Low-Water-Content Diazomethane-d_2 and Its Isotopic Assay

Paolo Strazzolini,* Angelo G. Giumanini, and Giancarlo Verardo

Department of Chemical Sciences and Technologies, University of Udine, I-33100 Udine, Italy

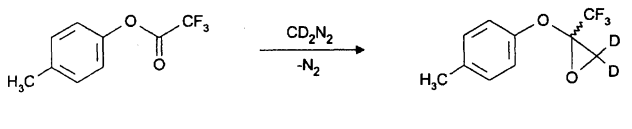
(Received April 24, 1996)

A multiple D_2O–CH_2N_2 exchange followed by a final anhydrification with K_2CO_3 gave an alcohol-free low-water-content ether solution of CD_2N_2. Procedural improvements for the exchange are reported. The extent of deuteration with a quantitative evaluation of the actual species present in any solution of diazomethane could be determined by a GC-MS analysis and ^{1}H NMR spectrometry on a suitable derivative. In addition, a procedure for the quantitative determination of water in diazomethane solutions has been developed.

Diazomethane (**1**, CH_2N_2) is a reagent with many applications and uses in both synthetic and analytic fields.[1] The present method of choice for preparing of sizable amounts of **1** is that involving Diazald®, producing a moist ethereal solution.[2] Ethanol is also employed in the normal protocol, and some alcohol ends up in the final CH_2N_2 solution; this occurrence may be avoided by using a nonvolatile substitute, such as 2-(2-ethoxyethoxy)ethanol. In a number of cases it is of interest to use a fully deuterated analog, **1**-d_2.[3] The use of CD_2N_2 involves a few problems ranging from its synthesis to an evaluation of the deuterium content, as well as conserving of its isotopic purity.[2] Some methods are used to introduce deuterium atoms before the formation of diazomethane, utilizing synthetic procedures other than the now more common one;[4,5] on the other hand, Diazald®-*N*-*methyl*-d_3, itself, was used as a deuterated precursor.[6] Alternatively, **1** was directly deuterated by exchange with D_2O, customarily using a base as a catalyst;[7] in one case of no preparative interest an acid catalyst was employed to effect the exchange.[8] It was not always easy to establish the actual enrichment and extent of recovered CD_2N_2 in the process from literature reports, either because of an unavailability of the relevant data, or uncertainties implied in the analytical methods.[7] The most detailed procedure is perhaps that reported in Organic Synthesis,[9] leading to a 98—99% deuterated diazomethane in 51—59% yield. In this case, the deuteration extent was laboriously determined and, perhaps, with some additional problems inherent in the mass–spectrometric analysis (based on the observation of a parent ion cluster) and ^{1}H NMR spectroscopy (based on the methyl vs. phenyl proton ratio) of the product of the reaction of diazomethane with *O*-deuterated benzoic acid. An alternative method involving isotope content analysis suggested the reaction of CD_2N_2 with I_2 to generate CD_2I_2, which was eventually analyzed by GC-MS (observation of the cluster of the $CH_nD_mI^+$ ions).[10] Our aim in the present work was to set up a simplified overall protocol for a rapid preparation of alcohol-free, low-water-content **1**-d_2 by exchange, as well as a reliable and simple determination of its isotope content.

Results and Discussion

To this end we equilibrated the alcohol-free ether solution of **1** a suitable number of times (Table 1) with D_2O containing K_2CO_3, the latter having the main function of depressing the losses of the substrate due to its partial solubility in an aqueous medium and possible reactions with it.[5] We observed, though, that NaCl gave practically the same final results as did K_2CO_3, being an indication that the protic reactivity may not be the more important problem. We could obtain ca. 0.13 M solutions (1 M=1 mol dm^{-3}) of **1**-d_2 with a deuterium content of 96%. The water content in these solutions (averaging 0.07 mol dm^{-3}) could be determined by the usual Karl–Fischer procedure,[11] with the proviso that **1**-d_2 had to be preliminary destroyed with anhydrous PhCOOH to avoid its reaction with I_2, interfering with the analysis. In order to monitor the *actual* deuteration extent of diazomethane and the distribution of deuterium, avoiding the interference of water, possibly present in the system, and/or handling of the (catalytically active) deuterated reagent, PhCOOD, itself amenable to a H/D exchange,[8] we used the methylenation



