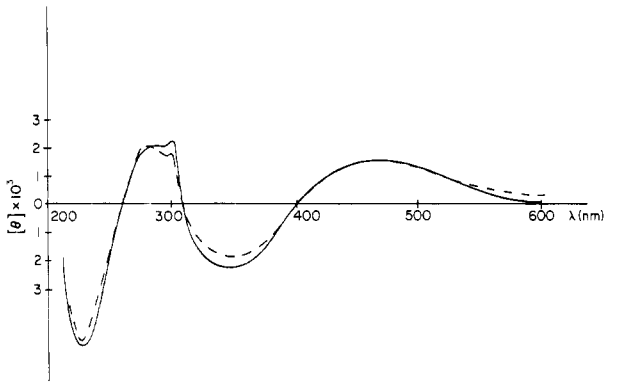

Figure 1.

metric centers since it can be converted into mitomycin C. Furthermore, their results obviate the need to postulate the occurrance of an inversion of the configuration of C_2 of D-glucosamine during the biosynthesis of mitomycins A and C. However, the Shirahata–Hirayama results generate uncertainty concerning the stereochemical relationships during the biosynthesis of mitomycin B since mitomycin B differs in its relative configuration from mitomycins A and C and since it was not certain from the X-ray studies whether this difference is manifest at one or at three chiral centers.

We sought to clarify the stereochemical relationship between mitomycin A and B by converting both compounds into the common optically active relay compound 7-methoxy-1,2-(*N*-methylaziridino)mitosene (III) following known procedures[13] and by comparing the optical properties of the two specimens by circular dichroism studies. A mixture of mitomycin A (20 mg, 57.4 μmol), dry acetone (2 mL), methyl iodide (1 mL), and anhydrous K_2CO_3 (83 mg, 600 μmol) was refluxed for 4 h to afford *N*-methylmitomycin A (Ib) in excellent yield. The reaction product was purified by column chromatography on silica gel (Merck, washed with NaH_2PO_4–Na_2HPO_4, 0.2 M, pH 7.0 buffer) using the system hexane/ethyl acetate/isopropyl alcohol (2:2:3) for elution. The identity of the product was proven by its facile conversion into porfiromycin (Id) by treatment with 3% ammonia. Subsequently, Ib (10 mg, 27.5 μmol), PtO_2 (1.25 mg), and ethyl acetate (3 mL) were treated with bubbling hydrogen gas for 15 min which yielded a yellow solution. N_2 was then bubbled through this solution for 5 min followed by O_2 which caused the appearance of the orange color of III. The reaction mixture was subjected to column chromatography in the system mentioned above, and the main compound isolated was recrystallized from acetone/hexane. This afforded III (3.8 mg) in 42% yield. The IR spectrum of this material showed the same absorptions as those reported for III by Patrick et al.[13] The CD spectrum of this specimen (1 mg, 3 μmol) dissolved in methanol (3 mL) and water (1 mL) was recorded on a Cary 60 spectropolarimeter equipped with a CD attachment. The resulting spectrum is presented in Figure 1 as a solid line. Mitomycin B (10 mg, 2.87 μmol) was converted directly into III by catalytic reduction and was isolated by column chromatography as described above. III (2.9 mg) was obtained in 30% yield. The IR spectrum of this material also showed exactly the same absorptions as reported for III by Patrick et al.[13] This specimen (1 mg, 3 μmol) was dissolved in methanol (3 mL) and water (1 mL), and its CD spectrum was recorded. The spectrum is shown in Figure 1 as a dotted line.

It is apparent from Figure 1 that both specimens of III have essentially superimposable CD spectra. The only chiral centers present in III are at C_1 and C_2 which must therefore have the same chiralty in both mitomycins A and B. It can be concluded that the fate of the chiral center at C_2 of D-glucosamine is the same for all mitomycins during their biosynthesis. Furthermore, it follows that mitomycin B differs stereochemically from mitomycins A and C only at C_9. Similar results, which have not been published, were obtained by W. A. Remers and J. S. Webb and their co-workers.

