REGIOSELECTIVE DEUTERIUM LABELLING OF AROMATIC ACIDS, AMIDES AND AMINES USING GROUP VIII METAL CATALYSTS

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SUMMARY

Ortho-deuterated arylcarboxylic acids and their sodium salts may be prepared with high regioselectivity by isotopic exchange with deuterium oxide in the presence of a range of commercially available group VIII metal complexes. When rhodium trichloride trihydrate is employed a range of arylcarboxamides and arylmethanamines are also selectively labelled at the ortho-positions.

Key Words: Ortho-deuteration, [2,6-$^{2}H_2$]Benzoic acid, [3,4,5-$^{2}H_3$] Benzoic acid, Rhodium trichloride, [2,6-$^{2}H_2$]Benzamide, [2,6-$^{2}H_2$]Benzylamine

INTRODUCTION

Arylcarboxylic acids, carboxamides and methanamines are important intermediates in many laboratory and industrial syntheses. Methods for the preparation of selectively tritiated or deuterated derivatives of such compounds are therefore of interest.

The selective ortho-deuteration of these classes of compounds, or of simple derivatives, is conventionally performed either from specific synthetic precursors (1,2,3) or via directed ortho-lithiation reactions. Thus, ortho-deuterated aromatic acids may be prepared via deuterium oxide hydrolysis of their ortho-lithiated oxazoline derivatives (4), whilst ortho-deuterated tertiary benzylamines (5) and ortho-deuterated secondary and tertiary benzamides (6) are available via similar ortho-lithiation procedures.

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Whilst of wide utility such ortho-lithiations are also subject to important limitations: the procedures are incompatible with many electrophilic substituent groups; they lead to preferential labelling of the benzylic positions in alkyl-substituted aromatics; and they may be complicated by metal-halogen exchange or by benzyne formation if the substrate contains halogen or other easily eliminated groupings (7).

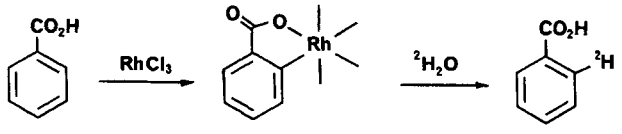
In a previous publication (8) the application of rhodium trichloride catalysed isotope exchange to the preparation of selectively deuterated aromatic carboxylic acids was described. The present paper reports more extensive investigations of this alternative ortho-labelling procedure. The studies include an evaluation of the potential of other commercially available group VIII metal complexes to promote ortho-deuteration of aromatic acids and their sodium salts.

In addition, the application of rhodium trichloride catalysed ortho-deuteration to the labelling of arylcarboxamides and aralkylamines is detailed.

RESULTS AND DISCUSSION

By analogy with the proposed mechanism of the ortho-lithiation reaction (7) it seems likely that the regioselectivity observed in the rhodium trichloride catalysed deuteration of aromatic carboxylates arises via an initial coordination of the catalytic rhodium species with the non-bonding electrons of the substrate carboxyl group. Subsequent reaction leading to preferential deuterium substitution at the nearby ortho-positions of the substrate would then be greatly facilitated over exchange at the non-adjacent meta- or para-positions. Clearly, many intermediates in this process could be formulated. In the absence of detailed kinetic studies there is little evidence for the intermediacy of any particular catalytic species. Nevertheless, a cyclometalation (9) process, such as that shown in

Scheme 1, would appear likely, since carboxylate complexes of rhodium in various oxidation states are well known (10,11) and since aryl-metal bonds are implicated in both the heterogeneous (12) and homogeneous (13) catalytic deuteration of aromatic hydrocarbons.



Scheme 1

If the regioselectivity of the rhodium trichloride catalysed reaction does arise via such a process, then other metals processing a co-ordination chemistry resembling that of rhodium might also yield similar specific or selective ortho-deuteration. Moreover, substituents other than carboxylate which possess heteroatom electron-donors beta to the aromatic ring might also prove able to direct isotope exchange to the ortho-positions.