2 **3-d_2** (1)

Table 1. Extent of Deuteration of CH_2N_2 during the Exchange Process

Iteration[a)]	Total residual proton (%)
1	67
2	39
3	21
4	9
5	4

a) According to the procedure described in the Experimental Part.

reaction of an appropriate ester (**2**),[12] which yields a stable, non-exchanging derivative (**3**-d_2). The obtained product is thermally stable and can be analyzed by GC-MS without any danger of an H/D exchange in the ionization chamber (as indicated by the consistency of the results with the NMR determinations) and by ^{1}H NMR spectroscopy, where the evaluation of the deuteration extent was based on the integral values relative to the methyl and methylene groups of **3**-d_2. No interference from other signals in the range of interest, e.g. methyl absorptions of compound **2** or 4-methylphenol (**4**), was observed (Fig. 1).

Experimental

Caution! The handling of CH_2N_2 precursors and solutions requires particular safety precautions due to the many dangers involved in the operations.[1,13]

The CH_2N_2 (**1**) precursor, Diazald®, and the other chemicals,

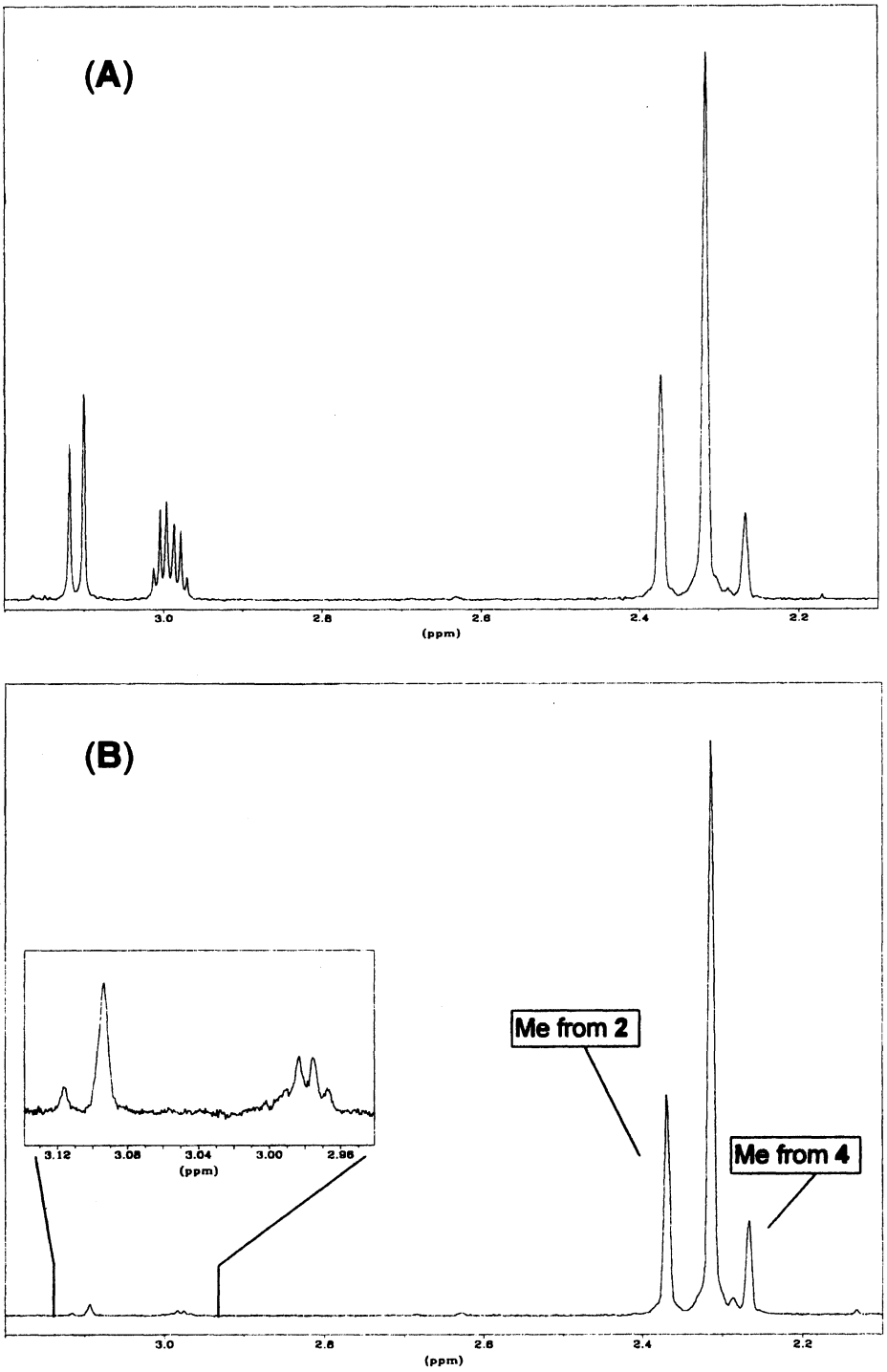


Fig. 1. Portion of the ^{1}H NMR spectrum relevant to the determination of the deuteration extent in **3**-d_2: (**A**) before the exchange process and (**B**) after the fifth exchange.

unless otherwise specified, were commercially available (Aldrich, Milano-I) and used as received. The D_2O employed was 99.9% deuterated. Anhydrous K_2CO_3 was activated by keeping it in a vacuo at 200 °C for 4 h. Alcohol-free ethereal solutions of **1**, prepared according to a described procedure,[2] averaged 0.3 M with a H_2O content of approximately 0.16 mol dm^{-3}. Titration of **1** and **1-*d*$_2$** was performed according to a well-established method.[9] The water content in diazomethane solutions was determined as described below by a modified Karl–Fischer method using the Metrohm Model 684 KF Coulometer. The reported boiling points refer to central cuts of small-scale distillations, and are uncorrected. The IR spectra were recorded on a Nicolet FTIR Magna 550 spectrophotometer using the KBr technique. