Microwave-enhanced hydrogen isotope exchange studies of heterocyclic compounds

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The microwave-enhanced hydrogen–deuterium exchange reaction of a number of nitrogen-containing heterocyclic compounds has been achieved extremely rapidly (<20 min) *via* their hydrochloride salts, whilst the corresponding Raney-nickel catalysed reactions of indole and *N*-methylindole are also complete in a similar time interval. Furthermore, the pattern of labelling in the latter reaction depends critically on the choice of solvent used.

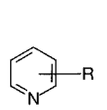
Introduction

Compounds labelled with either deuterium or tritium are widely used in the physical and life sciences and their syntheses have been greatly aided by the development of microwave-enhanced procedures.[1] Faster, cleaner, more selective reactions are possible with, in the case of tritium, the formation of much reduced levels of radioactive waste. Amongst the reactions that have been studied are hydrogenations,[2] borohydride reductions,[3] dehalogenations,[4] decarboxylations[5] and hydrogen isotope exchange.[6] The latter is a very versatile reaction[7] as it can be catalysed by acids, bases or metals, under both homogeneous and heterogeneous conditions. It has, therefore, also been used to test detailed features of reaction mechanisms and in the present study we touch on two such aspects.

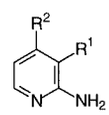
In the fourteen years that have elapsed since the publication of two papers[8,9] drew attention to the potential of using microwaves in synthetic chemistry more than 500 papers have been published.[10] Much of the work has inevitably been somewhat qualitative in nature, but now, with the emergence of more dielectric data[11] and mono-modal focused instrumentation, the opportunity has been created to design microwave-enhanced experiments which are more firmly based on theory. For organic compounds to benefit from the interaction with microwaves they, or the solvent in which the reaction is to be studied, need to be polar. Alternatively, the reactants need to be made more polar and one way of doing this, which is ideal for nitrogen-containing heterocyclic compounds, is *via* protonation and the formation of ionic salts. Here we illustrate such possibilities.

In 1987 Werstiuk[12] summarised his findings on the high temperature, dilute acid, deuteriation of many organic compounds. Extensive labelling could be obtained provided the heating times were long (typically 12–50 h). Not all compounds, particularly those of pharmaceutical interest, can withstand such demanding conditions. Furthermore, the development of new, combinatorial chemistry requires that the labelling reactions should be rapid so that high sample through-put can be achieved.

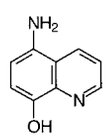
In an earlier study[6] we showed how the microwave-enhanced deuteriation of *o*-toluidine could be accomplished in less than 20 min by first forming the hydrochloride salt, and for the present investigation we have chosen nine heterocyclic compounds (**1**–**9**) which can be classified as mono-, di- and fused ring substituted pyridines.



1 R = 4-NH_2
2 2-NH_2
3 4-$N(CH_3)_2$
4 2-CH_2NH_2
5 4-CH_3



6 R^1 = H, R^2 = CH_3
7 R^1 = CH_3, R^2 = H



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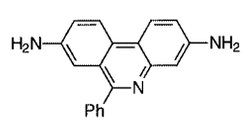

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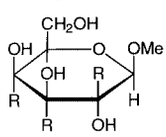

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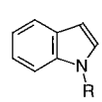

11 R = H
12 R = CH_3

Studies of heterogeneous metal-catalysed hydrogen isotope exchange have usually focused on the selectivity of the metal, but the introduction of microwaves provides an additional opportunity, namely to study the role of the solvent and its interaction with the catalyst. This can be done by using a number of deuteriated solvents and monitoring the deuteriation pattern of selected compounds. A somewhat similar approach would be to use solvent mixtures of which D_2O would be one component. This has already been done[13] in the Raney-nickel catalysed hydrogen–deuterium exchange of a model carbohydrate [1-*O*-methyl-β-D-galactopyranoside (**10**)] but under ultrasonic irradiation. Extensive deuteriation at the C-4 position occurred for all eight solvent systems, the C-3 position was deuteriated by seven solvent systems and the C-2 position

