Hydrogen–Deuterium Exchange in Thiazoles *via* Phase-transfer Catalysis [1]

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Hydrogen–deuterium exchange has been examined under phase-transfer conditions for 15 thiazoles and a number of other heteroaromatic compounds (pyridines, thiophens, and imidazoles). The effects of 11 quaternary (ammonium, phosphonium, and arsonium) salts and 17 solvents have been studied. The effect of chain-length of the salt $[Me(CH_2)_n]_4\overset{+}{N}Br^-$ (n = 1—5) has been examined. First-order kinetics (in thiazole) are reported for seven thiazoles. The present method offers a practical route to specifically and higher deuteriated (D ≥ 90%) thiazoles and other aromatics.

Some of the results (such as the effects of various catalysts and solvent polarity) are at variance with existing data in the field of phase-transfer catalysis and it is suggested that interfacial and micellar effects may arise.

PHASE-TRANSFER catalysis (and its variants) has been very widely used and examined in organic chemistry and there are numerous, recent reviews of the subject.[2-8] However, there are only a few reports of the use of phase-transfer catalysts to achieve isotopic (H–D) exchange. These involved replacement of the active hydrogens of octan-2-one [9] [at C(1) and C(3)] and of indene [at C(1) and C(3)] and fluorene [at C(9)] [10] by deuterium in a sodium deuterioxide–deuterium oxide medium. It has been predicted that in addition to ketones, other compounds, *e.g.* nitro-compounds and nitriles, *etc.*, should be amenable to ready H–D exchange under phase-transfer conditions.[6] We report herein several examples where the introduction of a nitro-group promoted H–D exchange and in earlier work [1b] we have shown that a cyano-group has a similar effect. In the present study we have examined H–D exchange in thiazole, benzothiazole, and a number of 2-, 4-, and 5-substituted thiazoles and also in several pyridines and thiophens, and in imidazole and *N*-methylimidazole. Many of the compounds examined underwent extensive isotopic exchange under the phase-transfer conditions used and this method offers a practical route to specifically labelled heteroaromatic compounds having a deuterium content ≥90%.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded with a JEOL JNM MH-100 spectrometer.

Materials.—Thiazoles were prepared and purified by the usual methods. The other heteroaromatic compounds were commercially available and were used without further purification and C_6D_6, $CDCl_3$, D_2O, phenylacetonitrile, and acetophenone were also used as obtained. All other solvents were laboratory-reagent grade. Most of the quaternary salts were commercially available and a few were prepared by standard methods. Sodium deuterioxide was prepared by the addition of sodium to an excess of methanol (the solution was allowed to stand overnight) and the unchanged methanol was distilled off under reduced pressure. The well-dried powdery residue was treated with D_2O, the deuteriated methanol (CH_3OD) formed was distilled, and the viscous sodium deuterioxide was filtered off. Titration with standard acid showed that the strength of the base prepared was 17.2M. This base was used to prepare weaker solutions of sodium deuterioxide in D_2O.

Exchange Experiments.—The following are details of a typical experiment. The reaction was carried out in a thermostatically controlled water-bath, with magnetic stirring. The quantities described in footnote *a*, Table 1, were those generally used (unless noted in the footnotes elsewhere). The reaction was initiated by strong magnetic stirring and stopped, after suitable periods, by termination of the stirring. After the two layers had separated a sample of the organic layer was analysed by ^{1}H n.m.r. and the % H–D exchange at a particular position(s) was determined by comparison of the integration of the non-exchanging protons (usually in a side-chain) with the integration of the exchanging proton(s).

