Kinetics and Mechanism of the Reaction of Mercuric Acetate with Substituted Phenylhydrazones. Part 4.† An Internal Cyclometallation. Reactions of Mercury(II) Acetate with Nitrogen Compounds

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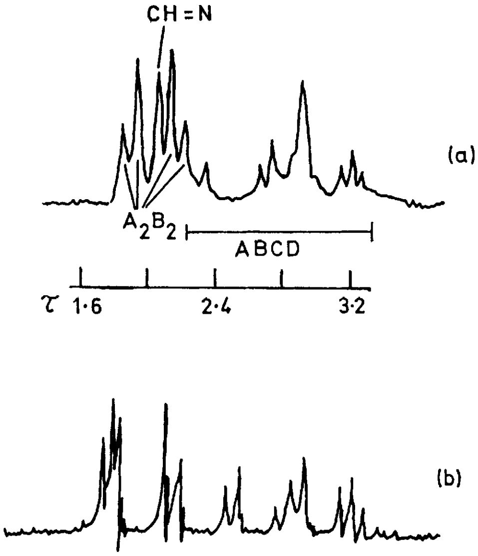
Treatment of substituted benzaldehyde phenylhydrazones with mercury(II) acetate in acetic acid resulted in exclusive mercuriation at the *ortho*-site of the *N*-phenyl ring. Kinetic measurements at 25 °C in acetic acid gave Hammett ρ values for methine phenyl substituents of -0.81 for the *p*-bromophenylhydrazone series and -1.02 for the *p*-nitrophenylhydrazone series (σ^+ correlation). The ρ values for amino-*N*-phenyl substituents were -2.30 for the *p*-tolualdehyde series and -2.99 for the *p*-nitrobenzaldehyde series (σ^n correlation). Thermodynamic parameters ΔE_{act} 17.5, ΔH_{act} 16.9 kcal mol^{-1}, and ΔS_{act} -14.1 cal K^{-1} mol^{-1} were measured for benzaldehyde *p*-bromophenylhydrazone. The *ortho*-mercuriation occurred by an internal cyclometallation process involving the hydrazone imino-moiety. The comparison between the reactions of mercuric acetate and lead tetra-acetate with phenylhydrazone systems is discussed.

DIRECT displacement of a proton from a C–H moiety by a metal cation with the formation of a metal–carbon bond is rare with molecules containing amino N–H bonds since the metal usually displaces the N–H proton preferentially giving a metal–nitrogen bond. Recently, we have noted [1] such a reaction between some *p*-nitrophenylhydrazones and mercury(II) acetate (Hg2A) in acetic acid, which involved mercuriation of the *N*-phenyl ring at the *ortho*-position, *e.g.* (I) ⟶ (II), rather than proton displacement from the hydrazone N–H site. This contrasted with the reaction of phenylhydrazones with mercuric oxide [2,3] where dimeric bishydrazone type products were formed in a reaction involving cleavage of the amino N–H bond. Herein, we report [4] a mechanistic study of this *ortho*-mercuriation, which allows it to be included in the recent classification of [5,6] cyclometallation reactions where an organic ligand of a transition-metal complex undergoes intramolecular metallation with the formation of a metal–carbon σ bond.

RESULTS AND DISCUSSION

Selectivity.—Treatment of a range of substituted aromatic aldehyde phenylhydrazones with Hg2A in acetic acid resulted in high yields of *ortho*-mercuriation of the *N*-phenyl ring (Table) establishing a wide applicability for the reaction. Products from attack at the *meta*-position were not detected in any case. Cleaner reactions were observed when the *N*-phenyl ring contained electron-withdrawing *para*-substituents, *e.g.* NO_2 and Br. When this ring contained either a hydrogen or an electron-donating *para*-substituent, intractable red–brown oils were formed (*cf.* ref. 4). These were found by control reactions to be due to secondary decomposition of the *ortho*-mercuriated product. A strong electron-withdrawing *para*-substituent in the benzaldehyde ring counteracted the *N*-phenyl substituents and relatively clean reactions were obtained. Thus for *p*-nitrobenzaldehyde *p*-methoxyphenylhydrazone the *ortho*-mercuriated product was isolated in 48% yield along with the brown oils [No. (13), Table]. The *ortho*-selectivity was strkingly evident with *p*-nitrobenzaldehyde phenylhydrazone [No. (14), Table] where the *ortho*-mercuriated product (Figure) was isolated in 86% yield along with a brown oil which arose from product decomposition suggesting a higher, and probably quantitative, true yield. In this case the *N*-phenyl *para*-position was vacant but no trace of the *para*-mercuriated product was encountered. Careful proton n.m.r. analysis of the oils failed to detect the easily identifiable *para*-substituted A_2B_2 pattern which could be easily distinguished from the ABCD pattern (Figure) of *ortho*-substitution. The *ortho*-substitution of the other compounds was confirmed by the characteristic [1] H_P, H_Q, H_R, (AMX) proton n.m.r. pattern. For the *p*-Br series [Nos. (1)—(6), Table] the shifts in $(CD_3)_2SO$ were H_P τ 3.00—3.11, H_Q τ 2.68—2.80, and H_R τ 2.48—2.54. The methine CH=N signal was at τ 2.00—2.08 and the HgOAc signal at τ 8.04—8.08. Demercuriation reactions with iodine and bromine were also achieved, giving easy syntheses of *ortho*-substituted phenylhydrazones, and these will be reported elsewhere.



