Synthesis of 3-Acyl Tetramic Acids via Aspartimide Rearrangement[1,2]

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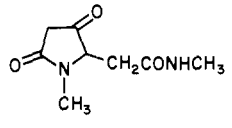
Abstract: The synthesis of 3-acyl tetramic acids via an intramolecular aspartimide rearrangement provides a new entry into the synthesis of these biologically active compounds. Limitations of this route are also described.

Streptolydigin (**1**)[2a,3] and tirandamycin (**2**)[2b,3] are complex 3-dienoyl tetramic acids whose relative and absolute configurational assignments were recently completed by x-ray investigation[4] of a derivative of tirandamycic acid (**3**),[3] a degradation product of **2**. Both antibiotics, but especially streptolydigin, have been of considerable recent interest owing to their antimicrobial activity,[5] to their inhibition of bacterial RNA polymerase,[6] and to streptolydigin's inhibition of terminal deoxynucleotidyl transferase from leukemic cells.[7]

We have described elsewhere[1b] two routes to streptolydigin analogues, one involving acylation of enolates of 2,4-pyrrolidiones such as 1-methyl-2,4-pyrrolidione-5-(*N*-methylacetamide) (**4**) with an appropriate dienoyl halide such as 2,4-hexadienoyl fluoride and a second involving cyclization of α-[*N*-(dienoylacetyl)amino] esters. Those two routes, having general applicability, were employed in synthesizing a number of acyl tetramic acids, including several dienoyl tetramic acids. In the present report we describe a new procedure for the synthesis of acyl tetramic acids which involves the rearrangement of α-[*N*-(acylacetyl)amino] cyclic imides. Although the scope of the reaction is relatively limited, yields in successful reactions are excellent and the procedure is simpler than the two previous routes in applicable systems.



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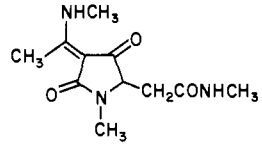

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The report on the acylation and cyclization routes noted that mild acidic hydrolysis (0.2 N HCl) of 1-methyl-3-(1-methylaminoethylidene)-2,4-pyrrolidione-5-(*N*-methylacetamide) (**5**) gave moderate yields of **3**.[1b] However, similar treatment of 3-(1-methylaminoethylidene)-2,4-pyrrolidione-5-(*N*-methylacetamide) (**7**), prepared in three steps from diethyl DL-aspartate (Figure 1), did not afford the analogous product **8**. Instead, the mass spectral and microanalytical data showed the elemental composition of the product to be $C_9H_{12}N_2O_4$ (rather than $C_7H_{10}N_2O_3$), while the infrared absorptions at 1785 and 1710 cm^{-1} suggested a cyclic imide and the proton magnetic resonance spectra indicated the structure **9a**.

The imide **9a** was unambiguously synthesized from DL-aspartic acid in five steps (Figure 1). DL-Aspartic acid (**10a**) was converted to *N*-benzyloxycarbonyl-DL-aspartic acid (**11a**)[8] and **11a** was converted by acetic anhydride to the anhydride **12a**. Treatment of **12a** with aqueous methylamine followed by acetic anhydride gave the *N'*-methyl imide (**13a**). Hydrogenolysis of **13a** gave *N'*-methyl-DL-aspartimide (**14a**), which on treatment with distilled diketene gave the acetoacetamido imide **9a** whose physical and spectroscopic properties were identical in all respects with those of the product obtained via acidic hydrolysis of **7**.

Consideration of the structure of the product **9a** suggested the possibility of the reverse reaction, i.e., rearranging *N*-dienoylacetyl-*N'*-methylaspartimides (such as **15**) to 3-dienoyl tetramic acid analogues of streptolydigin. Preliminary tests of this hypothesis were successful. Treatment of the imide **9a** with a slight excess of sodium methoxide gave moderate yields of 3-acetyl-2,4-pyrrolidione-5-(*N*-methylacetamide) (**15a**),[9] a compound also obtained by alkaline hydrolysis of tetramate **7** in 65% yield.