To investigate the first of these possibilities, the activity and also the regioselectivity found in the ortho-deuteration of model substrates by a number of commercially available group VIII metal complexes was studied. Since the solution chemistry of most of the catalysts is either complex (14) or unknown the mass ratio of substrate to catalyst rather than the molar ratio was held constant. The results, therefore, constitute an empirical guide to synthetic utility rather than a formal kinetic comparison. Table 1 summarises the findings. Regioselectivities were estimated either by comparison of the ^{1}H-nmr resonance intensities with the expected molecular ion isotope distribution, or, more accurately by ^{1}H-nmr studies of the

protiodedeuteration of [$^2H_5$]benzoic acid or sodium [$^2H_5$]benzoate. In one case, the deuteration of sodium benzoate in the presence of rhodium trichloride, the regioselectivity was also estimatedby ^{13}C-nmr spectroscopy (15) and by ^2H-nmr spectroscopy.

Only those metal salts or complexes which promoted significant deuteration are included in the table. A number of other group VIII metal compounds were either inactive per se, e.g. $FeSO_4$, $CoCl_2$, $NiCl_2$, $PdCl_2$, $PtCl_2$, $Rh(CH_3CO_2)_2$, $Fe(acac)_3$, $Rh(acac)_3$, $Pd(acac)_2$, or decomposed so rapidly under the standard reaction conditions employed that catalytic activity, if any, would not have been observed, e.g. K_2PtCl_4, $OsCl_3$, $FeCl_3$, $(Ph_3P)_3RhCl$, $PtCl_4$. A small degree (~5%) of non-specific labelling of sodium benzoate was observed with K_2PtCl_4 and $PtCl_4$, though this degree of labelling might have resulted from heterogenous catalytic exchange promoted by the metal precipitated during decomposition of the complexes.

With the exceptions of iridium trichloride and rhodium trinitrate, all the selected catalysts were able to promote ortho-deuteration with high regioselectivity. Indeed, even when the incorporation of deuterium approached the maximum abundance for ortho-deuteration, regioselectivity remained high. The maintenance of such high selectivity as equilibrium is approached, conditions under which labelling of the slower exchanging sites would normally become significant, implies that not only is the rate of ortho-exchange large in comparison with exchange at other sites but that it is also large with respect to the rates of any competing isotopic randomisation processes (16).

Also of interest are the marked differences in the activity of the catalysts towards the labelling of benzoic acid or sodium benzoate. Thus, whilst the metal trichlorides show greatest activity towards the sodium salt, tris(2,4-pentanedionato)ruthenium and tris(triphenylphosphine) ruthenium dichloride show marked preferences for the free acid. A similar selectivity is shown with other aromatic acids and their sodium salts.

Table 1: Comparison of Active Catalysts

Catalyst	Substrate	Percent Reaction (%)[a]	Regiospecificity (%)
$RhCl_3.3H_2O$	benzoic acid	46	95[b]
	sodium benzoate	98	98[bcd], 99.5[e]
	o-anisic acid	68	98[c]
$RuCl_3$	benzoic acid	60	95[b]
	sodium benzoate	98	98[bc]
$IrCl_3.3H_2O$	benzoic acid	19	80[b]
	sodium benzoate	75	90[b]
$Ru(acac)_3$	benzoic acid	94	98[b]
	sodium benzoate	61	95[c]
	o-anisic acid	98	97[c]
$Rh(NO_3)_3$	sodium benzoate	63	94[c]
	o-anisic acid	74	93[c]
$Ru(Ph_3P)_3Cl_2$	benzoic acid	95	98b[c]
	sodium benzoate	7	-
	o-anisic acid	90	98[c]

[a] Calculated from: 100 x atom percent abundance obtained/atom % abundance for complete exchange at available ortho-position(s).

[b] Estimated from ^{1}H-nmr resonance intensities after protiodedeuteration of sodium [$^2H_5$]benzoate or [$^2H_5$]benzoic acid.

[c] Estimated by comparison of ^{1}H-nmr resonance intensities with molecular ion isotope distribution of the derived acid.

