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DIRECT DEUTERIUM LABELLING OF XANTHONE WITH THE LITHIUM SALT OF 1,3-DIAMINOPROPANE-N,N,N',N'-d_4

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SUMMARY

A direct method for selective deuteration of xanthone 1 employing the lithium salt of 1,3-diaminopropane-N,N,N',N'-d_4 is described. Dibenzofuran is also found to be deuterated selectively under these conditions.

Key words: aromatic deuteration, 1,3-diaminopropane-N,N,N'N'-d_4, xanthone, dibenzofuran, diphenyl ether

INTRODUCTION

Deuteration of aromatic compounds is normally carried out by exchange under acidic or catalytic conditions (1, 2). In practice, base is less often employed because of the weak acidity of protons on aromatic rings (pK_a approx. 37), and very strong bases and vigorous conditions are required for exchange. Recently, however, a phase transfer system developed by Rabinovitz et al (3) employing sodium deuteroxide has been shown to exchange the protons of 1,2,3,4-tetrafluorobenzene (pK_a 31.5). The limit of the pK_a of exchangeable protons has been estimated to be about 34 with this system. Several other highly basic reaction media have been developed for deuteration of aromatic compounds but do not appear to have been employed for preparative purposes. Shatenshtein (4) has used potassium amide in liquid deuterated ammonia to study the rates of deuteration of naphthalene and of benzene, and Streitwieser (5) has, over the past twenty years, employed alkali metal salts of cyclohexylamine in cyclohexylamine to determine

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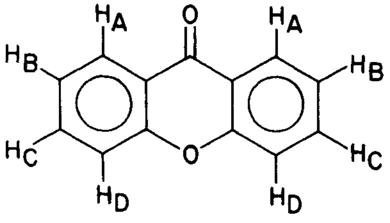
acidities of very weakly acidic hydrogens. Brown (6) reported that the potassium salt of 1,3-diaminopropane in 1,3-diaminopropane was sufficiently basic to cause exchange of the deuteria of deuterobenzene, but no reports of deuteration of aromatic compounds with this reagent system have appeared.

We have employed alkali metal amides of 1,3-diaminopropane-N,N,N',N'-d_4 to isomerize triple bonds of alkynols and cycloalkynes with concomitant deuteration of the methylene chain (7, 8). We wish now to report a study of the deuteration of the aromatic system xanthone employing the deuterated isomerization reagent, the lithium salt of 1,3-diaminopropane-N,N,N',N'-d_4.

RESULTS AND DISCUSSION

Xanthone (1), whose deuterated analogs were required for other studies (9), was found to be stable to the lithium salt of 1,3-diaminopropane at room temperature, but not to the more basic potassium salt (7).



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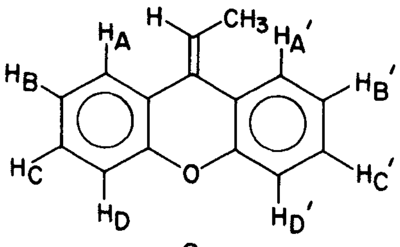

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Xanthone was subjected to the lithium salt of 1,3-diaminopropane-N,N,N',N'-d_4 employing the deuterated diamine as solvent and aliquots of the reaction were quenched with deuterium oxide at intervals. Results are presented in Table 1. Deuterium incorporations were determined by calculations based upon integration of the signals of the ^1H NMR spectrum (360 MHz) (10) and the molecular weights obtained from the mass spectrum, after correction for M-1 and M+1 ions. Confirmation was obtained by comparison of the integration of the vinyl signals with residual proton signals in the NMR spectrum of the ethylidene derivative 2.

Table 1: Deuteration of Xanthone with Li $DN(CH_2)_3ND_2$ [1]

Number of deuteria at each position

	reaction time				
position	5 min	15 min	1.0 h	20 h	40 h
A	1.0	1.6	1.9	1.9	1.9
B	0.0	0.0	0.1	0.2	0.6
C	0.1	0.1	0.2	1.7	1.9
D	1.8	1.8	1.9	1.9	1.9

1. Experimental conditions are those described in the Experimental Methods section.

As can be seen from the tabulated data, selective deuteration of the four different aromatic proton positions of xanthone is observed. The proton at position (D), proximal to the ether oxygen, is exchanged most rapidly, followed by that adjacent to the carbonyl carbon (A). After a reaction time of 1.0 hour, the protons at positions A and D are essentially completely exchanged. The proton (C) *meta* to the ether oxygen suffers slight exchange and the remaining proton (B) *meta* to the carbonyl carbon remains essentially unaffected. Prolonged exposure of xanthone to the deuteration reagent affords product that is essentially completely exchanged at the A, C, and D positions.

