Observation of Methyl H–D Exchange for $CH_3(CH_2)_3N^+H_2D$ in $DFSO_3$–SbF_5[1a]

Summary: H–D exchange has been observed in superacid media at room temperature for $CH_3(CH_2)_3$–N^+H_2D ion at the methyl group; it was monitored by ^1H NMR.

Sir: Activation of C–H and C–C bonds by protolysis in superacid media has been elegantly demonstrated by Olah and co-workers.[1b] Thus, hydrogen–deuterium exchange must be considered a typical electrophilic substitution at saturated carbon.[2] In line with theoretical calculations and IR studies,[3] H–D exchange of molecular hydrogen with deuterium under pressure in deuterated superacid solvents helped establish the involvement of a trigonal isotopic H_3^+.[4] Gold and co-workers[5] were able to observe directly all three possible H–D exchange species (H_3O^+, H_2DO^+, and HD_2O^+) by NMR, using H_2O as base in deuterated magic acid. In relation to our detailed studies of the acidity of superacid media and basicity of weak bases by DNMR,[6,7] we now report preliminary results of a study of H–D exchange in several long-chain aliphatic amines in $DFSO_3$ containing various amounts of SbF_5.

Deuteration of *n*-propylamine with a threefold excess of $DFSO_3$–SbF_5 (58.3%) in SO_2 followed by slow evaporation of solvent under a stream of dry nitrogen gave a colorless solution of the ion C_2H_5–CH_2–N^+H_2D (**1**) at room temperature. The ^1H NMR signals were monitored over a period of three weeks (C_2H_5/NH_2D^+, C_2H_5/CH_2, and $C_2H_5/CH_2{}^+NH_2D^+$ integral ratios were measured), no noticeable change was observed and no side reactions detected.

Deuteration of *n*-butylamine with the same superacid system and under identical conditions similarly gave a clean colorless solution of the ion C_3H_7–CH_2–N^+H_2D (**2**) which was stable at room temperature after removal of SO_2. In contrast to the behavior of ion **1**, H–D exchange of the methyl protons was observed for **2** with simultaneous formation of the protio-superacid. A plot of the variation in the C_3H_7/NH_2D^+ integral ratio vs. time (Figure 1, curve I) indicates that H–D exchange is initially fast (qualitatively) but gradually slows down over a period of 2 weeks. In order to account for any side reactions which might have occurred resulting in proton removal from the side chain, in control experiments *n*-butylamine was protonated in light acid and the integral ratios were monitored and plotted against time (Figure 1, curve II). Subtration of the curves I and II resulted in curve III which is indicative of the magnitude of H–D exchange in the absence of any side reactions.

In control experiments we found that H–D exchange is taking place in ion **2** even when the acidity (H_0 function) of the superacid solutions is considerably reduced from $DFSO_3$–SbF_5 (58.3%) down to $DFSO_3$–SbF_5 (22%).[6] In neat $DFSO_3$, however, exchange was very slow. With superacid solutions containing more than 63% SbF_5 slow

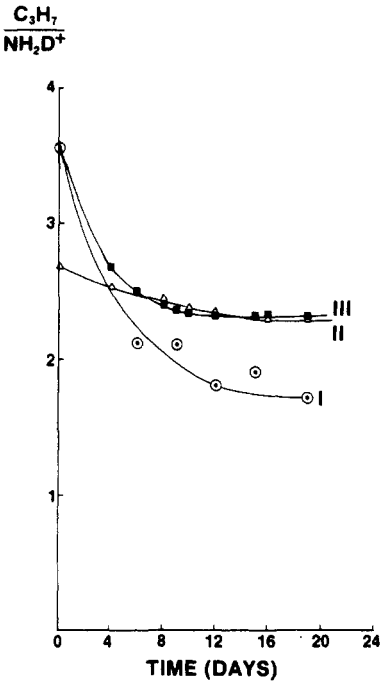

Figure 1.

decomposition and darkening of the samples was observed.

Whereas a colorless solution of CH_3–$(CH_2)_4N^+H_2D$ (**3**) was obtained by deuteration of *n*-pentylamine with $DFSO_3$–SbF_5 (1:1), the ion slowly polymerized at room temperature. Deuteration of *n*-octylamine similarly yielded the ion $CH_3(CH_2)_6$–N^+H_2D (**4**) at low temperature, but the ion polymerized immediately at room temperature.

