REGIOSELECTIVE LABELLING OF ANILIDES WITH DEUTERIUM

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SUMMARY

N-Aryl amides may be deuterated by exchange with deuterium oxide in the presence of rhodium(III) chloride. Under such conditions deuterium is introduced into positions ortho to the anilide nitrogen atom with a high degree of regioselectivity.

Key Words: Deuterium, Isotope-exchange, Rhodium(III) chloride, Anilides, N-Arylcarboxamides, Ortho-deuteration.

INTRODUCTION

In addition to their use as intermediates in many laboratory and industrial syntheses, compounds containing the anilide grouping are of significant medicinal importance. The acetamido grouping is present in a number of pharmaceutical agents exemplified by paracetamol, phenacetin, acebutalol, etc., whilst the pyrazolones phenylbutazone, antipyrine, aminopyrine and their derivatives may be considered as masked anilides. In addition, biotransformation of aromatic amines often leads to N-acylated metabolites, e.g. N-acetylation of the benzamide class of drugs can yield pharmacologically active metabolites. Methods for the hydrogen isotope labelling of N-aryl amides are therefore of particular interest.

Indeed, a range of procedures have been employed for the deuterium-labelling of acetanilide pharmaceuticals. Thus ring deuterated paracetamol has been prepared from perdeuteronitrobenzene (1) and via acid-catalysed exchange and acetylation of para-aminophenol (2), whilst the trideuteroacetyl-labelled compound has been prepared by acylation of para-aminophenol (3) and the monodeuteroacetyl derivative via lithiation and

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dealkylation of para-methoxyacetanilide (4). However, no simple one-step ring-deuteration procedures have been reported for this class of drugs.

Highly regioselective deuterium exchange between aromatic compounds and a deuterium donor has been observed in the presence of a number of metal catalysts (5,6,7,8). In some cases the orientation of labelling has been ascribed to heteroatom-binding to the catalyst surface (6,9,10) and in others to an orthometalation (8,11,12) process.

The regioselective ortho-deuteration of aromatic acids (13), C-aryl amides and benzylamines (14), via exchange with deuterium oxide in the presence of rhodium(III) chloride, has previously been reported. This paper describes the application of the catalyst to the analogous single-step regioselective labelling of anilide derivatives.

DISCUSSION

During the course of investigations of the rhodium(III) chloride catalysed ortho-deuteration of a range of substituted C-aryl carboxamide derivatives, the labelling of salicylanilide was studied. In contrast to the expected (14) introduction of a single deuterium atom at the 6-position of the salicyloyl grouping, two additional deuterium atoms were introduced at the 2- and 6-positions of the anilide residue. The anilide grouping is therefore able to act as an effective ortho-deuteration directing group. The generality of this behaviour was investigated by examination of the deuteration of a range of substituted anilides. Table 1 summarises the results obtained.

Generally, recoveries and isotopic enrichments were good and the procedure was found to be applicable to a wide range of anilides substituted in the aromatic ring and, with the exception of phenylurea, on the anilide carbonyl carbon atom. The procedure was not, however, applicable to the tertiary anilides studied, a situation similar to that found with tertiary methanamines and tertiary C-arylamides (14). Whether this lack of

Table 1. Rhodium(III) chloride catalysed deuterium labelling of anilide derivatives

Substrate	Recovery (%)	Percentage reaction[a]	Purified by recrystallisation from:
acetanilide	67	94	H_2O
acetoacetanilide	56	63[b]	EtOH/H_2O
4-acetoxyacetanilide	85	95	EtOH/H_2O
benzanilide	90	86[c]	EtOH/H_2O
4-bromoacetanilide	87	92	EtOH/H_2O
4-carboxyacetanilide	80	83[d]	EtOAc
4-ethoxyacetanilide	55	90	EtOH/H_2O
4-formylacetanilide	87	95	EtOAc/hexane
2-hydroxyacetanilide	96	89	EtOH/H_2O
4-hydroxyacetanilide	78	86	H_2O
3-hydroxy-4-carboxyacetanilide	30	67	H_2O
4-methoxyacetanilide	79	92	H_2O
N-methylacetanilide	80	1	H_2O
N-methylformanilide	93	5	-
N-phenylurea	27	1	EtOH/H_2O
salicylanilide	93	95[c]	EtOH/H_2O

(a) Calculated from atom percentage ^{2}H obtained/atom percentage ^{2}H for complete exchange at available *ortho*-positions.