This sample was then returned from the n.m.r. tube to the reaction vessel and the reaction resumed for further periods. With some solvents the solvent and heterocycle had to be separated by microdistillation, because of interference from proton peaks of the solvent with the proton peaks of the heterocycle. On separation the partially deuteriated heterocycle was dissolved in deuteriated benzene or carbon tetrachloride before the n.m.r. analysis. With most

TABLE 1

Effect of quaternary salts on the % H–D exchange in 5-ethylthiazole (2)

Expt.	Salt	% Exchange [a] 0.25 h [b]	1 h [b]	3 h [b]
1	$Me_3(C_{18}H_{37})N^+Br^-$	38(8)	90(8)	90
2	$Me_3(C_{16}H_{33})N^+Br^-$	36(8)	77(8)	91(6)
3	$Et_3(PhCH_2)N^+Cl^-$	*c*	*e*	79(7)
4	$Bu^n_4N^+Br^-$	55	90	*c*
5	$Me_4N^+Cl^-$	0(0)	*c*	16(10) [d]
6	$Me_3(Ph)N^+Br^-$	0(0)	0(0)	7(0)
7	$(C_{16}H_{33})N^+C_5H_5Cl^-$ [e]	6(6)	*c*	13(10)
8	$2,4\text{-}Me_2C_6H_3CH_2N^+C_5H_5Br^-$	0(0)	*c*	0(0) [d]
9	$Bu^n_3(C_{16}H_{33})P^+Br^-$	44(19)	*c*	88(28)
10	$Ph_3(PhCH_2)P^+Cl^-$	8(8)	*c*	*c*
11	$Ph_4As^+Cl^-$ [f]	0(0)	0(0)	10(0)

[a] Reaction conditions: compound (4 mmol) in C_6D_6 (2.5 ml) and salt (0.12 mmol) in 10M sodium deuterioxide (2.0 ml) at 50 °C. [b] The first figure gives the % exchange at the 2-position and the figure in brackets gives the % exchange at the 4-position. [c] Not determined. [d] After 19 h. [e] Monohydrate used. [f] All reaction quantities were halved.

substrates a suitable internal standard was provided by a non-exchanging proton(s) in a side-chain, but with a few compounds no such standard was available. However, for example, with imidazole (Table 4) the integration of the protons was unchanged after reaction and the shapes of the signals were also unchanged. If exchange had occurred at one or two positions then the integration would have revealed this. The remaining and rather improbable possibility is that equal amounts of exchange in all three positions containing C–H occurred. In this event the line shapes should have changed because of the very different coupling involving ^2H. Since neither the integration nor the line shapes changed it was concluded that no exchange occurred. The 4-position in thiazole did not exchange over the period of reaction and thus it could be used as a standard to assess exchange at the other positions.

TABLE 2

Effect of chain-length in $[Me(CH_2)_n]_4N^+Br^-$ on % H–D exchange in 5-isopropylthiazole [a]

Expt.	n	% Exchange 0.25 h	1 h	3 h
1	1	0 [b]	13	5
2	2	13	42	83
3	3	12	32	50
4	4	0	62	91
5	5	4	40	78

[a] For the reaction conditions see footnote *a*, Table 1. [b] Exchange at the 2-position.

Test Experiments and Precision.—In trial experiments, under our conditions (Table 1, footnote *a*, using $Bu^n_4N^+Br^-$), both acetophenone (reaction temperature 30 °C) and phenylacetonitrile (60 °C) had exchanged >90% of their labile α-hydrogens in 30 min and 3 h, respectively.[1b] The precision of the experiments was generally *ca.* 10% for the position(s) of primary exchange and *ca.* 20% for the position(s) of secondary exchange [see footnote *c*, Table 3; compare expt. 3 (Table 3) and expt. 4 (Table 1), and compare expt. 4 (Table 3) and expt. 3 (Table 2)].