Considering the mechanism, it is expected that exchange at C_4 should be faster than at other carbons. The substitution mechanism which goes through a five-coordinated carbon, involves a doubly charged cation as an intermediate or a nearly doubly charged transition state in which charge–charge repulsion will diminish with distance. Olah and co-workers found that aliphatic carbodications can be generated in superacid media when the carbocation centers are separated by at least two carbon atoms.[8] This infers that even though methyl H–D exchange for ion **2** is too slow to be measurable at room temperature, it should be detectable under forcing conditions or at higher acidities (DF–SbF_5). We plan to test this argument.

The initial concentration of the acid is given by eq 1. Since the molar ratio of acid to base is 3:1 and the formation of ion **2** is complete, this equation can be transformed into eq 2.

$$[DFSO_3]_{initial} = [DFSO_3]_{stoich} - [amine]_{stoich} \quad (1)$$

$$[DFSO_3]_{initial} = \tfrac{2}{3}\,[DFSO_3]_{stoich} \quad (2)$$

Equation 3 represents the ratio of deuterated and light acid after the exchange, and eq 4 shows the total exchangeable hydrogens (H + D) in the system.

$$\frac{\text{D in acid}}{\text{H + D in acid}} = \frac{\text{D in methyl}}{\text{H + D in methyl}} \quad (3)$$

$$[DFSO_3]_{initial} + 3\,[CH_3] = \tfrac{2}{3}[DFSO_3]_{stoich} + 3(\tfrac{1}{3})$$
$$[DFSO_3]_{stoich} = \tfrac{5}{3}[DFSO_3]_{stoich} \quad (4)$$

On this pool of H + D, H is provided only by the methyl group and D is supplied by $DFSO_3$ initial. Thus the final

(1) (a) Presented at the 18th Central Regional Meeting of the American Chemical Society, Bowling Green, OH, June 1986. (b) For a detailed discussion, see: Olah, G. A.; Surya Prakask, G. K.; Sommer, J. *Superacids*; Wiley-Interscience: New York, 1985; Chapter 5.
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H/H + D ratio in every species of the exchanging system can be given by eq 5.

$$\frac{3[CH_3]_{stoich}}{5/3[DFSO_3]_{stoich}} = \frac{[DFSO_3]_{stoich}}{5/3[DFSO_3]_{stoich}} = 3/5 \qquad (5)$$

Accordingly, the final average number of hydrogens in C_3H_7 should be $4 + 3^3/_5 = 5.8$ and the final C_3H_7/NH_2 ratio: $5.8/2 = 2.9$. However, the experimentally observed C_3H_7/NH_2 integral ratio falls below this limit (2.3), suggesting that additional processes must be operative which remove C_3H_7.

We are currently exploring these exchange phenomena in more detail by ^2D and ^{13}C NMR.

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Registry No. 1, 102283-88-5; 2, 102283-89-6; 3, 102283-90-9; 4, 102283-91-0; *n*-propylamine, 107-10-8; *n*-butylamine, 109-73-9; *n*-pentylamine, 110-58-7; *n*-octylamine, 111-86-4; hydrogen, 1333-74-0.

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[2 + 2] Cycloaddition of Sulfonyl and Acyl Isocyanates to Glycals

Summary: [2 + 2] Cycloaddition of sulfonyl and acyl isocyanates **1–3** to glycals **4–8** proceeds stereospecifically to afford the β-lactam ring anti with respect to the C-3 substituent. Unblocking of the electron-withdrawing N-substituent produces the relatively stable β-lactams.

Sir: [2 + 2] cycloaddition of active isocyanates to 3,4-dihydro-2*H*-pyran derivatives has already been attempted several times,[1-5] but in only a few cases were the corresponding β-lactams obtained.[1,2,5] Simple derivatives of 3,4-dihydro-2*H*-pyran afforded open-chain α,β-unsaturated amides,[1-5] whereas tri-*O*-acetyl-D-glucal was found to be unreactive.[6] It can be assumed that the nature of substituents attached to the dihydropyran ring determines the equilibrium state of this reversible cycloaddition,[7-9] which in the case of acetylated glycals under normal pressure is entirely shifted toward substrates.[6] Application of 10 kbar pressure, however, resulted in cycloaddition of tosyl and trichloroacetyl isocyanate (**1** and **3**) to acetylated glycals and led to the formation of unstable β-lactams.[7-9]

Assuming that thermodynamics controls product formation in these reactions, we chose to investigate the cycloaddition of isocyanates **1–3** to glycals **4–8** having nonpolar blocking groups, under normal pressure. The reactions were performed in absolute $CDCl_3$ at room temperature and were monitored by ^1H NMR spectroscopy.[10]

Cycloaddition of **1** and **2** (3 molar equiv) to glycals **4–8** (1 equiv) proceeds regio- and stereospecifically with formation of the β-lactam ring anti to the C-3 substituent (Scheme I). Tosyl isocyanate (**1**) gives the respective β-lactams **9** after 6–40 h in 75–90% yield (Table I). The isocyanate **2** is more reactive under the same conditions. Cycloaddition to all glycals **4–8** is completed in about 2 h, affording **9**; thereafter slow decomposition of product is observed. After 20 h substantial amounts (10–60%) of the respective α,β-unsaturated amide **10** is detected.