Aromatic region of the ^1H n.m.r. spectrum of (a) compound (II; X = NO_2; Y = H) [Table, No. (14)] and (b) for comparison, *p*-nitrobenzaldehyde 2-tolylhydrazone

Kinetics and Substituent Effects.—The product studies

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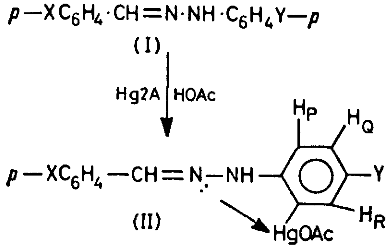
† Part 3 is ref. 26.

indicated an unexpectedly strong influence by distant *para*-substituents of the methine phenyl ring. Kinetic measurements at 25 °C in acetic acid under conditions comparable to the product studies, confirmed the substituent response. The rates fitted second-order plots only, and for No. (14) (Table) the second-order reaction was also confirmed by the half-life method. The substituent response for *para*-substituents of the methine phenyl ring was ρ −0.81 (r = 0.999). This is typical of electrophilic attack on a hydrazone system and is a higher negative ρ value than for electrophilic attack on a hydrazone moiety by diazonium ion,[7] bromine,[8] and lead tetra-acetate.[9] Significantly, σ^+ values [10] for the substituents were necessary and normal σ values did not give a correlation. These data imply a strong interaction of the methine *para*-substituent with a cationic reaction centre and they suggest that the aromatic mercuriation involves the hydrazone chain. Similar results were obtained for the *p*-nitrophenylhydrazone series, Nos. (7)—(10) (Table), which gave a higher negative ρ value, −1.02 (r = 0.998), also requiring σ^+ values.



No.	Cpd (I) X	Y	Product (II) Yield (%)	M.p. (t/°C)	$k \times 10^3$ (at 298 K)/ dm^3 mol^{-1} s^{-1}		
(1)	MeO	Br	72 [a]	160—161	9.58	(−0.778) [c]	
(2)	Me	Br	70 [a]	172—174	4.56	(−0.311) [c]	(0.265) [d]
(3)	H	Br	75 [a]	163—165	2.13	(0) [c]	
(4)	Cl	Br	82.5	165—166	1.91	(0.114) [c]	
(5)	Br	Br			1.66	(0.150) [c]	
(6)	NO_2	Br	90	187—188	0.503	(0.79) [c]	(0.265) [d]
(7)	MeO	NO_2	88	181—183	0.96		
(8)	Me	NO_2	78 [b]	194—196	0.36	(0.778) [c]	
(9)	H	NO_2	78 [b]	203—205	0.157		
(10)	Cl	NO_2	35 [b]	201—203	0.118		
(11)	Me	H		*e*	27.6— 22.4 [e]		(0.0) [d]
(12)	Me	MeO		*e*	52.9— 12.6 [e]		(−0.111) [d]
(13)	NO_2	MeO	48 [a]	180—182	8.96		(−0.111) [d]
(14)	NO_2	H	86 [a]	176—178	6.7		(0.0) [d]
(15)	NO_2	NO_2			0.025		(0.778) [d]
(16)	Benzophenone		55 [f]	210—212	0.135		

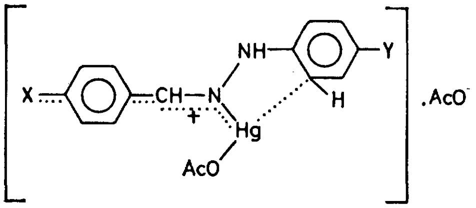
[a] Red-brown oils were obtained due to decomposition of the product. [b] From ref. 1. [c] Parentheses contain σ^+ values (ref. 10) used. [d] Parentheses contain θ^n values (ref. 10) used. [e] Red-brown resins and HgOAc were the only products encountered. The range quoted was obtained from attempted rapid measurements in the early stages. The mean value was used. [f] Benzophenone *p*-nitrophenylhydrazone (46%) was recovered after 2 h at 55 °C followed by 15 h at 40—45 °C.