TABLE 3

% H–D Exchange in various thiazoles [a]

Expt.	Compound	Salt	% Exchange 0.25 h	1 h	3 h
1	(1)	$Bu^n_4N^+Br^-$	90(82) [b,c]		93(90) [b]
2	(2)	$Me_3(C_{18}H_{37})N^+Br^-$	38(8) [d]	90(8) [d]	90 [d]
3	(2)	$Bu^n_4N^+Br^-$	53(4) [d]	96(10) [d]	
4	(3)	$Bu^n_4N^+Br^-$		34 [e]	55 [e]
5	(4)	$Me_3(C_{18}H_{37})N^+Br^-$	73(0) [b]	93(23) [b]	93(30) [b]
6	(4)	$Bu^n_4N^+Br^-$	79 [c]	97 [e]	
7	(5)	$Bu^n_4N^+Br^-$		89(11) [b]	90(33) [b]
8	(5)	$Me_3(C_{16}H_{33})N^+Br^-$	34(0) [b]		86(3) [b]
9	(6)	$Me_3(C_{16}H_{33})N^+Br^-$		61(0) [b]	
10	(6)	$Me_3(C_{18}H_{37})N^+Br^-$	37(12) [b]	53(11) [b]	83(8) [b]
11	(7)	$Bu^n_4N^+Br^-$	78(83) [b]		
12	(8)	$Me_3(C_{18}H_{37})N^+Br^-$	32(34) [f]	50(57) [f]	
13	(9)	$Bu^n_4N^+Br^-$	23(15) [f]		80(20) [f]
14	(10)	$Bu^n_4N^+Br^-$	18 [f]	46(0) [f]	79(7) [f]
15	(11)	$Me_3(C_{18}H_{37})N^+Br^-$	0 [g]		0
16	(11)	$[Me(CH_2)_4]_4N^+Br^-$	45 [g]	46 [g]	53 [g]
17	(12)	$Me_3(C_{18}H_{37})N^+Br^-$	10 [h]		13 [h]
18	(13)	$Me_3(C_{18}H_{37})N^+Br^-$			23 [h,i]
19	(14)	$Bu^n_4N^+Br^-$	37(17) [j]	50(22) [j]	61(44) [j]
20	(15)	$Bu^n_4N^+Br^-$	>90 [c,k]		

[a] For the reaction conditions see footnote *a*, Table 1; gap = not determined. [b] Exchange at 2-position (exchange at 5-position). [c] In a duplicate experiment, 82(81) was obtained after 0.25 h. [d] Exchange at 2-position (exchange at 4-position). [e] Exchange at 2-position. [f] Exchange at 5-position (exchange at 4-position). [g] Exchange at 5-position. [h] Exchange at 4-position. [i] After 19 h. [j] Exchange of 2-methyl hydrogens (exchange of isopropyl α-hydrogen). [k] Using twice the quantities in *a* at 60 °C for 0.5 h.

TABLE 4

% H–D Exchange in various heterocycles [a]

Expt.	Compound	0.25 h	1 h	3 h
1	(16)	8(0) [b]	14(0) [b]	13(0) [b]
2	(17)	17(0) [b]	19(0) [b]	
3	(18)		82 [c]	86 [c]
4	(19)	0(0) [d]	0(0) [d]	0(0) [d]
5	(20)	44(74) [e]	53(76) [e]	69(77) [e]
6	(21)	79 [f]	84 [f]	
7	(22)		0	0 [g]
8	(23)	0		0 [h]
9	(24)	0		

[a] For the reaction conditions see footnote *a*, Table 1; gap = not determined; $Bu^n_4N^+Br^-$ was used, unless otherwise stated. [b] Exchange at the 6-position (exchange at the 3-position). [c] Exchange in acetyl methyl group. [d] Exchange at the 2,6-positions (exchange at 3,5-positions). [e] Exchange of 2-methyl hydrogens (exchange of 6-methyl hydrogens). [f] Exchange at the 5-position. [g] After 27 h; $Me_3(C_{18}H_{37})N^+Br^-$ used. [h] Small amount of exchange at two positions.

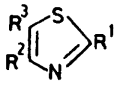
Kinetic Experiments.—The kinetic experiments were conducted in the same way as the exchange experiments except that the reaction was stopped six or more times to obtain readings. Reasonably good first-order plots were obtained during *ca.* 2 half-lives by plotting log (fraction exchanged for a particular position in the thiazole) *vs.* time (min). Some substrates also gave good second-order plots when the reciprocal of the fraction exchanged was plotted against time (min).