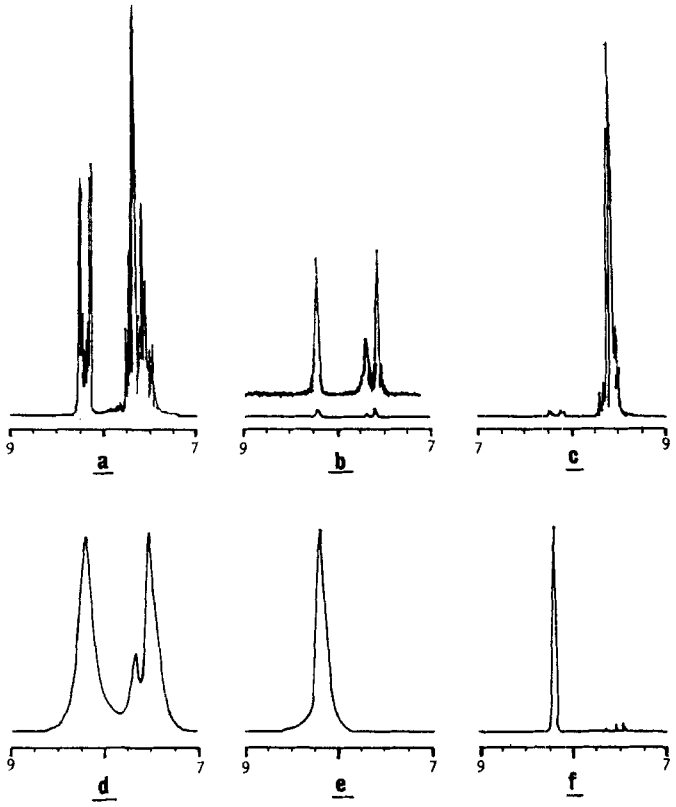
[d] Estimated from ^{13}C-nmr spectroscopy.

[e] Estimated from ^{2}H-nmr spectroscopy.

The [$^2H_5$]benzoic acid and sodium [$^2H_5$]benzoate used in the above studies were synthesised via heterogeneous platinium catalysed exchange of sodium benzoate with deuterium oxide (17). The isolated benzoic acid from this process had a residual ring proton content of 5.5% which was shown by both ^{1}H- and ^{2}H-nmr to be essentially equilibrated amongst the ring positions (18).

The nmr spectra of the variously labelled benzoic acids prepared in the course of these studies are shown in Figure 1.

Both rhodium trichloride catalysed ortho-deuteration, and heterogeneous platinum catalysed perdeuteration of aromatic carboxylic acids are generally applicable labelling methods. By analogy with the above syntheses,



(a) ^{1}H-nmr spectrum of unlabelled benzoic acid. (b) ^{1}H-nmr spectrum of the residual protons in [$^{2}H_5$]benzoic acid. (c) ^{1}H-nmr spectrum of [2,6-$^{2}H_2$]benzoic acid from a single cycle deuteration of sodium benzoate using rhodium trichloride. (d) ^{2}H-nmr spectrum of [$^{2}H_5$] benzoic acid. (e) ^{2}H-nmr spectrum of [2,6-$^{2}H_2$]benzoic acid (see (c) above). (f) ^{1}H-nmr spectrum of [3,4,5-$^{2}H_3$]benzoic acid prepared by one step protiodedeuteration of sodium [$^{2}H_5$]benzoate using rhodium trichloride.

Figure 1: Nmr Spectra of Labelled Benzoic Acids in the Range 7 to 9 δ

therefore, a wide range of selectively labelled aromatic carboxylic acids should be easily prepared in one or two steps by the appropriate choice of catalyst and isotopic water.

To investigate the direction of deuteration by groupings other than carboxylate, the labelling of a selection of substrates in the presence of rhodium trichloride was studied. The extent of deuterium labelling obtained with each substrate was assessed, after removal of labile deuterium, by mass spectrometry. The results are listed in Table 2. None of the substrates showed labelling in the absence of catalyst, whilst both benzamide and benzylamine hydrochloride showed substantial catalytic labelling. The directing effects of both the alkylamine and carboxamide groupings were therefore investigated. The results are summarised in Table 3. Assessment of the extent of labelling was made from ^{1}H-nmr integration and from mass spectral molecular ion isotope clusters. In some cases, structurally significant fragment ions rather than molecular ions were analysed since the spectra displayed significant M-1 ions (19). When necessary, ^{1}H-nmr spectra were simplified by the use of lanthanide induced shifts.

Deuteration of the alkylamine substrates was performed after adjusting the pD of the reaction medium to 7.0 with deuterium chloride solution. In the absence of such pD adjustment, bright yellow solutions or precipitates were formed and both the yield and extent of deuteration were much reduced.

