Configurational Biasing of Tertiary Amide Ionophores by Alkali Metal Chelation[1,2]

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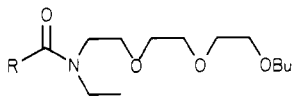
Abstract: Configurational analysis can be used as a probe for association constants for chelation of amides with alkali metals. Carbon-13 NMR spectroscopy indicates that tertiary amides **1**, **2**, and **3**, each bearing a triethylene oxide substituent at nitrogen, exist as a mixture of *E* and *Z* isomers. Addition of alkali metal cation (KSCN) increases the concentration of species with the *Z* configuration since this configuration can chelate potassium ion. High-field ^1H NMR spectra have been used to determine the chelation constants for amides **1–6** in the presence of KSCN. It has been determined that (a) the carbonyl oxygen is involved in chelation and (b) the number of ether oxygens on the substituent at nitrogen is the significant factor in the chelating ability of these ionophores.

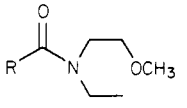
It is well-known that alkali metal cations interact with amide and ether oxygens. This phenomenon is responsible for the behavior of ionophores such as the cyclic peptides and depsipeptides, the synthetic crown ethers, and synthetic acyclic amido-ether molecules. In addition, such interactions can affect the biological properties of naturally occurring proteins.[4-6] However, in only a few cases has NMR spectroscopy been used in direct experimental demonstrations of alkali metal coordination by amide carbonyl oxygen.[7-10]

One possible consequence of interaction with a metal cation is a change in the conformation of the ionophore. Since amide isomers can easily be distinguished by NMR spectroscopy, monitoring perturbations in the equilibrium of amide conformers can provide a useful approach for the quantitative study of alkali metal coordination.

Previous work using this approach has demonstrated that complexation of alkali metal cations by diacetamide affects the configurational equilibrium of the imide, increasing the mole fraction of the conformer preferred for complexation at the expense of the non-complexing conformer.[8] We have made a preliminary report of similar observations on amides **1** and **3**.[2] We now report on the extention of this method which allows association constants for amide–cation complexes to be determined from the change in configurational ratio. We have extended the series of amides studied to include **2** and **4–6** and can draw some conclusions about the nature of complexation and the atoms involved as ligands.



1, R = CH_3
2, R = CH_2OCH_3
3, R = $CH_2(OCH_2CH_2)_2OBu$



4, R = CH_3
5, R = CH_2OCH_3
6, R = $CH_2(OCH_2CH_2)_2OBu$

Scheme I

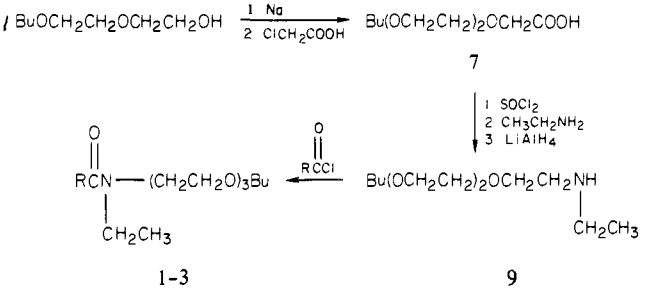


Table I. Assignment of Chemical Shifts for the Methylene Carbons Attached to Nitrogen in Amides 1-3

compd	carbon	δ_E	δ_Z
1	NCH_2CH_3	40.8	44.6
	NCH_2CH_2O-	48.1	45.4
2	NCH_2CH_3	41.1	42.9
	NCH_2CH_2O-	46.4	45.5
3	NCH_2CH_3	41.9	43.6
	NCH_2CH_2O-	46.4	45.4
4	NCH_2CH_3	40.8	44.6
	$NCH_2CH_2OCH_3$	48.0	45.3
5	NCH_2CH_3	40.9	42.8
	$NCH_2CH_2OCH_3$	46.3	45.2
6	NCH_2CH_3	41.3	42.9
	$NCH_2CH_2OCH_3$	46.5	45.4

Results

Amides **1–3** were prepared by reaction of ethyl(3,6,9-trioxadecyl)amine (**9**) with the corresponding acid chloride (including that of **7**) as indicated in Scheme I. Similarly, amides **4**, **5**, and **6** were prepared by using the same set of acid chlorides and ethyl(2-methoxyethyl)amine derived from 2-methoxyethylamine which was prepared in a similar sequence.