RESULTS AND DISCUSSION

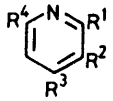
In previous work [1a] using 5-ethylthiazole (2) as the substrate and trimethyloctadecylammonium bromide as the catalyst we examined the effect of temperature, strength of base (sodium deuterioxide in deuterium oxide), and concentration of catalyst on the exchange reaction. The results indicated that for the work reported herein we needed a temperature of 50 °C, 10M

sodium deuterioxide, and a catalyst concentration of 1.2×10^{-4} mol. It was also established that no exchange occurred after almost 3 d when the catalyst was omitted. The effect of doubling the amount of organic solvent (usually C_6D_6) was small, so generally the minimal quantity of deuteriated benzene (or other solvent) was employed.

In Table 1 the effects of various (ammonium, phosphonium, and arsonium) quaternary salt catalysts are compared for various reaction times. Some of the findings of Herriott and Picker [11] are corroborated by the results in this Table. Thus, larger ions (Table 1, expts. 1, 2, 4, and 9) are more effective than smaller ions



(1)



R^n = H unless stated otherwise

(2) R^3 = Et
(3) R^3 = Pr^i
(4) R^2 = Me
(5) R^2 = Et
(6) R^2 = Bu^t
(7) R^2 = Ph
(8) R^1 = Me
(9) R^1 = Pr^n
(10) R^1 = Bu^t
(11) R^1 = R^2 = Me
(12) R^1 = R^3 = Me
(13) R^1 = Me, R^3 = Et
(14) R^1 = Me, R^2 = NO_2, R^3 = Pr^i
(15) R^2,R^3 = $-C_4H_4-$
(16) R^1 = Et
(17) R^1 = NMe_2
(18) R^1 = Ac
(19) R^3 = Bu^t
(20) R^1 = Me, R^2 = NO_2, R^4 = Me

(expt. 5); the more symmetrical ions (expt. 4) are more effective than those with one long chain (expts. 1, 2, and 9) and phosphonium ions appear to be somewhat better than comparable ammonium ions (*e.g.* compare expts. 9 and 2), although, as a referee has pointed out, $Bu^n_3(C_{16}H_{33})P^+Br^-$ is appreciably larger and more spherical than $Me_3(C_{16}H_{33})N^+Br^-$, and might reasonably be expected to function better on that basis alone, regardless of the nature of the heteroatom. Interestingly, $Bu^n_3(C_{16}H_{33})P^+Br^-$ induced a large amount of exchange at the 4-position in 5-ethylthiazole. Arsonium ions (expt. 11) are less effective than phosphonium ions (expt. 10), though interesting examples of the use of this ion as an effective catalyst have been cited.[8] The total (expt. 8) and comparative (expt. 7) failure of the two pyridinium salts employed as catalysts may be due to a reaction between these salts and the deuterioxide base (*e.g.* hydrogen abstraction from the position α to the nitrogen atom) [1a] or to poor solubility.

Table 2 gives the results of a study of the effect of chain-length in a series of symmetrical ammonium bromides, $R_4N^+Br^-$. After periods of 1 or 3 h the most effective catalyst is seen to be tetra-n-pentylammonium bromide. Surprisingly, the tetra-n-butyl catalyst is less effective than those with 3, 5, or 6 carbon atoms in their chains. This result may be compared with that of Dockx [12] who studied the influence of chain-length on catalytic activity in the conversion of phenethyl bromide into styrene using $Me[CH_2]_nEt_3N^+Br^-$ as catalysts. For the nine catalysts used (n = 1—7, 9, and 11) a single maximum (for n = 5) was evident in a plot of styrene formed (%) *vs.* chain-length of catalyst. If the data for % exchange in Table 2 are plotted *vs.* chain-length, the plots obtained using the 1- or 3-h data are similar and show two maxima corresponding to the tetra-n-propyl- and tetra-n-pentyl- bromides. The efficacy of tetra-n-pentylammonium bromide is strikingly shown by the data given in Table 3; extensive exchange is produced in 2,4-dimethylthiazole which underwent no exchange when trimethyloctadecylammonium bromide was used (Table 3, expts. 16 and 15).