In all cases those substrates which showed an appreciable degree of labelling were deuterated exclusively or predominantly in positions ortho to the carboxamide or methanamine group. Clearly, therefore, in addition to carboxyl and carboxylate, both the carboxamide and methanamine groups are effective directors of ortho-deuteration. In this context it is interesting to note the reduction in the extent of labelling which occurs in both the carboxamides and methanamines with increasing alkyl substitution of the nitrogen atom. Whether this reflects steric or electronic factors requires

Table 2: Deuteration of Selected Aromatic Substrates in the Presence of Rhodium Trichloride

Substrate	Percentage of Molecules Bearing One or More Deuterium Atoms
ethyl benzoate	< 2
nitrobenzene	< 2
azobenzene	15
benzenesulphonamide	12
benzamidine hydrochloride	8
para-methoxybenzaldehyde	< 2
para-methoxybenzyl alcohol	4
benzylamine hydrochloride	50
benzamide	100
benzoic acid	80
phenylacetic acid	17[a]
3-phenylpropionic acid	< 2

[a] Labelled exclusively in the benzylic methylene group.

Table 3: Deuteration of Aromatic Amides and Amines in the Presence of Rhodium Trichloride

Substrate	Percentage Reaction[a]
benzamide	93
ortho-ethoxybenzamide	98
para-methoxybenzamide	95
N-methylbenzamide	95
N-benzylbenzamide	80
N-benzoylglycine	73
N,N-dimethylbenzamide	34[b]
N,N-diisopropylbenzamide	15[b]
benzylamine	34
p-methoxybenzylamine	66
m-methoxybenzylamine	34
p-chlorobenzylamine	77
α-methylbenzylamine	62
N-methylbenzylamine	9
N-ethylbenzylamine	4
N,N-dimethylbenzylamine	< 2
2-phenylethylamine	< 2
3-phenylpropylamine	< 2

[a] Calculated from: 100 x atom % abundance found/atom % abundance for complete exchange at the available ortho-position(s).

[b] Mass spectrometric assessment of percentage reaction based upon M/Z 105 and M/Z 77 ions (6).

further study. Also noteworthy is the absence of significant deuteration of the longer chain aralkylamines. The same unreactivity is observed with aralkylcarboxylic acids (see Table 2) and provides further support for the possible involvement of a five-ring species in the deuteration process.

EXPERIMENTAL

^{1}H-nmr spectra were recorded in deuterochloroform at 90 MHz (Varian EM 390) or 80 MHz (Bruker WP-80). The latter instrument was also used to record ^{13}C-nmr spectra. ^{2}H-nmr spectra were recorded for solutions in chloroform using a Bruker AM-360 spectrometer. Mass spectra were determined using a Kratos MS 30 or MS 50 spectrometer linked to a DS-55 SM data system. N,N-dimethylbenzamide mp 41 - 43° (20), N,N-diisopropylbenzamide mp 69 - 70° (21), and N-benzylbenzamide (22) mp 105 - 107° were prepared by reactions between benzoyl chloride and the corresponding amine. All other substrates were obtained from recognised commercial suppliers. Deuterium oxide (99.8 atom % D), sodium borodeuteride (98 atom % D) and 20% deuterium chloride in deuterium oxide (99 atom % D) were obtained from the Aldrich Chemical Company Ltd., Poole, UK, as were the group VIII metal trichlorides and platinum dioxide. Rhodium trinitrate and tris(2,4-pentandionato)ruthenium were obtained from Ventron-Alfa Ltd., Coventry, UK. Tris(triphenylphosphine) ruthenium dichloride was obtained from Lancaster Synthesis Ltd., Lancaster, UK.

[$^2H_5$]Benzoic acid

To a stirred suspension of platinum dioxide (350 mg) in deuterium oxide (99.8 atom % D, 3.5 cm^3) was added, solid sodium borodeuteride (98 atom % D) in small portions until reduction of the oxide was complete. After decantation of the supernatant solution, the black reduced platinum metal was washed by resuspension in deuterium oxide (5 cm^3) and the washings decanted. A solution of sodium benzoate (500 mg) in deuterium oxide (11 cm^3) was added to the catalyst and the resulting suspension heated at

130° under nitrogen in a sealed vessel for 18 hours. After cooling, the mixture was filtered and the filtrate made strongly acid with hydrochloric acid (10 cm^3, 4 mol dm^{-3}) and extracted twice with ethyl acetate (30 cm^3). The combined ethyl acetate layers were extracted twice with saturated sodium hydrogen carbonate solution (5 cm^3) and the aqueous layers combined and acidified to pH 2 with hydrochloric acid solution (4 mol dm^{-3}). The resulting solution was extracted twice with ethyl acetate (30 cm^3) and dried over anhydrous magnesium sulphate. Filtration and removal of the solvent under reduced pressure yielded the crude [$^2H_5$] benzoic acid which was purified by three recrystallisations from hot water to yield [$^2H_5$]benzoic acid (280 mg, mp 121° undepressed upon admixture with an authentic sample of unlabelled benzoic acid).

