investigation, as well as the $^2J(^1\text{H}-^{199}\text{Hg})$ coupling constants as a guide to the type of co-ordination involved (e.g. amino- or carboxylato- in the case of the amino acid complexes studied). The amino acid complexes are known from previous work to show a pH-dependent equilibrium between amino- and carboxylato-bound species, the latter being favoured at low pH when the amino group is protonated [1, 7, 8].

We have also compared the structure of the complex formed with *L*-tyrosinate ion in solution with that observed in the solid state [7], using the chemical shift of the methyl group and the backbone proton coupling constants, as an indicator of the complex conformation in solution. An analogous conformational analysis for the complex formed with *L*-3-phenylalanine is also reported.

Experimental

Physical Measurements

^1H nmr spectra were obtained at 90 MHz with a Bruker WH 90 Fourier-transform spectrometer. Chemical shifts are quoted relative to dioxane as internal standard ($\delta = 3.56$ ppm). Typically, a sweep width of 1200 Hz and 8K data points were used for data acquisition. Estimated errors are ± 0.5 Hz for the coupling constants and ± 0.01 ppm for the chemical shifts. Theoretical spectra were calculated with the Nicolet BNC-12 computer of the Bruker WH 90, using the program NMRCAL. Iterative fitting of observed spectra to obtain vicinal coupling constants was carried out with the program ITRCAL.

Preparation 2-Phenylethylmercaptan

Thiourea (7.5 g) was dissolved in water (31 cm^3) and bromoethylbenzene (18.5 g) added. The mixture was refluxed with vigorous stirring for 2 h, sodium hydroxide (6.6 g) added, and the mixture refluxed for a further 2 h. The aqueous (lower) layer was separated, acidified and then extracted several times with ether. The ether extracts were combined with the separated upper layer and dried over anhydrous magnesium sulphate. Ether was removed under reduced pressure and the resulting oil distilled *in vacuo* (b.p. 104° , 17 mm).

Other ligands were of the highest grade commercially available and were used without further purification.

The mercaptide complexes were prepared mixing equimolar amounts of mercaptan, methylmercury(II) chloride (Pfaltz and Bauer) and sodium hydroxide in methanol. The solvent was removed by rotary evaporation, the solid extracted with ether and dried over anhydrous magnesium sulphate. Ether was removed to give products which were used without further purification. Methylmercury(II) nitrate was prepared from methylmercury(II) chloride and silver nitrate [10] and recrystallized from water. Both amine and carboxylate complexes were prepared *in situ* by mixing equimolar amounts of methylmercury(II) nitrate and the appropriate ligand in either D_2O or CD_3OD .

Results and Discussion

The $^2J(^1\text{H}-^{199}\text{Hg})$ coupling constants (Table I) confirm previous findings [7] and allow a distinction to be made between amino- and carboxylato-bound species in the case of the amino acids.

Several of the complexes show the expected upfield shift (Δ) of the methyl resonance of $[\text{MeHg}(\text{II})]$ indicating an aromatic ring interaction (Table I). Only when $[\text{MeHg}(\text{II})]$ is co-ordinated to a carboxylate group is there no evidence for such an interaction in any of the complexes studied. Presumably this is because of the lower flexibility of the carboxylate moiety which restricts the ease with which the ligand can bend to bring the phenyl ring into a 'co-ordinating' position. Although the carboxylato-complexes are less stable than the other complexes studied [1–3], all of the complexes are very labile [2], and the absence of an interaction for the carboxylato-species cannot be attributed to a kinetic effect.

The dependence on the length of the alkyl chain can be seen to be similar for all of the amino- and mercapto-ligands examined. A mercury(II)-arene interaction is present for $\text{Ph}(\text{CH}_2)_n\text{X}$ ($\text{X} = \text{S}^-$, NH_2) or NH_2 -bound $\text{Ph}(\text{CH}_2)\text{CH}(\text{CO}_2)\text{NH}_2$ whenever $n = 1$ or 2 ; these produce five- and six-membered 'chelate' rings respectively. When $n = 3$, entropy considerations presumably overcome the relatively weak binding energy, the 'chelate' ring is not formed (except possibly for 3-phenyl propylamine where the shift is small), and there is no upfield shift of the methyl resonance. The findings in solution are entirely in accord with the two published crystal structures [7].