By the same series of reactions, DL-*threo*-β-methylaspartic acid (**10b**)[10] was converted to *N*-benzyloxycarbonyl-DL-*threo*-β-methylaspartic acid (**11b**) and that to the anhydride **12b**. The anhydride **12b** (which underwent reconversion to acid **11b** within 24–36 h) was converted to the imide **13b** in methylamine–ether at −20 °C. Hydrogenolysis, acetoacetylation, and cyclization yielded the desired 3-acetyl-2,4-pyrrolidione-5-(*N*-methyl-α-propionamide) (**15b**)[9] in 50% yield (based on starting imide **13b**).

Unfortunately, attempts to synthesize a dienoyl tetramic acid analogue of streptolydigin by the same route failed when attempted condensation of ethyl 3-oxo-(*E,E*)-4,6-octadienoate with imide **14a** to give the dienoylacetamido imide **16** proved unsuccessful. The imides **14a,b** were highly labile at temperatures above 70 °C.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus. Infrared (IR) spectra were determined on a Beckman infrared spectrophotometer, Model IR-12. Proton magnetic resonance (^1H NMR) spectra were determined by Mr. Robert Thrift and associates on Varian A-60A and HA-100 spectrometers. Chemical shifts (δ) are reported in parts per million from Me_4Si as internal standard. All ^1H NMR spectra were taken at 60 MHz unless otherwise stipulated. Low-resolution and high-resolution mass spectra were respectively obtained by Mr. J. C. Cook, Jr., and his associates on Varian MAT CH-5DF and 731 mass spectrometers. Microanalyses were determined by Mr. J. Nemeth and his associates. Chromatography was carried out on silica gel employing the solvents indicated.

3-Acetyl-2,4-pyrrolidione-5-(methyl acetate) (6). Freshly distilled diketene (14.1 g, 168 mmol) was added dropwise to a solution of 28.89 g (153 mmol) of diethyl aspartate and 200 mL of benzene. The solution was stirred overnight at 26 °C and concentrated in vacuo. The residue was taken up in 150 mL of toluene and added dropwise to 100 mL of 2 N methanolic sodium methoxide. The mixture was heated at reflux for 2 h and the precipitate (sodium salt) was collected, dissolved in water, and acidified. The tetramate was extracted into chloroform, worked up, and crystallized from benzene to afford 25.85 g (78%) of **6**: mp 111–112 °C; IR ($CHCl_3$) 1740–1725, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) 2.47 (s, 3 H, CH_3CO), 2.50 and 2.88 (dd, 1 H, J = 18, 5 Hz; dd, 1 H, J = 18, 4 Hz; CH_2), 3.76 (s, 3 H, OCH_3), 4.17 (m, 1 H, $CHCH_2$), 7.08 (bs, 1 H, NH), and 13.3 ppm (s, 1 H, OH).

Anal. Calcd for $C_9H_{11}NO_5$: C, 50.71; H, 5.20; N, 6.57. Found: C, 50.77; H, 5.48; N, 6.46.

3-(1-Methylaminoethylidene)-2,4-pyrrolidione-5-(*N*-methylacetamide) (7). A solution of 10.0 g (47 mmol) of **6** and 100 mL of saturated methanolic methylamine was heated at reflux for 5 h and concentrated