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Table 1 Microwave-enhanced hydrogen–deuterium exchange of various pyridines (**1**–**9**)

Compound no.	Weight/mg	D_2O/cm^3	Irradiation time/min	Site(s) deuteriated	Deuterium incorporation (%)
1	50	1	3 × 1	3, 5	71
2	32	2	5 × 2	3, 5	95
3	50	2	5 × 2	3, 5	74
4	50	2	6 × 2	CH_2	100
5	50	2	6 × 2	Me	97
6	50	2	6 × 2	5	92
				Me	75
7	50	2	6 × 2	5	97
8	30	0.3	11 × 2	6, 7	95, 30
9	30	1	12 × 1	4, 7	95, 95

Table 2 Thermal and microwave-enhanced deuteriation (%) of *N*-methylindole (**12**) in D_2O

Position	Thermal		Microwave-enhanced[a]
	Ref. 14	Present work	
1(Me)	88	86	54
2 + 6	n.d.[b]	80	79
3	89	80	66
4	86	91	18
5	76	64	2
7	17	25	91

[a] The irradiation time was 10 × 2 min. [b] n.d. – not determined by the authors, but highly deuteriated.

Table 3 Extent of deuteriation (%) at different sites for *N*-methylindole (**12**) using various solvents and microwave irradiation[a]

Position	D_2O	CD_3COCD_3	CD_3OD	$CDCl_3$
1(Me)	54 (88)	54 (0)	86 (88)	65 (0)
2 + 6	79 (n.d.)[b]	59 (94)	15 (n.d.)[b]	
3	66 (89)	54 (76)	12 (89)	89 (76)
4	18 (86)		7 (86)	
5	2 (76)		10 (76)	
7	91 (17)		0 (17)	

[a] The irradiation times (min) for the various solvents were as follows: D_2O 10 × 2, CD_3COCD_3 10 × 2, CD_3OD 1 × 2, $CDCl_3$ 3 × 2. Figures in brackets are taken from ref. 14 and refer to the thermal reaction. [b] Not determined.

Table 4 Extent of deuteriation (%) at different sites for indole (**11**) using various solvents and microwave irradiation[a]

Position	D_2O	CD_3COCD_3	CD_3OD	$CDCl_3$
2	98 (88)	93 (72)	96 (81)	
3	97 (75)	0 (33)	93 (55)	26 (23)
4	36 (48)	5 (0)	0 (25)	
5	40 (66)	47 (0)	0 (34)	
6	44 (97)		0 (45)	
7	94 (100)	80 (11)	80 (73)	

[a] The irradiation times (min) for the various solvents were as follows: D_2O 10 × 2, CD_3COCD_3 10 × 2, CD_3OD 4 × 2, $CDCl_3$ 5 × 2. Figures in brackets are taken from ref. 14 and refer to the thermal reaction.

deuteriated less extensively, also by seven solvent systems. For 1,4-dioxane–D_2O no labelling at the C-2 position occurred and for 1,2-dimethoxyethane–D_2O no C-3 labelling was observed. Controlling the regiospecificity in this way is an attractive possibility for which we have chosen the microwave-enhanced Raney-nickel catalysed hydrogen–deuterium exchange of indole (**11**) and *N*-methylindole (**12**) as our test case.

Results and discussion

The extraordinarily efficient deuteriation that we witnessed in the case of *o*-toluidine has been repeated for various pyridines (Table 1) with substantial incorporation of the isotope being achieved in 12 min, or less, of microwave irradiation. A relatively short pulse of 2 min optimises safety considerations, but equally satisfactory results can be obtained using other pulse sequences. The patterns of labelling are those expected as a result of protonation on the amino, or substituted amino, group and where this is not possible as, for example, in compound **5**, exchange *via* another mechanism takes place. Pyridine and quinoxaline were two of the compounds that failed to undergo hydrogen–deuterium exchange under microwave irradiation.