The ambient temperature ^{13}C NMR spectra of **1–3** in deuteriochloroform revealed the presence of *E* and *Z* isomers at the amide configurational unit. The resonances listed in Table I were observed and could be assigned to the two configurational isomers in accord with previous assignments in simple amides.[11,12] In each case, the upfield resonances for each carbon were assigned to the isomer in which that carbon atom is syn to the carbonyl oxygen. These assignments could be confirmed by using 300 MHz ^1H NMR spectra (vide infra).

Upon addition of KSCN to a solution of **3** in methanol the intensities of the ^{13}C resonances assigned to the *Z* isomer increased

(1) (a) Stereochemistry in Trivalent Nitrogen Compounds. 39. For part 37 see: Kost, D.; Raban, M. *J. Am. Chem. Soc.* **1982**, *104*, 2960. (b) This work was supported by the National Institute of General Medical Sciences and the MBRS program of the National Institutes of Health.
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(3) (a) University Fellow of Wayne State University. (b) Guest Undergraduate Research Participant from Kalamazoo College.
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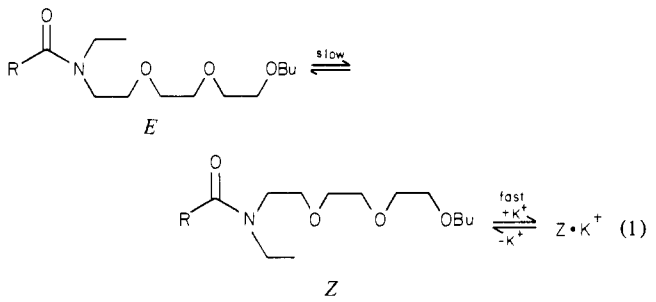
relative to those of the *E* isomer. In addition the *Z* resonances were shifted upfield, while those from the *E* isomer showed no change in chemical shift. Thus, the methylene carbons of the *N*-ethyl group exhibit the following chemical shifts upon addition of KSCN: 0 equiv, δ_E 42.0, δ_Z 43.7; 0.5 equiv, δ_E 41.9, δ_{Z+MZ} 43.3; 1.0 equiv, δ_E 41.9, δ_{Z+MZ} 43.0. Similar upfield shifts for carbons attached to ether oxygens have been observed in crown ethers in the presence of alkali and alkaline earth cations.[13] These observations lead to the conclusion that metal ion chelation perturbs the configurational equilibrium at the amide configurational unit, increasing the mole fraction of the *Z* isomer at the expense of the non-chelating *E* isomer (eq 1). Furthermore a



(1)

rapid dynamic equilibrium between the complexed and non-complexed forms of the *Z* isomer accounts for the upfield shift of the *Z* resonances upon addition of KSCN. These upfield shifts also suggest that the ether oxygen proximal to the amide nitrogen is involved in the complexation. Thus the observed resonance for the *Z* configuration corresponds to a chemical shift which is a weighted average of the chemical shifts of complexed and uncomplexed forms of the *Z* isomer. The observation of similar behavior in the ^{13}C spectra of amide **1**, in which it is clear that only the *Z* isomer can chelate, provides confirming evidence for the chemical shift assignments in amide **3**, as well as for the perturbational effect on the configurational distribution due to preferential chelation by the *Z* isomer.