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Bruker AC-200 spectrometer at 200, 50 and 188 MHz, respectively. The ptoton chemical shifts are reported in ppm on the δ scale relative to TMS as an internal reference (0.00); the carbon chemical shifts are reported in ppm relative to the center line of the $CDCl_3$ triplet (77.00); the fluorine chemical shifts are reported in ppm, and are referenced to CF_3COOH (0.00) as an external standard. The coupling constants are given in Hz. The abbreviation qn is used for quintet. GC-MS analyses were carried out with a Fisons TRIO-2000 apparatus, working in the positive-ion electron impact (70 eV) mode, equipped with a fused-silica capillary column (Supelco SE 54®, 30 m, 0.32 mm i.d., 0.25 μm phase film); operative conditions: inj. temp 250 °C, temp prog. from 60 to 250 °C, heating rate 10 °C min^{-1}. None of the deuterated samples exhibited scrambling during the analyses. Five most intense MS peaks, with bracketed intensity values, are reported. The deuterium contents determined by the two methods coincided to the unit figures.

Water Content Determination in Diazomethane Solutions. Ethereal diazomethane (1.0 mL) was treated with a solution (1.0 mL) prepared by dissolving anhydrous benzoic acid (1.22 g, 10 mmol) into dry Et_2O (10.0 mL); the obtained mixture was introduced as such into the Karl–Fisher apparatus, and the determined water content was subsequently corrected by subtracting the corresponding value measured for the benzoic acid solution alone.

Exchange of 1 with D_2O. A typical preparation involved Diazald® (12 g, 56 mmol) dissolved into Et_2O (160 mL) and treated with a solution of KOH (4 g, 85%, 60 mmol) in 2-(2-ethoxyethoxy)ethanol (80 mL). Distillation yielded some 120 mL of ca. 0.3 M ethereal solution of **1** (65% yield), containing 0.16 mol dm^{-3} of H_2O. This solution was introduced into a rubber stoppered Erlenmeyer flask and equilibrated at 0 °C, under very vigorous magnetic stirring and moisture protection, five times during 30 min with 5 mL portions of a 5% solution of NaCl (or K_2CO_3) in D_2O. The extent of the exchange could be monitored at any time by the method described below. After the final exchange the solution was dried twice on K_2CO_3 (10 g each, 10 min, occasional shaking); the decanted clear solution (ca. 110 mL) was 0.14 M in **1-*d*$_2$** (43% yield) and 0.07 M in D_2O.