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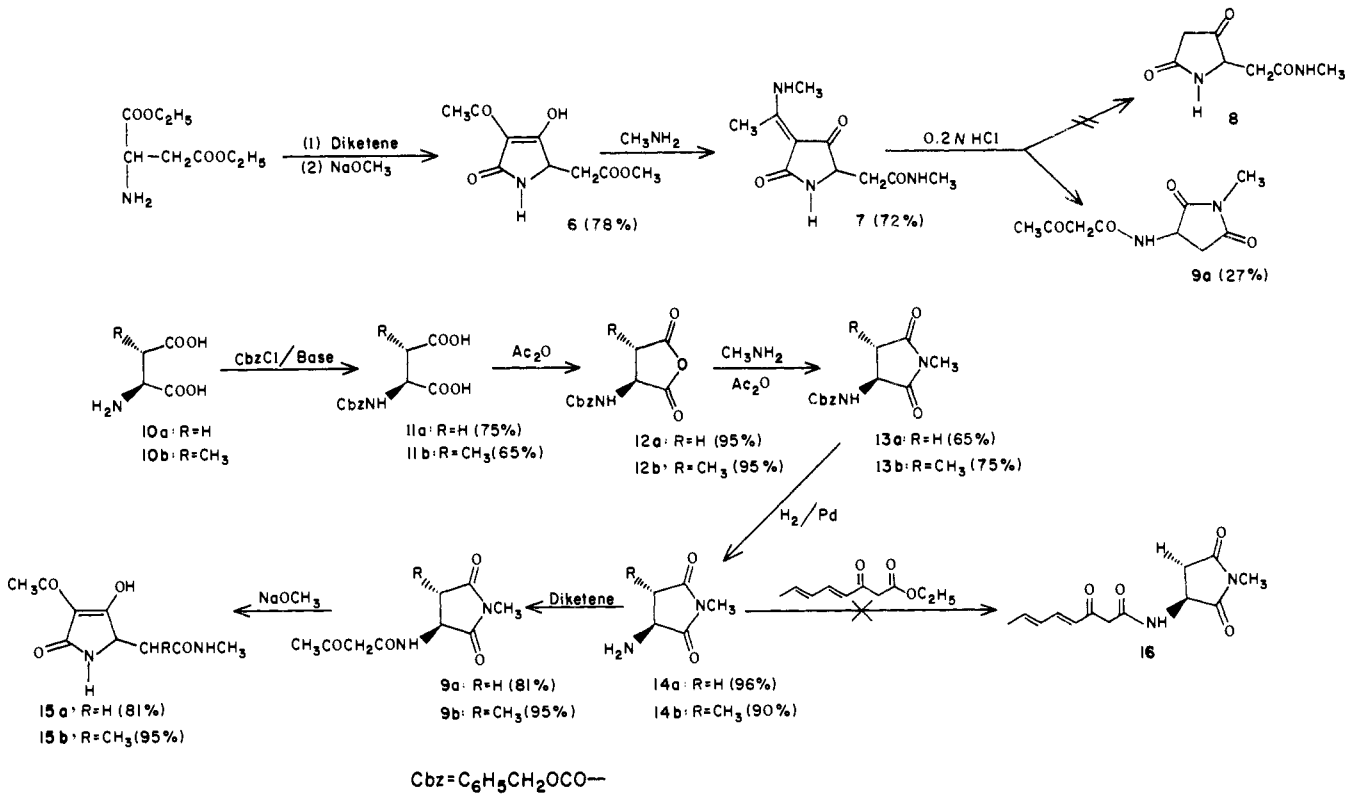

Figure 1. Syntheses and rearrangements of *N*-acetoacetyl-*N'*-methylaspartimides (**9a,b**).[9]

in vacuo. The residue was recrystallized from methanol, affording 7.7 g (72%) of **7**: mp 210–214 °C; IR (KBr) 3310, 1683, 1660, and 1600 cm^{-1}; ^1H NMR (TFA) 2.76 (s, 3 H, CH_3C), 3.04 and 3.39 (d, 3 H, $NHCH_3$), 3.14 (m, 2 H, CH_2CH), and 4.47 ppm (m, 1 H, $CHCH_2$).

Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.33; H, 6.71; N, 18.65. Found: C, 53.35; H, 6.87; N, 18.42.

***N*-Benzyloxycarbonyl-DL-aspartic Acid (11a).** A solution of 50.0 g (375 mmol) of DL-aspartic acid and 105.1 g (1.24 mol) of sodium bicarbonate in 800 mL of water was stirred vigorously overnight at 25 °C with 68.2 g (400 mmol) of benzyl chloroformate. Workup and recrystallization from ethyl acetate–hexane afforded 75.2 g (75%) of **11a**, mp 116–117 °C (lit.[8] 116–117 °C).