(b) Refers to exchange of *ortho*-positions. Aliphatic positions showed extensive labelling.

(c) Percentage reaction was essentially the same at all available *ortho*-positions.

(d) Percentage reaction *ortho* to the carboxylic acid group was 69%.

reactivity arises from steric effects, electronic effects of the substituent, or from the absence in these substrates of an easily exchangeable proton, requires further study.

Information about the regioselectivity of labelling was obtained in two ways, via comparison of mass and ^{1}H-nmr spectra of the deuterated compounds with that of the unlabelled substrate and, in two cases, directly via ^{2}H-nmr spectra of the labelled compounds. In several substrates the presence of groups already known to promote ortho-deuteration (14) led to deuteration ortho to those functions in addition to ortho to the anilide group. This was the case with salicylanilide and 3-hydroxy-4-carboxyacetanilide (three deuterium atoms introduced per molecule) and with benzanilide and 4-carboxyacetanilide (four deuterium atoms introduced per molecule). In the case of acetoacetanilide the active methylene position was almost entirely deuterated and some exchange at the acetyl group had also occurred. With these expected exceptions however, the regioselectivity of exchange ortho to the anilide nitrogen was high, ca. 95% in most cases.

The regioselectivity of the reaction was investigated directly by ^{2}H-nmr in the case of two selected substrates. By analogy with their 360 MHZ ^{1}H-nmr spectra both acetanilide and 2-hydroxyacetanilide would yield field-equivalent ^{2}H-nmr spectra in which the deuterons ortho to the anilide nitrogen atom would be resolved from the other aromatic deuterons. This was subsequently verified by natural abundance ^{2}H-nmr spectroscopy in the case of acetanilide. ^{2}H-Nmr spectroscopy of the deuterated substrates therefore provides a direct method for the determination of regioselectivity in these cases.

The ^{2}H-nmr spectrum of [(n)2,6-$^{2}H_{2}$]acetanilide consisted of a single resonance at δ 7.68, corresponding to the expected position for ortho-deuterium in this compound. There was no resonance associated with deuteration of the acetyl group and the regioselectivity of ortho labelling

in this case could be assigned as at least 97%. The ^{2}H-nmr spectrum of [(n)6-^{2}H]2-hydroxyacetanilide also consisted of a single major resonance at δ 7.5, the position expected for the ortho-deuterium. However small resonances at δ 2.0 and 6.9 were also present accounting, respectively, for 2 and 8 percent of the total intensity. In the case of this substrate therefore the regioselectivity for ortho-labelling was reduced to 90%. Such reduction in regioselectivity with substrates activated towards electrophilic substitution has previously been noted in the case of rhodium(III) chloride catalysed deuteration of aromatic carboxylic acids (13).

The regioselective ortho-labelling of various classes of aromatic compounds on metal catalyst surfaces have been well-described in the literature over many years (6,9,10) and such a mechanism should therefore be considered a possibility in this case also since some precipitation of metallic rhodium occurred during deuteration of all the anilide substrates. Previous studies of the deuteration of sodium benzoate over rhodium metal prepared thermally from rhodium(III) chloride have shown the material to be devoid of catalytic activity under the standard conditions employed (13). Nevertheless, the deuteration of salicylanilide, a compound possessing both C- and N-arylamide groupings, was studied over a number of heterogeneous rhodium catalysts. The results are summarised in Table 2.