Acknowledgment. We gratefully acknowledge receipt of samples of mitomycins A and B from Dr. S. Wakaki, Kyowa Hakko Kogyo, Tokyo, Japan, of mitomycin C from Dr. W. Bradner, Bristol Laboratories, Syracuse, NY, of profiromycin from Dr. G. B. Whitfield, Upjohn Company, Kalamzoo, MI, of information by Dr. Remers on his results, and of financial support by Grant CA14378 from the National Cancer Institute.

Registry No. Ia, 4055-39-4; Ib, 18209-14-8; Id, 801-52-5; II, 4055-40-7; III, 15973-07-6.

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New S-Protection from Known N-Protection: Thio Esters of *N*-Urethanyl-*N*-methyl-γ-aminobutyric Acid as a Class of Protective Groups for Thiols in Peptide Synthesis

Nicholas G. Galakatos* and D. S. Kemp

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received July 17, 1984

For the last few years we have been engaged in the development of a novel methodology for peptide synthesis which relies heavily on the chemistry of thiols and unsymmetrical disulfides.[1] A major concern in this work has been the problem of temporary protection of reactive arene and cysteine thiol intermediates generated by the chain elongation and acyl-transfer processes, respectively. Since most of the existing S-blocking functions require for removal either harsh condtions (e.g., HF, Hg(II), Na/NH_3) or reagents (e.g., phosphines) which are incompatible with our synthetic scheme,[2] we sought to advance new methodology. In 1973 Geiger reported a stragety in which S-deprotection is triggered by the liberation of a neighboring N-blocked amine.[3] Although promising, this tactic does not meet all of our requirements and has been cited only in reviews[2,4] without experimental details. Consequently, we describe in full a form of thiol protection, similar to Geiger's, that offers versatility and requires exceptionally mild deblocking conditions.

Saponification of *N*-methylpyrrolidone-generated zwitterion 1 (58%)[5] which was functionalized at its N-terminus

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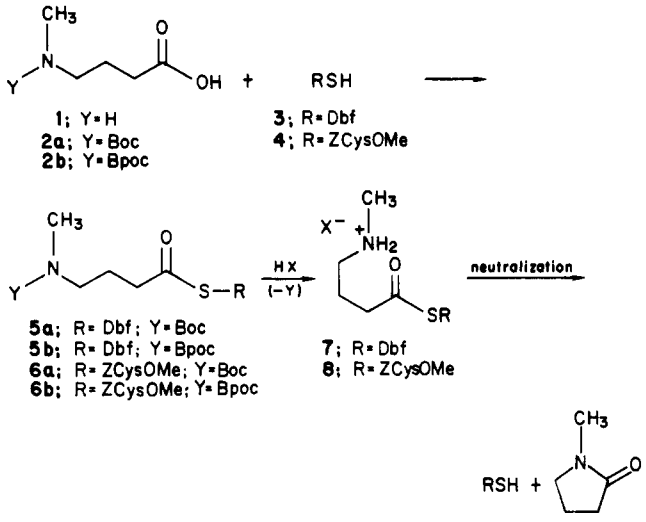
to afford *tert*-butyloxycarbonyl (Boc)[6] or [(biphenylyl)-isopropyloxy]carbonyl (Bpoc)[7] derivatives **2a** (91%) or **2b** (DCHA salt; 82%) as stable crystalline solids. Efforts to



prepare thio ester **5** by dicyclohexylcarbodiimide and active ester methods[8,9] produced unsatisfactory results.[10] However, when 4-mercaptodibenzofuran (**3**) was treated with the symmetrical anhydride of **2a** or **2b**, the respective thio esters were obtained quantitatively in less than 0.5 h. For **5a** similar efficiency was observed by the mixed anhydride method.[11] With the procedure for **5**, cysteine derivatives **6a** and **6b** were prepared from **4** in high yields.[12]