Using the crystal geometry for methyl(tyrosinato)-mercury(II), the relationship can be examined between the centroid of the methyl protons (calculated positions) and plane of the phenyl ring; it is 4.8 Å above the plane of the ring and in the notation of Johnson and Bovey [9], the co-ordinates of this position are $\rho = 1.19$ and $Z = 3.43$. Therefore, using published tables [11] one can predict an upfield shift

TABLE I. ^1H Nmr Shifts (δ /ppm relative to TMS) and $^2\text{J}(^{199}\text{Hg}-^1\text{H})$ Coupling Constants in Various CH_3HgL Complexes ($\text{L} = \text{C}_6\text{H}_5(\text{CH}_2)_n\text{X}$ or $p\text{-RC}_6\text{H}_4(\text{CH}_2)_{n-1}\text{CH}(\text{CO}_2^-)\text{NH}_2$).

n	L	δ /ppm	$^2\text{J}/\text{Hz}$	Δ^a/Hz	Solvent
$X = \text{S}^-$					
1	Benzyl mercaptan ^b	0.57	156.6	18.9	CDCl_3
2	2-Phenylethylmercaptan	0.25	156.9	47.7	CDCl_3
3	3-Phenylpropylmercaptan	0.74	156.7	0	CD_3OD
3	3-Phenylpropylmercaptan	0.75	152.5	0	CDCl_3
$X = \text{NH}_2$					
1	Benzylamine	0.62	211.7	25.2	D_2O
2	2-Phenylethylamine	0.43	210.0	42.3	D_2O
2	<i>L</i> -3-Phenylalanine ^c	0.27	213.6	56.7	D_2O
2	<i>L</i> -Tyrosine ^c	0.22	216.5	51.2	D_2O
3	3-Phenylpropylamine	0.77	208.8	11.7 ^d	CD_3OD
3	2-Amino-4-phenylbutanoic acid ^c	0.78	216.0	0	$\text{CD}_3\text{OD}/\text{D}_2\text{O}^e$
$X = \text{CO}_2^-$					
0	Benzoic acid	0.86	225.3	0	CD_3OD
1	Phenylacetic acid	0.83	231.5	0	CD_3OD
2	3-Phenylpropionic acid	0.83	231.2	0	CD_3OD
2	<i>L</i> -2-Phenylalanine ^f	0.92	232.0	0	D_2O
2	<i>L</i> -Tyrosine ^f	0.89	233.0	0	D_2O
3	2-Amino-4-phenylbutanoic acid ^f	0.89	232.0	0	$\text{CD}_3\text{OD}/\text{D}_2\text{O}^e$

^a Δ = upfield shift in Hz = [δ (observed) - δ (typical complex with some donor group but for a ligand without a phenyl ring)] $\times$ 90.0. ^b Ref. 14. ^c NH_2 -bound species. ^d Considered as having no interaction. ^e 50:50 (v/v). ^f CO_2 -bound species.

TABLE II. Coupling Constants and Estimated Dihedral Angles (in parentheses) of the ABX Backbone Protons in *L*-Tyrosine, *L*-3-Phenylalanine and their NH_2 -bound Methylmercury(II) Complexes.

Species	J_{1-2}/Hz	J_{2-3}/Hz	J_{1-3}/Hz
<i>L</i> -3-Phenylalanine	-14.3	8.5	4.4
Methyl(<i>L</i> -3-Phenylalaninato)mercury(II)	-14.0	5.5 (50°)	4.1 (59°)
Methyl(<i>L</i> -Tyrosinato)mercury(II)	-14.6	5.6 (50°)	4.5 (57°)
Methyl(<i>L</i> -Tyrosinato)mercury(II) ^a		(57°)	(62°)

^a In the solid state; ref. 7.

of 0.36 ppm for the methyl resonance. Although the observed shifts in the case of tyrosine (0.68 ppm) and phenylalanine (where there are no substituents in the phenyl ring to perturb the ring current, A , $m = 1$, $R = \text{H}$; shift = 0.63 ppm) are greater than expected, in view of the non-linear variation of the anisotropic shift parameter with ρ and Z , the agreement can be regarded as satisfactory.

An alternative way of comparing the structures formed in solution with those in the crystal makes use of the Karplus equation. This equation is used here to relate ^3J vicinal coupling constants to the dihedral angle about the backbone C-C bond for the complexes formed by NH_2 -bound tyrosine and phenylalanine (ABX systems). The three hydrogen

atoms attached to the two backbone carbon atoms are labelled in Fig. 1, and the corresponding coupling constants and calculated dihedral angles are collected in Table II. In these calculations, the Karplus equation constants give by Shaw [12] were used. For comparison, the hydrogen atom positions (H1, H2 and H3 in Fig. 1) were calculated from the crystal structure assuming tetrahedral carbon atoms, and the corresponding dihedral angles are shown in Table II. The coupling constants (J_{1-3} and J_{2-3}) for free phenylalanine are close to those expected for a $\text{CH}_2\text{-CH}$ group with a freely rotating C-C bond [13]. The dihedral angles for the complexes of tyrosine and phenylalanine show that in solution there is an

interaction imposing stereochemical rigidity on the carbon backbone, and that both complexes have a similar conformation to that observed for methyl-(tyrosinato)mercury(II) in the crystal.

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