The data assembled in Table 3 show the extent of hydrogen–deuterium exchange in thiazole and 14 different substituted thiazoles during 0.25, 1, and 3 h, respectively. Thiazole exchanged substantially and to an approximately equal extent at the 2- and 5-positions after 15 min. As would be expected,[13] the 2-position is the most reactive and for those thiazoles substituted in the 5- or 4-positions the predominant exchange occurred at the 2-position with generally minor exchange occurring in the 4- or 5-position(s) after 1 h. However, when the 4-position carries a phenyl group the lability of the hydrogen at the 5-position is increased and it exchanged to the same degree as that at the 2-position.

When the 2-position is substituted the 5-position and the 4-position exchange extensively, but with substitution by successively bulkier groups at the 2-position the degree of exchange at the 4-position drops considerably (expts. 12, 13, and 14, Table 3). 2,4- or 2,5-Dialkyl-substituted thiazoles do not readily undergo exchange at the unsubstituted (4- or 5-position), but, as seen above, judicious choice of the added salt can lead to exchange (see expt. 16). Introduction of a nitro-group into a dialkythiazole produced considerable side-chain exchange in the adjoining alkyl groups (see expt. 19). Benzothiazole underwent virtual complete exchange at the 2-position in 0.5 h at 60 °C (expt. 20).

In Table 4 the results of some exchange experiments with other heteroaromatic compounds are shown. Exchange of ring hydrogen in substituted pyridines was

(21) R = NO_2 (23) R = Me
(22) R = Me (24) R = H

sluggish, but the introduction of a nitro-group at the 3-position gave rise to considerable exchange in the methyl hydrogens of 2,6-dimethylpyridine (expt. 5). Very substantial exchange of the hydrogen at the 5-position took place in 2-nitrothiophen (expt. 6) compared with 2-methylthiophen (expt. 7), which appeared to undergo no exchange. *N*-Methylimidazole gave a small amount of exchange at two positions and imidazole did not appear to exchange after 27 h.

The effect of a wide range of solvents on the H–D exchange reaction in 4-ethyl- and 4-methyl-thiazoles is shown in Table 5. n-Heptane is seen to be a more effective solvent than either benzene (deuteriated) or 1,2-dichlorobenzene. This contrasts with the findings of Herriott and Picker,[11] who found that the more polar solvents were more effective. The best solvent for exchange is cyclohexane and in Table 6 the differences between benzene and cyclohexane are clearly shown. The % exchange of the ' poor ' substrate, 5-isopropylthiazole, was dramatically improved by changing the solvent from benzene to cyclohexane. With the ' good ' substrate, 4-ethylthiazole, there was a slight increase in the % exchange during 1 h. With the same substrate and the less efficient salt, trimethylhexadecylammonium bromide, there was a large increase in the amount of exchange at the 2-position after 1 h. It is worth noting here, also, that the 5-position underwent a very large exchange on changing from benzene to cyclohexane. This is of interest since in previous experiments (see Table 3, expts. 7 and 8) this position did not undergo very much exchange after 1 h.

In Table 7 the results of some kinetic experiments are given. An Arrhenius plot of the data for 4-methylthiazole in methylene chloride at 20, 40, and 50.9 °C gave a good straight line with $E^+ = 32$ kJ mol^{-1} and $\Delta S^{\ddagger} = -187$ J K^{-1} mol^{-1}. As observed by Olofson *et al.*[14] the exchange reaction was first-order in the thiazole. In the case of thiazole, second-order plots of the exchange at the 2- and 5-positions were also quite linear. Again, for 4-methylthiazole the data seemed to fit either a first- or a second-order plot. However, for the other thiazoles studied the kinetics were clearly first-order. Examination of the rate constants for exchange at the 2-position shows that the trend is (position of substituent) 4- or 5-H > 4-Ph > 4-Me > 5-Et > 4-Et > 4-Bu^t. Thus, thiazole itself undergoes the fastest exchange and 4-t-butylthiazole is the slowest exchanger. No obvious correlation with σ_m, σ_p, σ^*, or E_s is apparent.