Deprotection conditions for thio ester **5** were selected according to the nature of function Y. Thus, **5a** was converted to **7** by treatment with either HCl–dioxane or neat CF_3CO_2H–anisole, whereas **5b** required only 1.5% CF_3CO_2H–anisole to afford the same species.[13] Both transformations were quantitative, and, after evaporation of excess acid, **7** was neutralized with either triethylamine or $NaHCO_3$ in aqueous methanol. The intramolecular aminolysis of the thio ester appeared to be complete (^1H NMR) within 4 min at 25 °C and the liberated thiol **3** was isolated in high yields (**5a** to **3**, 95%; **5b** to **3**, 92%). Similar results were obtained with the deblocking of cysteine thio esters **6**, although longer reaction times were required (10 min) for the cyclization step and the product was isolated as the cystine derivative.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 283B spectrometer. ^1H NMR spectra were recorded on a Bruker WM-270 instrument, chemical shifts (δ) are reported in ppm downfield from Me_4Si, and splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad). Field-desorption mass spectra were courtesy of Dr. C. E. Costello (MIT) and were obtained on a Finnigan MAT-731 spectrometer. Microanalyses were performed by Galbraith Laboratories.

Di-*tert*-butyl dicarbonate (Boc_2O) was purchased from Fluka and benzyltrimethylammonium methoxide (40% in MeOH) from Sigma; 2-*p*-biphenylyl-2-propyl phenyl carbonate,[14] 4-mercaptodibenzofuran,[15] and N^{α}-(benzyloxycarbonyl)-L-cysteine methyl ester (ZCysOMe)[16] were prepared according to literature procedures. *N*-methylpyrrolidone (NMP) and dicyclohexylcarbodiimide (DCC) were distilled under reduced pressure and stored at 4 °C. Preparative layer chromatography was performed on Analtech GF 1000-μm plates with $CHCl_3$–EtOAc (9:1) as eluent.

***N*-Methyl-γ-aminobutyric Acid (1).** To NMP (5.00 mL, 51.75 mmol) in water (55 mL) was added barium hydroxide octahydrate (11.40 g, 31.61 mmol). The heterogenous mixture was heated to 110 °C for 3 h and then cooled to 0 °C and saturated with CO_2 gas. The resulting white precipitate was collected by filtration and washed with ice-cold water. The clear filtrates were evaporated to dryness and the resulting moist solid residue (5.09 g) was triturated with CH_3CN, filtered, washed with Et_2O, and dried over P_2O_5 in vacuo to afford **1** as white crystals (3.48 g, 58%); mp 151.5–153.0 °C (lit.[5] mp 146 °C; ^1H NMR (CD_3OD) δ 1.81–1.92 (2 H, m, β-CH_2), 2.34 (2 H, t, J = 7 Hz, α-CH_2), 2.66 (3 H, s, NCH_3), 3.01 (2 H, t, J = 7 Hz, γ-CH_2).

***N*-(*tert*-Butyloxycarbonyl)-*N*-methyl-γ-aminobutyric Acid (2a).** A suspension of **1** (558 mg, 4.76 mmol) and anhydrous K_2CO_3 (1.32 g, 9.56 mmol) in dioxane–water (2:1, 15 mL) was cooled to 0 °C and Boc_2O (1.14 g, 5.23 mmol) was added in one portion. The heterogeneous mixture was allowed to warm up to room temperature (1.5 h) and then the dioxane was removed in vacuo. The residual suspension was diluted with water, washed with EtOAc, cooled to 0 °C, and acidified to pH 3 with 5% $KHSO_4$. The product was extracted into EtOAc, and the organic layers were washed with H_2O, dried ($MgSO_4$), and evaporated to give an oil that solidified upon seeding (940 mg, 91%). Recrystallization (hexane) yielded **2a** as white needles (882 mg, 85%); mp 60.5–61.5 °C; IR ($CHCl_3$) ν_{max} 2962, 1705, 1681, 1392, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (9 H, s, Boc), 1.80–1.90 (2 H, m, β-CH_2), 2.37 (2 H, t, J = 7 Hz, α-CH_2), 2,85 (3 H, s, NCH_3), 3.28 (2 H, t, J = 6 Hz, γ-CH_2).

Anal. Calcd for $C_{10}H_{19}O_4N$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.45; H, 8.67; N, 6.49.