The product studies also suggested a strong influence by substituents in the *N*-phenyl ring. Hammett ρ values for this ring were determined for the *p*-tolualdehyde series (2), (8), (11), and (12) (Table), and for the *p*-nitrobenzaldehyde series (6), (13), (14), and (15) (Table). The former gave ρ −2.30 (r = 0.997) and the latter gave ρ −2.99 (r = 0.974). In both cases the MeO substituent was correlated by σ^n rather than σ^+. For normal aromatic mercuriation [11] the ρ value was −4.0,[11] and the MeO substituent was correlated by σ^+ values rather than σ^n. The low ρ values are comparable to those reported for direct attack on hydrazone systems by electrophiles such as bromine (ρ −2.2) [8] and lead tetra-acetate (ρ −1.95).[12] These data agree with those from the methine phenyl ring in suggesting involvement of the hydrazone chain in the *ortho*-mercuriation reaction.

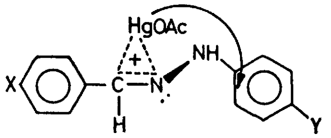
An Arrhenius plot for the parent compound, No. 3 (Table), gave thermodynamic data for the reaction, ΔE_{act} 17.5 kcal mol^{-1}, ΔH_{act} 16.9 kcal mol^{-1}, and ΔS_{act} −14.1 cal K^{-1} mol^{-1}. The entropy value is significantly lower than for mercuriation of other substituted benzenes (*ca.* −20 to −25 cal K^{-1} mol^{-1}),[11] and suggests a transition state in which the activation energy is distributed among a greater number of bonds. It is comparable to the value of −12.3 cal K^{-1} mol^{-1} [13] for *ortho*-mercuriation of azobenzenes which is reported [13] to involve complexation at the β-azo-nitrogen. The activation energy is also lower than for normal aromatic mercuriations (*ca.* 21—25 kcal mol^{-1}) [11] and is consistent with a reaction pathway stabilised by extra charge delocalization. Similar results were obtained for the *p*-nitrobenzaldehyde derivative No. (6) (Table), ΔE_{act} 17.1 kcal mol^{-1}, ΔH_{act} 16.6 kcal mol^{-1}, and ΔS_{act} −17.8 cal K^{-1} mol^{-1}. The somewhat higher negative entropy in this case, when combined with the higher negative ρ value for the *N*-phenyl ring of the *p*-nitrobenzaldehyde series may suggest a slightly different transition state when the methine phenyl ring contains a strong electron-withdrawing substituent, possibly involving less developed bonding to the imino-moiety.

Solvent Effects.—The reaction was inhibited by hydroxylic solvents such as water and methanol. For example, when benzaldehyde 4-nitrophenylhydrazone was treated with mercuric acetate in a mixture of water and acetic acid (20 : 80 v/v or 50 : 50 v/v), under conditions which gave high yields of mercuriation in pure acetic acid, the mercuriation was completely inhibited and the hydrazone was recovered quantitatively. Similarly, in pure methanol no reaction occurred and in methanol–acetic acid (50 : 50 v/v) mercuriation was reduced to 25% and the starting hydrazone was recovered in 75% yield. The mercuriated products (II) were stable in these hydroxylic solvents under the conditions and they did not de-mercuriate. This hydroxylic solvent inhibition is probably due to inactivation of the mercuric cation by solvation,[14b] *i.e.* more effective competition by the OH electrons than the hydrazone imino-electrons for the cation. A similar cation deactivation by water is observed in normal aromatic mercuriation.[14b] It is also possible that in these hydroxylic solvents the hydrazone recovery arose from solvent addition at the methine carbon of an intermediate (III) followed by loss of HgOAcOR from the resulting species which would be comparable to the tetrahedral intermediate involved in nucleophilic addition of phenylhydrazine to an aldehyde.