TABLE 5

Effect of solvent on the % H–D exchange in 4-ethyl- and 4-methyl-thiazoles [a]

Expt.	Solvent	% Exchange [b] 0.25 h	1 h	3 h
4-Ethylthiazole				
1	$C_6H_6(C_6D_6)$	46(5)	81(8)	92(23)
2	$CHCl_3(CDCl_3)$	26(5)	41(18)	
3	CCl_4	22(0)	24(0)	27(4)
4	CH_2Cl_2 [c]	17(0)	36(0)	57(7)
5	$C_6H_4Cl_2$-*o* [d,e]	58(6)		
6	CS_2	39(73)	6(0)	10(3) [f]
7	Et_2O [d]	70(22)	73(24)	
8	MePh [e]	45(0)	83(0)	88(0)
9	C_6H_{12} [d,e]	72(21)	92(62)	
10	C_5H_{10} [e]	48(19)	85(27)	97(45)
11	C_5H_{12} [d]	64(8)		
12	C_6H_{14} [d]	52(5)		
13	C_7H_{16} [d]	67(13)		
14	C_9H_{20} [d]	41(0)		
15	$C_{10}H_{22}$ [d]	54(16)		
4-Methythiazole				
16	C_5H_{10} [g]			79(75)
17	C_7H_{14}			94(89)

[a] For the reaction conditions see footnote *a*, Table 1; gap = not determined; $Bu^n_4N^+Br^-$ was used (2.5 ml of solvent). [b] Exchange at the 2-position (exchange at the 5-position). [c] Three readings were taken as the solvent peaks did not interfere with the required peaks. [d] Solvent removed by microdistillation. [e] All reaction quantities were quadrupled. [f] After 6 h. [g] All reaction quantities were halved.

TABLE 6

Comparison of benzene and cyclohexane as solvents for H–D exchange in thiazoles [a]

Expt.	Thiazole	Salt	Solvent	% Exchange 0.25 h	1 h	3 h
1	(3)	$Bu^n_4N^+Br^-$	C_6D_6		34 [b]	55
2	(3)	$Bu^n_4N^+Br^-$	C_6H_{12} [c]		91	
3	(5)	$Bu^n_4N^+Br^-$	C_6D_6 [a]		89(11) [d]	90(33)
4	(5)	$Bu^n_4N^+Br^-$	C_6H_{12} [c]	72(21)	92(62)	
5	(5)	$Me_3(C_{16}H_{33})N^+Br^-$	C_6D_6 [a]	34(0)		86(3)
6	(5)	$Me_3(C_{16}H_{33})N^+Br^-$	C_6H_{12} [c]	63(60)		

[a] For the reaction conditions see footnote *a*, Table 1; using 2.5 ml of solvent; gap = not determined. [b] Exchange at the 2-position. [c] Solvent removed by microdistillation; all reaction quantities were quadrupled. [d] Exchange at the 2-position (exchange at the 5-position).

TABLE 7

Rates of H–D exchange in thiazoles at various temperatures [a]

Substrate	Position of exchange	[k(min^{-1})] 20 °C	24.9 °C	40 °C	50.9 °C
(1)	2				0.87
	5				0.55
Ph	2				0.68
	5				0.70
(9)	5		5.0×10^{-3}		7.43×10^{-3}
(2)	2		6.9×10^{-3}		5.29×10^{-2} [b]
(5)	2				4.0×10^{-2}
(6)	2				1.4×10^{-2}
(4)	2				0.11
(4) [c]	2	2.42×10^{-3}		4.74×10^{-3}	8.42×10^{-3}

[a] For the reaction conditions see footnote *a*, Table 1; $Bu^n_4N^+Br$ was used. [b] At 75 °C, this rate was too fast to determine. [c] Using CH_2Cl_2 as solvent.