In testing the Raney-nickel catalysis of hydrogen–deuterium exchange for *N*-methylindole we were fortunate that the thermal reaction for this compound had been studied very recently.[14] The work was carried out at 40 °C over the course of a week and when we repeated the study we obtained very similar results (Table 2). A further comparison with the microwave-enhanced study, which could be carried out in 0.2% of the time, shows that the pattern of labelling is very similar, although the % deuteriation for some positions, notably C-4, -5 and -7, differ appreciably. This is not unexpected bearing in mind that our present instrument does not allow the temperature to be controlled.

Extending the investigations to a number of solvents we see, for both *N*-methylindole (Table 3) and indole itself (Table 4 and Fig. 1), widely different behaviour—D_2O is the best solvent for labelling all C–H positions, followed by CD_3OD, with $CDCl_3$ being the solvent that leads to the most selective deuteriation. Water and the alcohols, with their high relative permittivities, are seen to be good 'microwave solvents', acetone and chloroform less so. The observed trend does, therefore, parallel the ability of the solvents to interact with the microwave radiation and suggests that there might well be considerable potential in using selective solid donors in this rapidly emerging field. Whether this, in turn, will lead to different patterns of labelling in the thermal and microwave-enhanced experiments remains to be seen. As of now the differences in Tables 3 and 4 probably reflect limitations in the current microwave instrumentation.

Conclusion

The rapid deuteriation of a number of heterocyclic compounds can be achieved by their conversion to the hydrochloride salts followed by microwave irradiation in D_2O. In the microwave-enhanced hydrogen–deuterium exchange of both indole and *N*-methylindole, which are catalysed by Raney nickel, the reactions are equally rapid and some 500-fold faster than the corresponding thermal reaction (at 40 °C). Furthermore the pattern of labelling can be varied through judicious choice of solvent—the more polar solvents, such as D_2O and CD_3OD,

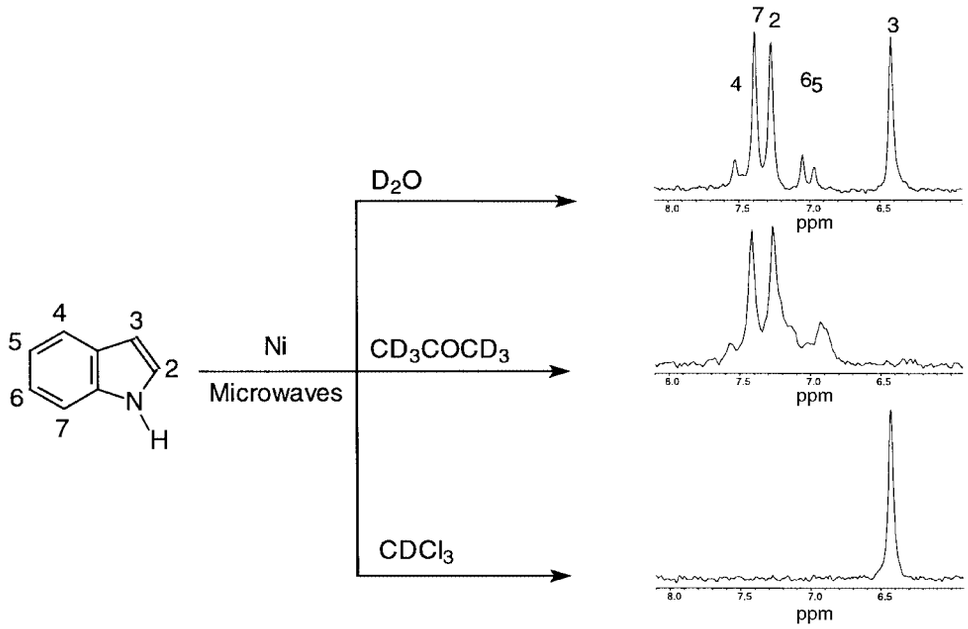

Fig. 1 ^{2}H NMR (^{1}H decoupled) spectra of indole (**11**) produced as a result of the microwave-enhanced Raney-nickel catalysed hydrogen–deuterium exchange in (a) D_2O, (b) CD_3COCD_3 and (c) $CDCl_3$.

give rise to general labelling whilst $CDCl_3$, for example, gives very regiospecific labelling.