Determination of Deuterium Content in CD_2N_2. The CD_2N_2 solution (5 mL) was treated with the ester **2** (20 mg, 0.1 mmol); after standing for 30 min at room temperature, the solvent was evaporated off under a vacuum, and the colorless oily residue was dissolved in $CDCl_3$ (0.5 mL) and analyzed by ^{1}H NMR. The same solution was analyzed by GC-MS, where the peak for **3-*d*$_2$** stood out well separated from both **2** and **4**. The obtained CD_2N_2 was found to be 96% enriched in deuterium by both methods.

4-Methylphenyl Trifluoroacetate (2). Compound **2** was prepared in a nearly quantitative yield from 4-methylphenol (**4**, 6.5 g, 60 mmol) and trifluoroacetic anhydride (10 mL, 70 mmol) in dry Et_2O (30 mL) during 1 h at 0 °C under an inert atmosphere; bp 68 °C at 2400 Pa (lit,[14] 88.5 °C at 5333 Pa); ν_{max}/cm^{-1} (KBr, neat) 3040w, 2985w, 2931w, 1800s, 1601w, 1509s, 1457w, 1384w, 1359s, 1231s, 1189s, 1167vs, 1128s, 1020m, 939w, 882m, 841w, 806m, 762m, 721m, 696w, 515m and 486w; ^{1}H NMR δ_H=2.36 (3H, *pseudo*-s, Me), 7.07 (2H, m, H_{arom}), 7.22 (2H, m, H_{arom}); ^{13}C NMR δ_C=20.80, 114.64 (q, J_{C-F}=285.7 Hz, CF_3), 120.14, 130.33, 137.24, 147.20, 156.05 (q, J_{C-F} 43.1 Hz, C=O); ^{19}F NMR δ_F=2.84;[15] MS *m/z* (El, 70 eV) 204 (M^+; 100%), 77(74), 107(66), 79(46), 90(44).[16]

2-(Trifluoromethyl)-2-(4-methylphenoxy)oxirane (3). This compound was obtained by the general procedure described for the preparation of alkoxyoxiranes[12] keeping the reaction mixture at room temperature during 3 h; 71% separated yield; bp 56 °C at 533 Pa; ν_{max}/cm^{-1} (KBr, neat) 3016w, 2929w, 2872w, 1611w, 1593w, 1508s, 1414m, 1325s, 1221vs, 1181vs, 1152w, 1115s, 1019m, 1001m, 936w, 916m, 851m, 835w, 820m, 766w, 724w and 502m; ^{1}H NMR δ_H=2.30 (3H, *pseudo*-s, Me), 2.97 [1H, dq, J_{gem}=3.7 Hz, J_{H-F}=1.6 Hz, $(CF_3-C-C-H)_{trans}$,], 3.08 [1H, d, J_{gem}=3.7 Hz, $(CF_3-C-C-H)_{cis}$,], 6.95 (2H, m, H_{arom}), 7.10 (2H, m, H_{arom}); ^{13}C NMR δ_C=20.62, 48.17 (q, J_{C-F}=1.5 Hz), 81.24 (q, J_{C-F}=41.2 Hz), 120.70, 121.06 (q, J_{C-F}=279.1 Hz, CF_3), 130.12, 135.04, 150.24; ^{19}F NMR δ_F=−0.71; MS *m/z* (El, 70 eV) 91 (100%), 77(87), 218(M^+; 65), 65(50), 79(48).

2-(Trifluoromethyl)-2-(4-methylphenoxy)oxirane-*d*$_2$ (3-*d*$_2$). Compound **3-*d*$_2$** was obtained as described for its protic counterpart using CD_2N_2; bp 67 °C at 1067 Pa; ν_{max}/cm^{-1} (KBr, neat) 3036w, 2927w, 2202w (ν_{C-D}), 1611w, 1594w, 1508s, 1424m, 1331s, 1220s, 1180vs, 1111s, 1050s, 1004m, 905m, 818m, 767w, 747m, 721w, 595w and 488m; ^{1}H NMR δ_H=2.31 (3H, *pseudo*-s, Me), 6.96 (2H, m, H_{arom}), 7.11 (2H, m, H_{arom}); ^{13}C NMR δ_C=20.61, 48.17 (qnq, J_{C-D}=13.6 Hz, J_{C-F}=1.2 Hz, CD_2), 81.13 (q, J_{C-F}=41.2 Hz), 120.66, 121.03 (q, J_{C-F}=279.1 Hz, CF_3), 130.11, 135.03, 150.23; ^{19}F NMR δ_F=−0.67; MS *m/z* (El, 70 eV) 91 (100%), 220 (M^+; 92), 107(89), 77(69), 79(47).