These findings are particularly interesting because the pattern observed is different and complementary to that observed for acid mediated exchange. Laposa and Bramley (11) reported that prolonged exposure of xanthone to 0.25 M DCl at 260 °C resulted in complete exchange of the B and D positions only, and that catalytic exchange afforded perdeuterated material.

The direct deuteration of other related aromatic systems was investigated. Benzophenone, which had poor stability to the reaction conditions, was found to exchange very slowly, and only at the positions *ortho* to the carbonyl. This system was not studied further. Deuteration of diphenyl ether and of dibenzofuran under conditions employed for xanthone yielded interesting results. Prolonged exposure (overnight) to the reagent afforded perdeuterated products in both cases. Treatment of dibenzofuran for an hour resulted in perdeuteration at the A, C, and D positions as in xanthone, while the protons at the B position were 50% deuterated.

The procedure described in this work provides a new method for deuterating weakly acidic compounds. The deuterated solvent and reagent are easily prepared, and the deuteration procedure can conveniently be carried out at room temperature. The most interesting feature is that access is possible to different deuteration patterns than those observed with acid or catalytic conditions.

EXPERIMENTAL METHODS

The deuterated solvent, 1,3-diaminopropane-N,N,N',N'-d_4, was prepared as previously described (7) or was purchased from MSD Isotopes (min. 97 atom % D). All reactions were performed in dry glassware (either dried in an oven at 110 °C for more than 2 hours, or flame dried under vacuum) under a slight positive pressure of argon.

Gas chromatographic separations were carried out with a Varian 3700 instrument equipped with a DB-5 capillary column (J and W Scientific, 30 m) and a flame ionization detector. Proton NMR spectra were recorded on a Bruker AM-360-WB (360 MHz) spectrometer with $CDCl_3$ or $(CD_3)_2CO$ as solvents. GC/MS were obtained by using a DB-5 column (60 m) in a

Finnigan 4000 E instrument with an Incos 2300 data system in the electron impact mode employing an ionization voltage which minimized M-1 peaks. Mass spectra are reported in mass to charge units (m/z) with the relative intensities as percentages of the base peak given in parentheses.

In this work the stability of aromatic compounds to non-deuterated reagents was tested first (Table 2). Deuteration studies were then carried out on compounds which were found to survive the strongly basic reaction conditions.

Table 2: Stability of Some Aromatic Compounds to Li $HN(CH_2)_3NH_2$[1]

Compound	% Recovery
xanthone	100
dibenzofuran	82
diphenyl ether	77
benzophenone	40
benzoic acid	25
cinnamic acid	0

1. Conditions employed are those reported for the stability of xanthone described in the Experimental Methods section.

Stability of xanthone (1) to reagents: To the lithium salt of 1,3-diaminopropane [prepared from lithium (42 mg, 6.0 mmol) and 1,3-diaminopropane (6.0 mL) according to Abrams (7)] at room temperature was added xanthone (196 mg, 1.0 mmol) as the solid. After stirring for 3 h, the blue reaction mixture was poured onto water and extracted with $CHCl_3$ (3X). The combined extracts were washed with dilute HCl solution (1X), and NaCl solution then dried over Na_2SO_4 and the solvent evaporated to afford 200 mg of xanthone (100% recovery) identical by TLC and NMR with the starting material.

Repetition of the reaction employing a reagent prepared from the lithium amide as above to which potassium t-butoxide (500 mg, 4.5 mmol) had been added (7) afforded 40 mg of impure xanthone after reaction for 1.0 h.

Deuteration of xanthone: To 1,3-diaminopropane-N,N,N',N'-d_4 (5.0 mL) was added lithium metal (42 mg, 6.0 mmol). The mixture was stirred and heated at 50 ^{0}C for approximately 1.0 h, or until the blue colour of the dissolved lithium had disappeared leaving a white suspension of the amide. The reagent was cooled to room temperature and xanthone (200 mg, 1.0 mmol) was added in one portion as the solid. After 1.0 h, 0.5 mL of the mixture was removed by syringe and added to deuterium oxide. The remaining mixture was stirred overnight then added to deuterium oxide. The products (from both the first sampling and the whole reaction mixture) were isolated by extraction with $CHCl_3$ (3X), then the combined extracts were washed with dil HCl (1X), then with saturated NaCl solution, and dried over anhydrous Na_2SO_4, followed by evaporation of the solvent. The starting xanthone and the two recovered products (20 mg, and 170 mg, 96% recovery) gave single spots of identical R_f on TLC (silica gel, 20% ether/80% hexane, R_f 0.3), and identical retention times on GC (21.5 min, 100-220 ^{0}C at 5 ^{0}C/min). GC/MS were obtained at 25 eV: xanthone 195 (3), 196 (100) and 197 (14); 1.0-hour product 198 (3), 199 (24), 200 (100), 201 (49) and 202 (10) for an average incorporation of 4.1 D; final product 200 (13), 201 (54), 202 (100), 203 (35), and 204 (5) for an average incorporation of 5.7 D. NMR spectra (ref. 10, for xanthone) were obtained in $CDCl_3$: 1.0-hour product δ: 8.25 (dd, J = 7.9, 1.6, 1.0 H, H_A), 7.62 (m, 17.3 H, H_C), 7.37 (d, J = 8.5 Hz, 1.5 H, H_D) and 7.28 (m, 18.4 H, H_B); final product δ: 8.25 (d, J = 7.9 Hz, 1.0 H, H_A), 7.62 (br d, J = 7 Hz, 2.3 H, H_C), 7.37 (br s, 1.0 H, H_D) and 7.28 (br s, 13.7 H, H_B). The final product was crystallized from methanol and gave m.p. 176-178 ^{0}C.