Sodium [$^2H_5$]benzoate

[$^2H_5$]Benzoic acid (253 mg) was added in small portions to a stirred suspension of sodium hydrogen carbonate (168 mg) in distilled water (3 cm^3). The resulting clear solution was evaporated to dryness under reduced pressure and dried at 40° under vacuum for 18 hours to yield sodium [$^2H_5$]benzoate (292 mg).

Deuteration of Acids and Sodium Salts

The substrate acid or sodium salt (75 mg) and catalyst (30 mg) were dissolved in a mixture of deuterium oxide (99.8 atom % D, 750 mm^3) and N,N-dimethylformamide (750 mm^3). The solution was placed in a screw-top thick-walled reaction vial and heated at 107° for an 18 hour period. After cooling the solution was poured into hydrochloric acid (4 mol dm^{-3}, 5 cm^3) and extracted twice with ethyl acetate (10 cm^3). The extracts were combined and extracted twice with saturated sodium hydrogen carbonate solution (2 cm^3). The aqueous layers were combined, acidified to pH 2 with hydrochloric acid (4 mol dm^{-3}) and extracted twice with ethyl acetate

(10 cm^3). After the removal of the solvent under reduced pressure the crude deuterated acid was purified by recrystallisation from water. All the products had satisfactory melting points which were undepressed upon admixture with analytical samples of the corresponding unlabelled benzoic or ortho-anisic acid.

Protiodedeuteration Reactions

These reactions were performed exactly as previously except that the deuterium oxide was replaced by distilled water. All the samples of protiodedeuterated benzoic acid had acceptable melting points which were undepressed upon admixture with an analytical sample of unlabelled benzoic acid.

Deuteration of Amides

The amide (75 mg) and rhodium trichloride trihydrate (30 mg) were dissolved in deuterium oxide (99.8 atom % D, 750 mm^3) and N,N-dimethyl-formamide (750 mm^3) and the solution heated in a screw-top thick-walled reaction vial at 107° for 18 hours. After cooling the solution was poured into hydrochloric acid (4 mol dm^{-3}, 5 cm^3) and extracted twice with ethyl acetate (20 cm^3). The combined ethyl acetate layers were washed with saturated sodium hydrogen carbonate solution (5 cm^3) followed by water (10 cm^3). After drying over anhydrous magnesium sulphate the ethyl acetate solution was filtered and evaporated to dryness under reduced pressure to yield the crude amide. The crude amides obtained were purified by crystallisation from water or from water/methanol mixtures. All the products had satisfactory melting points which were undepressed upon admixture with authentic samples of the corresponding unlabelled amide. The labelled amides were obtained in yields ranging from 70 to 90%.

Deuteration of Aralkylamines

The aralkylamine (75 mg) was weighed into a thick-walled screw-topped reaction vial and deuterium oxide (99.8 atom % D, 750 mm^3) added. The alkalinity of the solution was adjusted to pD 7 by the addition of deuterium chloride in deuterium oxide (20% weight/volume) after which rhodium trichloride trihydrate (30 mg) and N,N-dimethylformamide (750 mm^3) were added and the reaction vial closed. After heating at 107° for 18 hours the vial was cooled and poured into sodium hydroxide solution (1 mol dm^{-3}, 5 cm^3). The resulting suspension was extracted twice with ethyl acetate (10 cm^3) and the extracts filtered. The ethyl acetate solution was extracted twice with hydrochloric acid solution (4 mol dm^{-3}, 5 cm^3) and the acid extracts evaporated to dryness under reduced pressure when the crude aralkylamine hydrochloride crystallised. The crude hydrochlorides were purified by recrystallisation from ethanol/diethyl ether. The yields of the purified aralkyalmines obtained were in the range 60 to 90%.

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