Trichloroacetyl isocyanate (**3**) reacts with **4–8** more slowly than sulfonyl isocyanates **1** and **2**. Reactions are completed in about 50 h to produce [2 + 2] cycloadducts **9**, [4 + 2] **11**, and the open-chain amide **10**. In agreement with our earlier findings, **3** adds anti to the C-3 substituent to give cis-fused bicyclic systems **9** and **11**. The proportion of products **9**:**10**:**11** depends on the reaction time and glycal used. For example, **5** affords after 6 h about 12% of **9a** and 18% of **11a**, whereas after 50 h **9a** becomes the main component (50%) of the mixture and is accompanied by 32% of **10a** and 18% of **11a**. On the other hand, glycals **7** and **8** furnish [4 + 2] cycloadducts **11b** which are more stable than the β-lactams **9b** (Table I).

Our experiments clearly point to low stability of cycloadducts **9**. This is certainly caused by an electron-withdrawing group attached to the nitrogen atom. Therefore N-deprotection is necessary before isolation or chemical transformation of **9** are undertaken. Until now attempts to split the sulfonyl substituent without decomposition of the β-lactam ring in **9** were unsuccessful. In case of the trichloroacetyl protecting group, analogously to the trifluoroacetyl group,[4] addition of benzylamine to the reaction mixture leads to removal of the N-protection to afford stable bicyclic β-lactams. Compounds **12**, **13**, and **14** were isolated from respective post-reaction mixtures by silica gel chromatography in 30%, 50%, and 40% yield, respectively. Further deprotection with the hydrogen fluoride–pyridine 1:1 complex in THF affords crystalline, stable, water-soluble β-lactams **15** and **16**.[11]

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(10) The compounds **9** and **11** were characterized by chemical shifts and coupling constants for protons H-1 and H-2, whereas the amides **10** were characterized by chemical shifts of H-1 proton. For example, adducts derived from **3** and **4**: **9a** [6.02 (d, 1 H, J_{12} = 5.5 Hz, H-1), 3.47 (dd, 1 H, J_{23} = 3.0 Hz, H-2)] and **11a** [6.15 (d, 1 H, J_{12} = 3.7 Hz, H-1), 2.94 (dd, 1 H, J_{23} = 9.0 Hz, H-2)]; adducts derived from **2** and **4**: **9a** [5.95 (d, 1 H, J_{12} = 5.6 Hz, H-1), 3.40 (dd, 1 H, J_{23} = 3.2 Hz, H-2)] and **10a** [7.60 (s, 1 H, H-1)]. The composition of the reaction mixture was determined by the integration of the respective signals.

(11) **12**: mp 50–54 °C; $[\alpha]_D$ +61.5° (*c* 1, CH_2Cl_2); IR (film) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) 5.30 (d, 1 H, J_{12} = 4.6 Hz, H-1), 3.08 (dt, 1 H, $|J_{12} + J_{23}|$ = 6.0 Hz, H-2). **13**: mp 74–76 °C; $[\alpha]_D$ −5.7° (*c* 1, CH_2Cl_2); IR ($CHCl_3$) 3410, 1775 cm^{-1}; ^1H NMR (CCl_4) 5.40 (d, 1 H, J_{12} = 4.6 Hz, H-1), 3.15 (m, 1 H, H-2). **14**: mp 53–57 °C; $[\alpha]_D$ −53.5° (*c* 1, CH_2Cl_2); IR ($CHCl_3$) 3410, 1775 cm^{-1}; ^1H NMR (CCl_4) 5.30 (d, 1 H, J_{12} = 4.3 Hz, H-1), 3.12 (m, 1 H, H-2). **15**: mp 179–180 °C; $[\alpha]_D$ +65.4° (*c* 1, H_2O); IR (Nujol) 3320, 1715 cm^{-1}; ^1H NMR (Me_2SO-d_6) 5.50 (d, 1 H, J_{12} = 4.0 Hz, H-1), 3.20 (m, 1 H, H-2). **16**: mp 170–171 °C; $[\alpha]_D$ −112.4° (*c* 1, H_2O); IR (Nujol) 3380, 3240, 1750 cm^{-1}; ^1H NMR (Me_2SO-d_6) 5.28 (d, 1 H, J_{12} = 4.2 Hz, H-1), 3.13 (t, 1 H, H-2).

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