Ethylidene derivative of xanthone 2: To xanthone (20 mg, 0.1 mmol) was added a solution of ethyl magnesium bromide in THF (1.0 mL, 1.5 M). After 20 min, the orange solution was poured onto 5 % HCl in ice, and the product was extracted with ether (2X). The combined ethereal extracts were evaporated and dissolved in a mixture of 3N HCl and methanol and heated on the steam bath for 20 min. The mixture was poured onto water, and extracted with ether (2X), then washed with saturated NaCl solution and dried over Na_2SO_4 and evaporated to afford 16 mg of crude product which was chromatographed over silica gel eluting with hexane to give the pure derivative 2 that gave ^{1}H NMR ($CDCl_3$) δ: 7.58 (dd, J = 7.8, 1.5 Hz, 1.0 H, H_A), 7.49 (dd, J = 7.8, 1.5 Hz, 1.0 H, $H_{A'}$), 7.13-7.29 (m, 4.0 H, $H_{C,C',D,D'}$), 7.1 (m, 2.0 H, $H_{B,B'}$), 6.03 (q, J = 7.5 Hz, 1.0 H) and 2.11 (d, J = 7.5 Hz, 3.0 H).

Derivatization of xanthone (final deuterated product from above) was carried exactly as described affording the ethylidene derivative which gave ^{1}H NMR ($CDCl_3$) δ: 7.50 (m, 0.1 H, $H_{A,A'}$), 7.10 (m, 1.9 H, $H_{B,B'}$), 6.03 (q, J = 7.5 Hz, 1.0 H) and 2.11 (d, J = 7.5 Hz, 3.0 H).

Deuteration of dibenzofuran: Employing the same procedure as for xanthone, dibenzofuran (170 mg, 1.0 mmol) was deuterated, and products isolated at 1.0 h (17 mg from 10% of the mixture) and after reaction overnight (97 mg from the remainder). The products and starting material all gave single identical spots on tlc (silica gel, hexane, Rf 0.5) and identical retention times on GC (13.6 min, 100-220 ^{0}C at 5 ^{0}C/min). GC/MS were obtained at 70 eV: dibenzofuran 168 (100), 169 (13); 1.0-hour product 172 (3), 173 (22), 174 (73) 175 (100), 176 (51) and 177 (3) for an average incorporation of 6.7 D; final product 173 (3), 174 (25), 175 (77), 176 (100), and 177 (8) for an average incorporation of 7.3 D. NMR spectra were obtained in $(CD_3)_2CO$: 1.0-hour product δ: 8.05 (m, 1.0 H, H_A), 7.63 (s, 1.0 H, H_D), 7.50 (s, 1.0 H, H_C), and 7.37 (s, 5.0 H, H_B); final product gave four singlets with the chemical shifts as above in a ratio of 1:1:1:1.

Deuteration of diphenyl ether: Deuteration of diphenyl ether (170 mg, 1.0 mmol) was performed as above except that the whole mixture was worked up after reaction overnight affording 140 mg of material that gave TLC (silica gel, 20% ether/80% hexane, R_f 0.8), and GC (10.9 min, 100-220 ^{0}C at 5

°C/min) identical with that of diphenylether. GC/MS were obtained at 13.5 eV: diphenyl ether 169 (3), 170 (100), and 171 (13); product 177 (10), 178 (48), 179 (100), 180 (95), and 181 (6) for an average incorporation of 9.1 D, and NMR ($CDCl_3$) gave 3 signals δ: 7.34 (s, H_A), 7.10 (s, H_C), and 7.02 (s, H_B) in a ratio of 2:1:2.

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