This work was supported in part by grands to AGG (CNR 92.00391CT03, 93.03024CT03) and to PS (MURST 1991-93, 40%). We thank Mr. P. Polese for skillful assistance.

References

1) T. H. Black, *Aldrichimica Acta*, **16**, 3 (1983).

2) J. R. Campbell, *Chem. Ind.*, **1972**, 540. See also: "Technical Information Bulletin Number AL-180," Aldrich, (1989).

3) B. L. Crawford, Jr., and W. H. Fletcher, *J. Chem. Phys.*, **19**, 406 (1951).

4) a) D. E. Milligan and M. E. Jacox, *J. Chem. Phys.*, **36**, 2911 (1962); b) W. Grimme and W. von Eggers Doering, *Chem. Ber.*, **106**, 1765 (1973); c) J. S. Swenton, K. A. Burdett, D. N. Madigan, T. Johnson, and P. D. Rosso, *J. Am. Chem. Soc.*, **97**, 3428 (1975); d) S. P. Markey and G. J. Shaw, *J. Org. Chem.*, **43**, 3414 (1978); e) G. A. Olah, H. Doggweiler, and J. Felberg, *J. Org. Chem.*, **49**, 2116 (1984); f) G. K. Surya Prakash, R. W. Ellis, J. D. Felberg, and G. A. Olah, *J. Am. Chem. Soc.*, **108**, 1341 (1986).

5) a) S. P. McManus, J. T. Carroll, and C. L. Dodson, *J. Org. Chem.*, **33**, 4272 (1968); b) S. M. Hecht and J. W. Kozarich, *Tetrahedron Lett.*, **1972**, 1501.

6) a) H. Dahn, A. Donzel, A. Merbach, and H. Gold, *Helv. Chim. Acta*, **46**, 994 (1963); b) C. B. Moore and G. C. Pimentel, *J. Chem. Phys.*, **40**, 329 (1964); c) W. C. Mahone, W. Kolln, and J. W. Simons, *J. Chem. Phys.*, **89**, 3902 (1985).

7) a) L. C. Leitch, P. E. Gagnon, and A. Cambron, *Can. J. Res., Sect. B*, **28**, 256 (1950); b) W. B. DeMore, H. O. Pritchard, and N. Davidson, *J. Am. Chem. Soc.*, **81**, 5874 (1959); c) G. W. Robinson and M. McCarty, Jr., *J. Am. Chem. Soc.*, **82**, 1859 (1960); d) S. Damtoft, S. R. Jensen, and B. J. Nielsen, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1943.

8) K. J. Van der Merve, P. S. Steyn, and S. H. Eggers, *Tetrahedron Lett.*, **1964**, 3923.

9) P. G. Gassman and W. J. Greenlee, *Org. Synth.*, **53**, 38 (1973).

10) W. Von Eggers Doering and W. J. Ehlhardt, *J. Am. Chem. Soc.*, **109**, 2697 (1987).

11) a) A. Cassol, P. Di Bernardo, R. Portanova, M. Tolazzi, G. Tomat, and P. Zanonato, *Inorg. Chem.*, **29**, 1079 (1990); b) R. Karlsson and K. J. Karrmann, *Talanta*, **18**, 459 (1971); *Chem. Abstr.*, **75**, 29686n (1971).

12) P. Strazzolini, G. Verardo, and A. G. Giumanini, *J. Org. Chem.*, **53**, 3321 (1988).

13) "Reagents for Organic Synthesis," ed by L. F. Fieser and M. Fieser, John Wiley & Sons, London (1967), Vol. 1, p. 191.

14) A. Moffat and H. Hunt, *J. Am. Chem. Soc.*, **81**, 2082 (1959).

15) P. Sleevi, T. E. Glass, and H. C. Dorn, *Anal. Chem.*, **51**, 1931 (1979).

16) M. J. Saxby, *Org. Mass. Spectrom.*, **4**, 133 (1970).