The kinetic results for thiazole are in broad agreement with those obtained for hydrogen–deuterium exchange under non-phase-transfer conditions.[14,15] Thus, the 4-position did not exchange with OMe^- in MeOD or with OD^- in D_2O and the rate of exchange at the 2-position is somewhat greater than at the 5-position. The rates of reaction under phase-transfer conditions are much greater, but direct comparison is difficult because of differences in conditions. For example, the rate of exchange at the 2-position of thiazole was 0.03 min^{-1} at 60.7 °C in NaOD–D_2O–1M $NaClO_4$; at the 5-position it was 0.015 min^{-1} under the same conditions [15] (compare with Table 7).

Some of the results contained in this paper contradict existing data in phase-transfer catalysis, *e.g.* effects of some catalysts and the unexpected effect of solvent polarity (see above). There are two main mechanisms involved in phase-transfer catalysis. First, the true phase-transfer mechanism operating, for example, in reaction (1) where a partitioning of the catalyst exists

$$RBr + CN^- \longrightarrow RCN + Br^- \qquad (1)$$

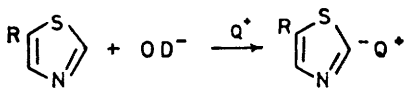
between the organic phase and the aqueous phase (solution of water saturated with KCN). In this particular case benzyltriethylammonium chloride (BTEAC) is not a good catalyst. The second mechanism is interfacial and arises mainly in alkylation reactions, as in equation (2),

$$PhCH_2CN + RBr \longrightarrow PhCHRCN + HBr \qquad (2)$$

where BTEAC is a good catalyst since it is not partitioned between the sodium hydroxide medium and the organic solvent.

In the case of deuteriation, since almost no exchange occurs without the catalyst it seems that the mechanism may be an interfacial one. The solubilities of the various catalysts in the organic media and their abilities to form inverted or reversed micelles will be important. Poor solubility should not lead to a decrease in reactivity since the salt will remain at the interface when the anions are formed. When the catalysts are very soluble, such as with long-chain quaternary ammonium salts, inverted micelles will certainly arise and this will decrease the true concentration of the salts present and the expected increase in catalysis will not occur.

The slow step of the exchange reaction is the formation of the carbanion as in equation (3), which will be



stabilised by the usual factors which stabilize carbanions,[16] *e.g.* electron-attracting groups, a benzene ring fused to the thiazole (note the greater reactivity of 4-phenyl- and benzo-thiazoles compared with other thiazoles, see Table 3). The large negative entropy indicates a very tight transition state.

It is clear that the present method, with judicious choice of quaternary salt and solvent, affords a practical route to thiazoles and certain other heteroaromatic compounds, both specifically and highly deuteriated. Hitherto, to synthesise, for example, [2-^{2}H]thiazoles the reduction of halogeno-derivatives by deuterioacetic acid in the presence of zinc powder [17] or the hydrolysis with D_2O of the lithio-derivatives [18,19] was necessary. However, these routes not only involved longer reaction paths but also gave mixtures. The direct exchange in NaOD–D_2O is possible for thiazole (not for alkylthiazoles because of their poor solubility in that medium), but about 15 h is necessary for full exchange even at the 2-position and moreover, by-products arising from the degradation of the thiazole ring may be obtained.[17]

Finally, a close relationship exists between alkylation and deuteriation reactions and it should be possible to deuteriate all the heterocyclic compounds already alkylated under phase-transfer conditions. Also, deuteriation under phase-transfer conditions seems to be a good method of obtaining specifically labelled compounds and recent deuteriation reactions with indole,[20] proline,[21] benzimidazoles,[22] 1,3-dioxan acetals,[23] vitamin D_3,[24] sulphones,[25] porphyrins,[26] and pyridylbutyramides [27] should be amenable to the phase-transfer method.

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