***N*-Benzyloxycarbonyl-DL-aspartic Anhydride (12a).** A suspension of 34.2 g (132 mmol) of **11a** and acetic anhydride (250 mL) was stirred vigorously at 25 °C for 8 h. Solvent was removed in vacuo and the solid residue was recrystallized from ethyl acetate–hexane to afford 31.3 g (95%) of **12a**: mp 125–126 °C; IR (KBr) 3390, 1862, 1772, and 1693 cm^{-1}; ^1H NMR (CD_3COCD_3, 100 MHz) 3.06 and 3.30 (two dd, 2 H, CH_2CH), 4.9 (m, 1 H, $CHCH_2$), 5.11 (s, 2 H, $ArCH_2$), and 7.33 ppm (s, 5 H, ArH).

Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.98; H, 4.38; N, 5.92.

***N*-Benzyloxycarbonyl-*N'*-methyl-DL-aspartimide (13a).** *N*-Benzyloxycarbonyl-DL-aspartic anhydride (**12a**, 20.3 g, 81 mmol) was added slowly to 150 mL of 40% aqueous methylamine. After the reaction had subsided, the mixture was concentrated in vacuo and the residue was stirred with 125 mL of acetic anhydride at 90–95 °C for 30 min, then concentrated in vacuo and chromatographed (5% MeOH in $CHCl_3$). The oily product crystallized from ethyl acetate–hexane as white needles (13.8 g, 65%): mp 95–96 °C; IR (KBr) 3340, 1780, 1710, and 1687 cm^{-1}; ^1H NMR (CD_3COCD_3, 100 MHz) 2.9 (m, 2 H, CH_2CH), 2.95 (s, 3 H, NCH_3), 4.3 (m, 1 H, $CHCH_2$), 5.08 (s, 2 H, $ArCH_2$), 5.82 (bs, 1 H, NH), and 7.31 ppm (s, 5 H, ArH).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.47; H, 5.26; N, 10.63.

***N'*-Methyl-DL-aspartimide (14a).** Hydrogen was bubbled for 36 h through a mixture of 4.7 g (18 mmol) of **13a** in 300 mL of methanol containing 50 mg of 5% palladium on carbon catalyst. The mixture was filtered and concentrated in vacuo, giving 2.2 g (96%) of a yellow oil which was utilized in the succeeding synthetic steps without further purification.

An analytical sample was obtained by preparative TLC (silica gel GF_{254}, 7% MeOH in $CHCl_3$): IR ($CHCl_3$) 3390, 1788, and 1712 cm^{-1}; ^1H NMR ($CDCl_3$) 1.86 (bs, 2 H, NH_2), 2.99 (s, 3 H, NCH_3), 2.50 and 2.97 (dd, 1 H, J = 18, 5 Hz; dd, 1 H, J = 18, 8 Hz; CH_2), 3.9 ppm (m, 1 H, CH).

Anal. Calcd for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.86. Found: C, 46.65; H, 6.33; N, 22.06.

***N*-Acetoacetyl-*N'*-methyl-DL-aspartimide (9a). A. From 14a.** Distilled diketene (1.25 g, 15 mmol) was added dropwise to a cold solution (0–5 °C) of 1.9 g (15 mmol) of **14a** in 50 mL of dry methanol. The solution was kept at 25 °C overnight and concentrated in vacuo. The oily residue was chromatographed (2% MeOH in $CHCl_3$) to afford an oily residue which crystallized from ethyl acetate–hexane as white needles (2.60 g, 81%): mp 70–71 °C; IR ($CHCl_3$) 3340, 1785, 1710, and 1670 cm^{-1}; ^1H NMR (CD_3COCD_3, 100 MHz) 2.21 (s, 3 H, CH_3CO), 2.80 (dd, 2 H, CH_2CH), 2.86 (s, 3 H, NCH_3), 3.38 (s, 2 H, CH_2CO), 4.56 (m, 1 H, $CHCH_2$), and 8.95 ppm (bd, 1 H, NH).

Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 51.03; H, 5.56; N, 13.21.