Experimental

Materials

All the chemicals were purchased commercially and their purities checked prior to use. The hydrochloride salts were prepared by adding a slight excess of hydrochloric acid solution (3 M) to the heterocyclic compound and the mixture allowed to stand overnight. The solvent was then removed from the salt, which was then taken up in D_2O.

Microwave irradiation of compounds 1–9

A Matsui M167 BT microwave oven (750 W) was used throughout the work. The quantities specified in Table 1 were placed in a small (25 cm^3) pear-shaped glass flask and subjected to microwave irradiation for short (mainly 2 min) periods using the low power (20%) setting. To avoid undue build-up of pressure the vessel was left unstoppered and also cooled in-between irradiation periods. In the event of solvent evaporation additional D_2O was added so that the effective volume remained constant over the course of the experiment.

Preparation of Raney nickel catalyst

For the proposed deuteriation study it was beneficial to prepare the catalyst using sodium deuteroxide solution.[15] The latter was prepared by first of all placing 50 cm^3 of dry toluene in a round-bottomed flask and slowly adding, in small portions, a total of 1 g of sodium metal. After each addition a few drops of D_2O were added and once effervescence ceased further D_2O added. The process was repeated at intervals until all the sodium had reacted.

The sodium deuteroxide solution appeared as a viscous solution under the toluene and was removed by pipette; the solution was further concentrated on a freeze drier. The Raney nickel catalyst (~2 g slurry in H_2O) was washed with D_2O (5 × 5 ml) before slowly adding it to the sodium deuteroxide solution at 0 °C. The mixture was then transferred to an oil bath and heated at 100 °C until the evolution of gas ceased. The liquid was then filtered off and the catalyst washed with D_2O until the solution pH reached 7; it was then stored in D_2O or the desired reaction solvent.

Thermal deuteriation of compounds 11 and 12

Indole (47 mg) or *N*-methylindole (52 mg) was placed in a 25 cm^3 pear-shaped flask and mixed with 2 cm^3 of the deuteriated Raney nickel slurry and a further 1.5 cm^3 of deuteriated solvent. The vessel was sealed using a stopper which incorporated a septum; it was then frozen in liquid N_2 and evacuated. The reaction vessel was allowed to return to room temperature prior to equilibrating in an oil bath at 40 °C for 1 week. At the end of the reaction the Raney nickel was filtered off and washed with petroleum ether 40–60 (2 × 10 cm^3) and water (3 × 5 cm^3) before adding the washings to the D_2O solution. The organic layer was further washed with water (2 × 5 cm^3), separated, and dried over anhydrous Na_2SO_4. The petroleum ether was removed by passing a stream of N_2 over its surface. Part of the deuteriated product was then taken up in acetone and the other part in d_6-acetone, prior to NMR analysis.

Microwave irradiation of compounds 11 and 12

For reasons of safety the amounts of substrate, catalyst and solvent were kept as low as possible. Typically 27 mg of indole or 30 mg of *N*-methylindole was placed in a small pear-shaped flask and mixed with 1.5 cm^3 of the deuteriated Raney nickel slurry and a further 0.5 cm^3 of deuteriated solvent. The flask was sealed and evacuated as described for the thermal experiments. Microwave irradiation was carried out using the 20% power setting for short periods (see Tables 3 and 4). On completion the substrates were recovered as described for the thermal experiments.

NMR measurements

The NMR spectra were obtained using a Bruker AC 300 instrument operating at 300 MHz for ^{1}H and 46 MHz for ^{2}H. For all compounds it was customary to obtain the ^{1}H NMR spectra before and after microwave irradiation and to compare these with the ^{2}H (^{1}H decoupled) spectra. In a large number of cases the decrease in the ^{1}H integral at a particular chemical shift could be related to the ^{1}H integral at a non-exchangeable site in order to obtain the % deuterium incorporation. In circumstances where all positions underwent exchange a set of

simultaneous equations were set-up using the peak integrations from both the ^{1}H and ^{2}H (^{1}H decoupled) spectra in order to calculate the % deuterium incorporation.

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