***N*-[[(*p*-Biphenylyl)isopropyloxy]carbonyl]-*N*-methyl-γ-aminobutyric Acid (2b).** A suspension of **1** (2.23 g, 19.04 mmol) in MeOH (17 mL) containing benzyltrimethylammonium methoxide (19.61 mmol) was stirred at 25 °C for 10 min and then the solvent was removed. To the resulting yellow oil was added 2-*p*-biphenylyl-2-propyl phenyl carbonate (6.32 g, 19.03 mmol) in DMF (50 mL) and the mixture was heated to 50 °C for 2.5 h. It was then cooled to 0 °C, diluted with water, washed with Et_2O, and acidified to pH 3.5 with 0.5 M citric acid at 0 °C. The product was extracted into Et_2O, and the organic phase was washed with water, and brine and dried ($MgSO_4$). The solvent was evaporated and the residues azeotroped with CH_3CN to afford **2b** as a clear oil (5.57 g, 82%). DCHA salt, white-solid (7.86 g, 98%), mp 123.5–125.0 °C. For **2b**: ^1H NMR ($CDCl_3$) δ 1.81 (6 H, s, Bpoc *i*-Pr), 1.78–1.83 (1 H, m, β-CH_2), 1.87–1.92 (1 H, m, β-CH_2), 2.27 (1 H, t, J = 7 Hz, α-CH_2), 2.43 (1 H, t, J = 7 Hz, α-CH_2), 2.83 (1.5 H, s, NCH_3), 2.99 (1.5 H, s, NCH_3), 3.26 (1 H, t, J = 8 Hz, γ-CH_2), 3.41 (1 H, t, J = 8 Hz, γ-CH_2), 7.32 (1 H, t, J = 7 Hz), 7.35–7.45 (4 H, m), 7.54–7.60 (4 H, m). For **2b** DHCA salt: ^1H NMR ($CDCl_3$) δ 1.12–1.42 (10 H, m, DCHA), 1.61–1.69 (2 H, m), 1.74–1.80 (6 H, m), 1.81 (6 H, s), 1.94–2.01 (6 H, m), 2.18 (1 H, t, J = 7 Hz, α-CH_2), 2.26 (1 H, t, J = 7 Hz, α-CH_2), 2.84 (1.5 H, s, NCH_3), 3.00 (1.5 H, s, NCH_3), 3.22 (1 H, t, J = 8 Hz, γ-CH_2), 3.39 (1 H, t, = 8 Hz, γ-CH_2), 5.02 (2 H, bs, ammonium ion), 7.34–7.49 (5 H, m), 7.53–7.59 (4 H, m); FD mass spectrum m/e 355 (M^+–DCHA). Anal. Calcd for $C_{33}H_{48}N_2O_4$: C, 73.84; N, 9.01; N, 5.22. Found: C, 74.01; H, 9.08; N, 5.21.

Representative Procedure for Thiol Protection. 2b DCHA salt (103.3 mg, 192 μmol) was converted to the free acid in 98% yield with sodium citrate buffer (0.5 M in citric acid, pH 3.5)[7] The resulting oil was dissolved in CH_2Cl_2 (1.60 mL) and cooled

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(9) The *N*-hydroxysuccinimide (HOSu) ester of **2a** (**2c**) was isolated as a stable white solid (79%): mp 88.5–90.0 °C, satisfactory analytical data (±0.4% for C, H, N).
(10) By DCC or DCC/HOSu methods, yield for **5a** was 40% or 55%; for **5b**, 37%.
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to 0 °C, DCC (17.9 mg, 86.9 μmol) was added, and the mixture was stirred at 0 °C for 1 h. The DCU formed was removed by filtration and the filtrates were evaporated to dryness. The oily residue was redissolved in THF (1.40 mL) and cooled to 0 °C under N_2, and DMAP (1.4 mg, 11.5 μmol) followed by **4** (21.1 mg, 78.3 μmol) was added. Ellman's test for thiols[17] was negative after 15 min at 0 °C and the mixture was poured into sodium citrate buffer pH 3.5. The product was extracted into CH_2Cl_2, and the combined organic phases were washed with 5% $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated. The moist solid residue was purified by preparative layer chromatography to afford **6b** as clear oil (45.0 mg, 95%): IR ($CHCl_3$) ν_{max} 2942, 1719, 1680, 1505, 1205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (6 H, s, Bpoc *i*-Pr), 1.82–1.88 (1 H, m, β-CH_2), 1.92–1.98 (1 H, m, β-CH_2), 2.47 (1 H, t, J = 7 Hz, α-CH_2), 2.63 (1 H, t, J = 7 Hz, α-CH_2), 2.80 (1.5 H, s, NCH_3), 2.95 (1.5 H, s, NCH_3), 3.24–3.34 (4 H, m), 3.72 (3 H, s, Cys OMe), 4.56–4.62 (1 H, m, Cys CH), 5.10 (2 H, s, Cys, Bzl), 5.62–5.70 (1 H, m, Cys NH), 7.28–7.44 (10 H, m), 7.53–7.61 (4 H, m); FD mass spectrum m/e 606 (M^+).