B. From 7. A solution of 1.00 g (4.45 mmol) of **7** in 50 mL of 0.2 N hydrochloric acid was heated at reflux for 5.0 h and concentrated in vacuo. The residue was worked up as in A to afford 249 mg (27%) of imide **9a**, whose physical and spectroscopic properties were identical with those of the sample from A above.

3-Acetyl-2,4-pyrrolidione-5-(*N*-methylacetamide) (15a). A. From 9a. A solution of 250 mg (1.18 mmol) of **9a** in 18 mL of 0.17 N methanolic sodium methoxide was stirred overnight at 25 °C and concentrated in vacuo. The solid residue was acidified and extracted with chloroform. Workup of the organic extracts gave the tetramate **15a**, which was recrystallized from methanol to afford 180 mg (71%) of white needles: mp 193–194 °C; IR (KBr) 3310, 1710, 1648, and 1620 cm^{-1}; ^1H NMR (TFA, 100 MHz) 2.62 (s, 3 H, CH_3CO), 3.10 (s, 3 H, CH_3N), 3.14 (d, 2 H, CH_2CH), 4.64 (t, 1 H, $CHCH_2$), and 8.24 ppm (bs, 2 H, NH).

Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.90; H, 5.65; N, 13.06.

B. From 7. A solution of 195 mg (0.87 mmol) of **7**, 2 mL of 33%

sodium hydroxide, and 15 mL of methanol was held at 25 °C overnight, then worked up as in A to give 119 mg (65%) of the desired tetramate **16a** whose physical and spectroscopic properties were identical with those of the sample from A above.

***N*-Benzyloxycarbonyl-DL-*threo*-β-methylaspartic Acid (11b).** Employing the same conditions utilized for the preparation of **11a**, 36.0 g (240 mmol) of DL-*threo*-β-methylaspartic acid (**10b**, obtained by recrystallizing a commercial sample of β-methylaspartic acid from water),[9] 30.0 g (750 mmol) of sodium hydroxide, 500 mL of water, and 51.5 g (360 mmol) of benzyl chloroformate gave, after recrystallization from ethyl acetate–hexane, 44.0 g (65%) of **11b**, mp 153–154 °C (lit.[8] 149–150 °C).

***N*-Benzyloxycarbonyl-DL-*threo*-β-methylaspartic Anhydride (12b).** Holding 14.6 g (50 mmol) of **11b** and 125 mL of acetic anhydride at 25 °C for 6 h gave 13.0 g (95%) of the desired anhydride **12b** as an oil: IR ($CHCl_3$) 3460, 1800, 1735, 1270, and 980 cm^{-1}; ^1H NMR (CD_3COCD_3, 100 MHz) 1.41 (d, 3 H, CH_3CH), 3.44 (m, 1 H, $CHCH_3$), 4.65 (m, 1 H, $CHNH$), 5.11 (s, 2 H, $ArCH_2$), 7.22 (bd, 1 H, NH), and 7.30 ppm (s, 5 H, ArH). The anhydride underwent reversion to the acid within 24–36 h in air.

Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.39; H, 5.14; N, 5.14.

***N*-Benzyloxycarbonyl-*N'*-methyl-DL-*threo*-β-methylaspartimide (13b).** Liquid methylamine (15 mL) was added to a cold solution of 13.0 g (49 mmol) of **12b** in 100 mL of anhydrous ether at −20 °C. The solution was warmed to 25 °C and concentrated in vacuo and the oily residue was stirred with acetic anhydride for 48 h, concentrated in vacuo, and chromatographed (3% MeOH in $CHCl_3$) to give 9.0 g (75%) of oily imide: IR ($CHCl_3$) 3440, 1782, and 1710 cm^{-1}; ^1H NMR (CD_3COCD_3) 1.28 (major component) and 1.14 (minor impurity) (d, 3 H, CH_3CH), 2.83 (m, 1 H, $CHCH_3$), 2.83 (s, 3 H, NCH_3), 4.13 (m, 1 H, $CHNH$), 5.02 (s, 2 H, $ArCH_2$), 6.83 (m, 1 H, NH), and 7.29 ppm (s, 5 H, ArH).