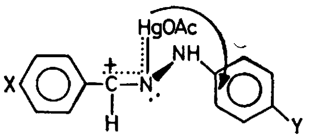
Mechanism.—The kinetic data require an electrophilic transition state allowing strong delocalization of positive charge into the methine phenyl ring and differing from a normal aromatic mercuriation. The *ortho*-specificity imposes steric requirements on the reaction pathway. The data are consistent with a transition complex of type (III) arising from an approach of the electrophile *via* the imino *n*-electrons and in which $HgOAc^+$ ultimately migrates to the *ortho*-position of the *N*-phenyl ring. The initial attack could also be facilitated by the methine π-electrons as in structures (IV) or (V). However, the data are less consistent with a bridged mercurinium species of type (IV), comparable to that involved in reactions of mercuric acetate with olefins,[14–20] since delocalization of positive charge to the methine phenyl ring would be considerably reduced in such a species and the orientation for specific *ortho*-migration is also less favoured. Recently, it has been suggested [21] that while bridged mercurinium species are likely with asymmetrical olefins, which do not allow for strong delocalization of positive charge to a resonance electron-donating substituent, when such resonance delocalization is possible, the transition state may resemble the open carbonium ion also proposed.[22,23] Recent observations of rearrangements in mercuriations of olefins capable of forming stabilized carbocations also supports the possibility of open carbonium-type transition states in certain cases.[18] By comparison, attack *via* the asymmetric imino π-cloud should then give a species of type (V) rather than (IV) and the kinetic data are consistent with such a species. If the species (V) and (III) have lifetimes longer than the bond vibrational and rotational periods, *i.e.* if they are intermediates, then they are, in effect, the same. If, however, the species (III) and (V) are transition complexes, then they are different, the former involving the imino *n*-electrons, the latter involving the imino π-electrons. The kinetic data do not allow such a fine distinction between these two close situations. However, since the *n*-electrons occupy the frontier orbital of the imino-moiety, and they are also considered to be the protonation site,[24] a transition complex of type (III) is the more likely.*



(III)

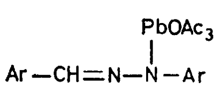


(IV)



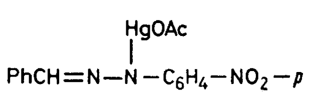
(V)

Comparison with Lead Tetra-acetate.—Oxidation of substituted aldehyde phenylhydrazones with lead tetra-acetate (LTA) involves the unstable intermediate (VI) which fragments to an azo-acetate or a nitrilimine depending upon the nature of the substituents.[12,25] The contrast between Hg2A and LTA is therefore of interest. Treatment of benzaldehyde 4-nitrophenylhydrazone with Hg2A in dichloromethane gave compound (VII), the mercury analogue of (VI), in a proton exchange



$\mathrm{Ar{-}CH{=}N{-}N(PbOAc_3){-}Ar}$

(VI)



$\mathrm{PhCH{=}N{-}N(HgOAc){-}C_6H_4{-}NO_2{-}}p$

(VII)

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* It is of interest that mercuriation of the second *ortho*-position was not observed, either using 2 mol. equiv. of mercuric acetate with the phenylhydrazone or on separate treatment of compound (II; X = H; Y = NO_2) with a further mol. equiv. of Hg2A. This would be expected for involvement of the *n*-electrons since these electrons are very likely complexed with the Hg^{2+} of compounds (II) (*cf.* also ref. 4).

The mechanism (III) embodies at least three separable steps, (i) complex formation with the imino-moiety; (ii) formation of the Wheland intermediate involving Hg–C bonding with the *N*-phenyl ring; (iii) proton loss from the Wheland intermediate. The rate-determining step is not readily identifiable but the relative magnitudes of the ρ values for the C- and N-phenyl rings may suggest a rate-determining formation of the Wheland intermediate. However low ρ values for the C-phenyl ring have also been observed for reactions involving rate-determining substitution by bromine [8] and diazonium ion [7] at the methine moiety. To investigate the nature of the transition state further we intend to measure quantitative solvent effects and also the deuterium isotope effect and these will be reported elsewhere.

reaction, the reagent being present as a solid which changed to the insoluble compound (VII). The compound (VII) was a stable solid and its stability relates to the weaker oxidising power of Hg^{2+} over Pb^{4+}. We have previously noted [26] the failure of Hg^{2+} to hydrogenate semicarbazone systems and also to affect dehydrogenative cyclization of heterocyclic hydrazones.[27] When compound (VII) was dissolved in acetic acid, it rapidly exchanged a proton giving parent benzaldehyde 4-nitrophenylhydrazone and Hg2A. Hence reactions comparable to those of LTA cannot occur with Hg2A since compound (VII) survives long enough for proton exchange to be preferred to possible fragmentation paths.