In this table the ability of each catalyst to promote deuteration of the substrate is compared with that of rhodium(III) chloride trihydrate. Clearly, none of the catalysts are comparable in efficacy. Even so, catalysis by colloidal rhodium metal generated in situ during the reaction cannot be excluded at this stage.

Whilst the studies reported are confined to the deuteration of simple anilide derivatives the labelling procedure is also applicable to a number of drugs possessing masked anilide groupings. The results of these studies will be reported in due course.

Table 2: Deuteration of salicylanilide in the presence of rhodium catalysts[a]

Catalyst	Relative molar amounts of rhodium present	Relative percentage deuteration[b]
Rhodium(III) chloride trihydrate	1	100.0
Commercial 5% rhodium on carbon[c]	0.43	1.1
Rhodium metal from thermolysis[d] of rhodium(III) chloride trihydrate	2	2.5
Rhodium metal from borodeuteride[e] reduction of rhodium(III) chloride trihydrate	2	5.7

(a) All reactions employed salicylanilide (75 mg) in DMF/D_2O (1:1 by volume, 1.5 cm^3) and were performed for 18 hours at 103 - 107°.

(b) Expressed as 100 x atom percent ^2H found/atom percentage ^2H found using rhodium(III) chloride trihydrate.

(c) 100 mg of this catalyst was used.

(d) Prepared by heating rhodium(III) chloride trihydrate (60 mg) in DMF/D_2O (1:1 by volume, 3cm^3) at 110° until precipitation of rhodium metal was complete (18 hr). The metal was isolated by centrifugation and washed with D_2O prior to use.

(e) Prepared by treatment of a solution of rhodium(III) chloride trihydrate (60 mg) in deuterium oxide (3 cm^3) with excess solid sodium borodeuteride. The precipitated metal was washed twice with deuterium oxide (1 cm^3) before use.

EXPERIMENTAL

^1H-Nmr spectra were recorded for solutions in deuterochloroform or deuterodimethylsulphoxide at 80 or 360 MHz using either a Bruker WP-80 or Bruker AM-360 spectrometer. The latter instrument was also used to record the ^2H-nmr spectra of deuterated acetanilide and 2-hydroxyacetanilide in

dimethylsulphoxide at 55 MHz. Mass spectra were determined using a Kratos MS30 or MS50 spectrometer linked to a DS-55 SM data system. All the anilide derivatives studied were obtained from recognised chemical supply houses and used as supplied. Rhodium(III) chloride trihydrate, sodium borodeuteride (98 atom % ^{2}H), 5% rhodium on carbon, and deuterium oxide (99.8 atom % ^{2}H) were purchased from Aldrich Chemical Co Ltd, Gillingham, Dorset, UK. N,N-Dimethylformamide (< 0.1% water) was obtained from Fisons Scientific Equipment, Loughborough, Leicestershire, UK.

Deuteration of Anilides

In order to study the rhodium(III) chloride catalysed exchange of the range of anilides, standard reaction conditions were used. Thus, the anilide (75 mg) and rhodium(III) chloride trihydrate (30 mg) were dissolved in a mixture of N,N-dimethylformamide (0.75 cm^3) and deuterium oxide (0.75 cm^3). The solution was heated in a 5 cm^3 thick-walled screw-top vial at 103 to 107° for 18 hours, cooled, acidified to pH < 3 with hydrochloric acid (2 mol dm^{-3}) and extracted with ethyl ethanoate (20 cm^3). The extract was washed with sodium hydrogen carbonate solution (50 g dm^{-3}) and with water. Finally the solution was evaporated to leave the crude deuterated anilide. Those anilides bearing acidic substituents were isolated by acidification of the sodium hydrogen carbonate solution washings with hydrochloric acid (2 mol dm^{-3}) followed by extraction into ethyl ethanoate and evaporation to dryness.

The crude deuterated anilides were purified by recrystallisation from an appropriate solvent. The yields and isotopic enrichments obtained were generally good and are listed, along with the recrystallisation solvent used in the purification procedure, in Table 1.

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