If 1:1 complexation is assumed for the *Z* isomer of **1** and K^+, and negligible complexation for the *E* isomer,[14] then the equilibrium constant for association K_a can be calculated by using eq 2, where *K* is the *E*/*Z* ratio in the absence of the metal ion, *R* is the observed ratio $E/(Z + Z{\cdot}M^+)$ in the presence of added metal ion, and *A* and *M* are the nominal concentrations of the amide and alkali metal salt, respectively.

$$K_a = \frac{K(K - R)(1 + R)}{R[MK(1 + R) - A(K - R)]} \qquad (2)$$

In order to provide further information concerning the structural requirements for complexation and quantitative assessment of the chelating ability of these ionophores, 300-MHz ^1H NMR spectra of amides **1** through **6** were measured.[15] Solutions of the amides at a concentration of 0.08 M in methanol-d_4 were examined with addition of regular increments of KSCN. The *E*/*Z* ratios previously established in the ^{13}C NMR spectra of these compounds permitted the unambiguous identification of proton resonances for the two isomers. In addition, the chemical shifts of the methyl protons of the ethyl substituent on nitrogen in these amides showed good agreement with those reported for *N*,*N*-diethylacetamide.[16] Association constants were calculated from the data thus obtained and are summarized in Table II.

Table II. Equilibrium Constants and Association Constants of Amides 1-6 with KSCN in CD_3OD[a]

amide	proton resonance[b]	K_{eq} (*E*/*Z*)[b]	$R(E/(Z + Z{\cdot}M^+))$[c]	K_a[b,d] (M^{-1})
1	NCH_2CH_3	1.10	0.62	1.19 (±0.06)
2	$OCH_2C{=}O$	1.42	0.65	1.71 (±0.04)
3	$OCH_2C{=}O$	1.39	0.79	1.02 (±0.07)
4	NCH_2CH_3	1.00	0.96	0.04 (±0.02)[e]
5	$OCH_2C{=}O$	1.26	1.19	0.12 (±0.06)
6	NCH_2CH_3	1.41	1.18	0.41 (±0.13)

[a] The concentration of the amide in all cases was 0.08 M. [b] The data for calculation of K_{eq} and K_a were based on the intensities of the indicated proton resonances, selected for best resolution. [c] Observed configurational ratio at KSCN concentration of 0.72 M. [d] The K_a is the mean of four calculated K_a's based on four different concentrations of KSCN: 0.24 M, 0.40 M, 0.56 M, and 0.72 M. The error ranges indicated are standard deviations except for 4 where the average deviation is given. [e] The K_a for 4 is the average of two data points (KSCN = 0.56 M, 0.72 M). Because of the small value of K_a, the values obtained at lower salt concentrations were considered to be unreliable.

Discussion

Examination of the association constants for the six amides clearly permits a division into two categories. Amides **1**, **2**, and **3** have K_a values equal to or greater than 1, while amides **4**, **5**, and **6** have K_a values much lower than those of the first group. The amides that are better chelators all possess one feature in common: a nitrogen substituent containing three ether oxygens. The presence or absence of ether oxygens in the chain attached to the carbonyl carbon does not significantly affect the chelating ability of these ionophores.

On the basis of these observations, the following conclusions can be drawn:

(1) The ether oxygens on the nitrogen substituent are required for substantial chelation, while those on the carbonyl carbon substituent are not. This can be clearly seen by contrasting the behavior of amides **6** and **2**, which have similar equilibrium constants (K_{eq}) and contain the same number of ether oxygens. They differ structurally only in the location of the substituents containing ether oxygens but have dramatically different association constants (K_a).

(2) The number and/or position of the ether oxygens in the nitrogen substituent has a significant effect on the chelating ability of the amides. One ether oxygen is not effective. At least two and perhaps three ether oxygens are required for effective chelation. This can be seen by contrasting amides **4**–**6** to amides **1**–**3**, respectively. Since ^{13}C chemical shift data indicate the chelation involves the proximal ether oxygen, this suggests that complexation by more than one ether oxygen occurs.