4-[[*N*-(*tert*-Butyloxycarbonyl)-*N*-methyl-γ-aminobutyryl]thio]dibenzofuran (5a): IR ($CDCl_3$) ν_{max} 2975, 2930, 1690, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (9 H, s, Boc), 1.94–2.02 (2 H, m, β-CH_2), 2.78 (2 H, t, J = 8 Hz, α-CH_2), 2.86 (3 H, s, NCH_3), 3.31 (2 H, t, J = 7 Hz, γ-CH_2), 7.32 –7.40 (2 H, m), 7.44–7.51 (2 H, m), 7.58 (1 H, d, J = 8 Hz), 7.93 (1 H, d, J = 8 Hz), 8.00 (1 H, d, J = 8 Hz); FD mass spectrum, m/e 399 (M^+).

4-[[*N*-[[(*p*-Biphenylyl)isopropyloxy]carbonyl]-*N*-methyl-γ-aminobutyryl]thio]dibenzofuran (5b): IR ($CHCl_3$) ν_{max} 2935, 1698, 1690, 1448, 1395, 1182 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82 (6 H, s, Bpoc *i*-Pr), 1.88–1.96 (1 H, m, β-CH_2), 2.01–2.09 (1 H, m, β-CH_2), 2.72 (1 H, t, J = 7 Hz, α-CH_2), 2.82 (1 H, t, J = 7 Hz, α-CH_2), 2.86 (1.5 H, s, NCH_3), 3.01 (1.5 H, s, NCH_3), 3.30 (1 H, t, J = 8 Hz, γ-CH_2), 3.45 (1 H, t, J = 8 Hz, γ-CH_2), 7.30–7.48 (9 H, m), 7.55–7.63 (5 H, m), 7.93 (1 H, dd, J = 8, 0.5 Hz), 8.00 (1 H, dd, J = 8, 0.5 Hz); FD mass spectrum, m/e 537 (M^+).

Methyl N^{α}-(benzyloxycarbonyl)[[*N*-(*tert*-butyloxycarbonyl)-*N*-methyl-γ-aminobutyryl]thio]-L-cysteinate (6a): IR ($CHCl_3$) ν_{max} 3005, 1720, 1685, 1505, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (9 H, s, Boc), 1.18–1.86 (2 H, m, β-CH_2), 2.55 (2 H, t, J = 7 Hz, γ-CH_2), 2.80 (3 H, s, NCH_3), 3..25 (2 H, b, α-CH_2), 3.32 (1 H, dd, J = 15, 6 Hz, Cys CH_2), 3.46 (1 H, dd, J = 15, 6 Hz, Cys CH_2), 3.75 (3 H, s, Cys OMe), 4.58–4.63 (1 H, m, Cys CH), 5.11 (2 H, s, Bzl), 5.75 (1 H, bd, NH), 7.34 (5 H, s, phenyl); FD mass spectrum, m/e 468 (M^+).

Representative Procedure for Deprotection. To **6b** (42.5 mg, 70.1 μmol) were added 1.5% CF_3CO_2H in CH_2Cl_2 (1.00 mL) and anisole (10 μl, 92.0 μmol). The solution was stirred at 0 °C under N_2 for 20 min and then diluted with MeOH (1.00 mL). $NaHCO_3$ (156 mg, 1.86 mmol) was added, the white suspension was stirred at 0 °C for 30 min and then diluted with water and CH_2Cl_2. The layers were separated, the aqueous phase was extracted with CH_2Cl_2, and the organic layers were combined, dried ($MgSO_4$), and evaporated. To the oily residue was added I_2 (71 mg, 279 μmol) in MeOH (2.0 mL) and the solution was stirred at 25 °C for 10 min. The mixture was then poured into chilled 5% ascorbic acid and extracted with CH_2Cl_2, and the combined organic layers were washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by preparative layer chromatography to afford a viscous oil (17.3 mg, 92%) which was identical with authentic N^{α},$N^{\alpha'}$-bis(benzyloxycarbonyl)-L-cystine dimethyl ester[16] by TLC, HPLC, and ^1H NMR.