EXPERIMENTAL

M.p.s were measured with an Electrothermal apparatus. N.m.r. spectra were measured with a JEOL JNM-MH-100 spectrometer $(CD_3)_2SO$ as solvent. The hydrazone substrates were prepared by standard procedures.[28] The synthetic mercuriation reactions for Nos (1)—(6) and (11)—(14) (Table) were carried out by stirring the hydrazone substrates with Hg2A in acetic acid for periods of 10 min to *ca.* 2 h depending on relative reactivity. Examples have been described previously [1] for Nos (7)—(10) (Table). The structures of the products were established unequivocally [1] from microanalyses and ^1H n.m.r. spectra. When benzaldehyde 4-nitrophenylhydrazone was treated with Hg2A for 1.5 h at 50—55 °C, followed by 15 h at 40—45 °C in methanol or acetic acid–water (80 : 20 v/v or 50 : 50 v/v), it was recovered quantitatively and mercuriation was not observed. A solution of benzaldehyde 4-nitrophenylhydrazone (I; $X = H$, $Y = NO_2$) (500 mg) in dichloromethane (25 ml) was treated with Hg2A (662 mg) and the mixture stirred at ambient temperature for 1.5 h. Insoluble material was removed and after leaching with warm water and then alcohol gave wine red N-*acetoxymercurio*-N-p-*nitrophenyl*-N'-*benzylidenehydrazine* (VII) (476 mg, 46%), m.p. 160—162 °C (Found: C, 35.6; H, 2.3; N, 8.2. $C_{15}H_{13}HgN_3O_4$ requires C, 36.0; H, 2.6; N, 8.4%), $\nu_{max.}$ 1 620—1 590 cm^{-1} (C=N, HgOAc), no NH; τ 7.98 (s, HgOAc), 2.58 and 1.94 A_2B_2 (J_{AB} 9 Hz, C_6H_4), 2.26—2.50 (m, Ph), and 1.46 (s, CH=N). Evaporation of the dichloromethane solution gave starting hydrazone (48%). When compound (VII) was treated with dilute hydrochloric acid, it immediately changed to the yellow parent hydrazone (I; $X = H$, $Y = NO_2$). Prolonged stirring of compound (VII) in acetic acid gave the *ortho*-mercurio-product (II; $X = H$, $Y = NO_2$) but brief stirring showed that the compound (VII) was first converted into the parent hydrazone and Hg2A.

Kinetics.—Rate constants (±5%) (Table) were measured under conditions similar to the synthetic reactions. Typically, a solution of hydrazone (500 mg) in acetic acid at 25 °C was treated with an equimolar proportion of Hg2A. At appropriate times (t) aliquots (1.00 ml) were withdrawn, treated with water (100 ml) containing concentrated nitric acid (2.0 ml), and extracted with chloroform. The unchanged Hg^{2+} in the aqueous layer was determined by thiocyanate titrations and the rate constants (k) were obtained from a plot of t *vs.* $x/(a - x)$ which was linear through the origin with slope ka. All the data fitted second-order plots only. For compound (I; $X = NO_2$, $Y = H$) [No. (14), Table] half-lives were measured for different initial concentrations (a) of hydrazone: a, 0.0414M, $t_{\frac{1}{2}}$, 63 min; a, 0.0207M, $t_{\frac{1}{2}}$, 120 min; a, 0.0103M, $t_{\frac{1}{2}}$, 256 min. These data confirmed the second-order nature of the reaction. Variable-temperature kinetic measurements gave the following Arrhenius plots for (i) benzaldehyde *p*-bromophenylhydrazone (I; $X = H$, $Y = Br$); $k \times 10^3/dm^3\ mol^{-1}\ s^{-1}$ (T K), 2.13 (298), 7.65 (310.5), 20.6 (323), and 44.6 (335.5); and (ii) *p*-nitrobenzaldehyde-*p*-bromophenylhydrazone (I; $X = NO_2$, $Y = Br$) 0.503 (298), 1.24 (310.5), 4.16 (323), and 9.005 (335.5).

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