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.56; H, 5.70; N, 10.20.

***N'*-Methyl-DL-*threo*-β-methylaspartimide (14b).** Hydrogenolysis of 2.16 g (10 mmol) of **13b** in 500 mL of methanol containing 5% palladium on carbon catalyst gave 1.25 g (90%) of the amine as a yellow oil which was used without purification. A small portion was purified by preparative TLC (silica gel GF_{254}, 5% MeOH in $CHCl_3$) to afford the amine as a white solid: mp ca. 60 °C; IR ($CHCl_3$) 3380, 1780, and 1700 cm^{-1}; ^1H NMR ($CDCl_3$) 1.41 (d, 3 H, CH_3CH), 1.82 (bs, 2 H, NH_2), 2.57 (m, 1 H, $CHCH_3$), 3.00 (s, 3 H, NCH_3), and 3.48 ppm (d, 1 H, $CHNH_2$).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.54; H, 6.92; N, 19.41.

***N*-Acetoacetyl-*N'*-methyl-DL-*threo*-β-methylaspartimide (9b).** Distilled diketene (760 mg, 9 mmol) and 1.25 g (9 mmol) of **14b** gave 1.90 g of **9b** as a yellow oil. A small sample was purified by chromatography (2% MeOH in $CHCl_3$): IR ($CHCl_3$) 3330, 1782, 1710, and 1675 cm^{-1}; ^1H NMR (CD_3COCD_3, 100 MHz) 1.30 (d, 3 H, CH_3CH), 2.18 (s, 3 H, CH_3CO), 2.82 (m, 1 H, $CHCH_3$), 2.85 (s, 3 H, NCH_3), 3.41 (s, 2 H, $COCH_2CO$), 4.24 (m, 1 H, $CHNH$), and 7.95 ppm (m, 1 H, NH).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.15; H, 6.14; N, 12.28.

3-Acetyl-2,4-pyrrolidione-5-(*N*-methyl-α-propionamide) (15b). A solution of 1.16 g (5 mmol) of **9b** in 26 mL of 0.24 N methanolic sodium methoxide was stirred overnight, then worked up as for **15a** to give a yellow solid which was recrystallized from ethyl acetate–hexane to give 850 mg (75%) of **15b**: mp 166–167 °C; IR (KBr) 3360, 3125, 1700, 1660, and 1602 cm^{-1}; ^1H NMR ($CDCl_3$) 1.07 (d, 3 H, CH_3CH), 2.47 (s, 3 H, CH_3CO), 2.83 (d, 3 H, $NHCH_3$), 2.85 (m, 1 H, $CHCH_3$), 4.09 (m, 1 H, $CHNH$), 5.96 and 6.77 ppm (bs, 2 H, NH).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.00; H, 6.20; N, 12.39.

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References and Notes

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The Dynamics of Cryptand Protonation

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Abstract: Proton transfer reactions of the [222] cryptand in aqueous solution have been studied by the conventional (Joule heating) temperature-jump technique at 25 °C and μ = 0.1 M tetramethylammonium chloride. For the reaction H_2O + [222] $\rightleftarrows$ $[222.H]^+ + OH^-$, the rate constants are $k_f \leq 1000\ s^{-1}$ and $k_r \leq 10^8\ M^{-1}\ s^{-1}$. The site which is being protonated is within the ligand cavity. These rate constants represent processes which are at least two orders of magnitude slower than normal proton transfer reactions of tertiary amines. This result permits a determination of the extent to which the ligand imposes dynamic constraints on the complexation process and is significant in understanding previously observed slow rates of metal cryptate formation.

Cryptands[1] are macrobicyclic ligands with structures such as I. This is known as the [222] cryptand. The ligand contains a cavity which is capable of completely enclosing a metal ion to form a complex known as a cryptate.[2,3] One reason for the considerable interest in these ligands is that the formation of inclusive complexes with metal ions is highly specific,[4,5] a property which suggests many uses for these ligands.

Both NMR[6,7] and stopped-flow techniques[8,9,10] have been

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