Acknowledgment. Financial support from the National Institutes of Health (Grant No. GM-13453-15) is gratefully acknowledged.

Registry No. 1, 1119-48-8; **2a**, 94994-39-5; **2b**, 94994-40-8; **2b**·DCHA, 94994-41-9; **3**, 94994-42-0; **4**, 53907-28-1; **5a**, 94994-43-1; **5b**, 94994-44-2; **6a**, 95018-02-3; **6b**, 95018-03-4; Boc_2O, 24424-99-5; NMP, 872-50-4; 2-*p*-biphenylyl-2-propyl phenyl carbonate, 18701-36-5; N^{α},$N^{\alpha'}$-bis(benzyloxycarbonyl)-L-cystine dimethyl ester, 6968-11-2.

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Equilibrium Studies of Water and 3-Mercaptopropanoic Acid Addition to Cyclic Ketones[1]

Theodore J. Burkey and Robert C. Fahey*

Department of Chemistry, University of California, San Diego, La Jolla, California 92093

Received August 21, 1984

In an earlier study we determined equilibrium constants for addition of thiols to α,β-unsaturated carbonyl groups of the type found in the A ring of steroids and concluded that their reactivity is sufficient to be of potential importance in steroid–protein interactions.[2] A study of thiol addition to methyl ketones suggested that these may also be potential sites of reaction with protein thiol groups when steric and electronic factors in the ketone are favorable.[3] Since keto groups are common substituents in rings of biologically active molecules, it is important to assess the effect of ring size on reactivity of ketones with thiols. We report here equilibrium constants for addition of 3-mercaptopropanoic acid to various cyclic ketones. In aqueous media water addition competes with thiol addition and can limit the extent to which a ketone reacts with the thiol. Where possible, equilibrium constants for water addition were also determined.

Results

Most determinations were made with 3-mercaptopropanoic acid-d_2 (3-MPA-d_2) in D_2O by ^1H NMR. Formation of hemithioketal could usually be monitored on the basis of the α-methylene proton resonance which occurred ~0.7 ppm upfield of the corresponding ketone resonance. In some cases this resonance was obscured by the β- and γ-methylene resonances of the ketone, in which case the β- or γ-methylene resonance of the hemithioketal, shifted 0.2–0.3 ppm upfield from the corresponding ketone signals, was used. Formation of 1,1-diol in water was measured by using the analogous resonances of the diol. The assignment of resonances to hemithioketal or diol was tested by showing: (1) that the signals were absent when the ketone or second reactant (3-MPA or water) was measured separately, (2) that the area of the signal for each adduct was directly dependent upon thiol or water concentration and also upon the ketone concentration, and (3) that the area of the signals for each adduct decreased reversibly with an increase in temperature. Values of K_{RSH} = [hemithioketal]/([ketone][3-MPA]) and K_{D_2O} = [diol]/([ketone][D_2O]), computed from peak area ratios as described previously,[3] are given in Tables I and II, respectively. Also included in Table I are a few values for K_{RSH} determined in dioxane in an analogous fashion. The value of K_{D_2O} for cyclobutanone is listed as tentative (Table II) because the only signal attributable to the α-protons of the diol was unresolved from the downfield ^{13}C-satellite signal of the β-methylene group of cyclobutanone, and it was necessary to correct for the satellite contribution in assessing the diol concentration.

Side reactions were not observed except in the case of cyclohexanone in D_2O. After 12 days, a solution containing an initial threefold excess of 3-MPA-d_2 over cyclohexanone showed no cyclohexanone proton signals but exhibited a triplet and two multiplets at 1.74, 1.5, and 1.3 ppm in the ratio 2:2:1. Each signal appeared at the same rate and this

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