(3) The amide carbonyl oxygen is involved in chelation and is more strongly bound than a single ether oxygen. This result, which could be predicted from the relative donicities[17] of amide vs. ether oxygens, is confirmed in the experimental results. In amide **1**, the carbonyl oxygen is undoubtedly involved in chelation (**10**). The clear preference for the *Z* conformer in amide **3** when KSCN is introduced is indicative that a conformer (**11**) in which the amide carbonyl oxygen can coordinate with the metal ion is preferred over a conformer (**12**) in which ether oxygens alone can chelate.

The ^1H and ^{13}C NMR chemical shift change data of previous studies[10,18] suggest that amide carbonyl oxygens in acyclic ionophores participate in complexation with alkali and alkaline earth metal cations. The method employed in this study provides a more direct confirmation of this phenomenon.

This method for determining association constants compares favorably with more established NMR methods, which involve iterative procedures based on changes in chemical shift, or

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(14) In view of the small value of the association constants ultimately obtained, it is reasonable to assume that the major stoichiometry of complexation is 1:1. Also, complexation of the *E* conformer or of the ether oxygens alone can be ruled out as significant competitors. Otherwise, the use of eq 2 would not have afforded consistent values for K_a at different concentrations of added salt.

(15) Although qualitative data were obtained from ^{13}C NMR data, the quantitative determination of ratios of amide conformers was found to be unreliable. Hence, no weight should be given to the quantitative data in ref 2.

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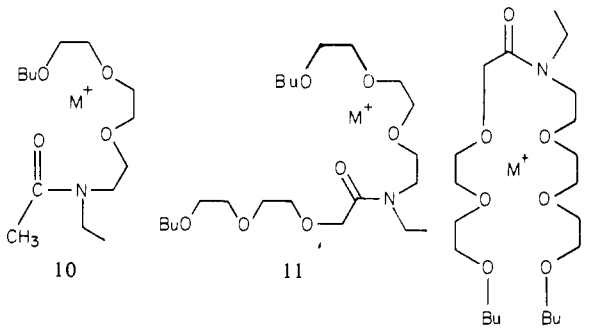

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longitudinal relaxation times. The iterative methods, based on eq 3, assume that the parameters p_i have fixed values for the

$$p_{obsd} = \chi_a p_a + \chi_b p_b + \ldots \quad (3)$$

system being examined. In fact, this assumption may not be reliable because of the many factors which can affect chemical shifts and relaxation times. Therefore, the experiments must be carefully controlled (for temperature, ionic strength, pH) to assure their validity. The use of eq 2, in contrast, only assumes that K_{eq} for the two configurations of the ionophore remains a constant under the experimental conditions. This can be more easily verified.

In addition, the sensitivity of this method is comparable to those of the chemical shift and relaxation time change methods, by which Jagur-Grodzinski et al. determined a stability constant of 1.1 M^{-1} for the NDA-$LiClO_4$ complex in pyridine.[9] The low association constants found for the KSCN complexes of amides **1**, **2**, and **3** tend to give quantitative confirmation to the finding of Marchelli et al.,[7] whose chemical shift data for similar acyclic amido-ether ionophores indicated qualitatively that these ligands do not complex appreciably with KSCN in CD_3OD. It is clear that the association constants for compounds **1–3** can be determined by the present technique, although the much lower constants for compounds **4–6** are not much larger than experimental error.

In summary, this study illustrates a simple, direct, and reasonably sensitive method for determining the complexing abilities of ionophores. It can be used effectively for ionophores with configurations that interconvert slowly on the NMR time scale and for which the equilibrium of conformers is perturbed in one direction by the addition of metal ions.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer 267 infrared spectrometer. ^{13}C NMR spectra were taken on a Jeol JNM-FX60 Fourier transform spectrometer. The 60-MHz ^1H NMR spectra were recorded on a Varian T-60 CW spectrometer, and the 300-MHz ^1H NMR spectra were taken on a Nicolet Model 1180 FT spectrometer. The mass spectra for compounds **3** and **8** were taken on an AEI MS 902. Elemental analyses were performed by Midwest Microlab, and were within 0.4% agreement with the calculated percent composition.

NMR Experiments. The ^{13}C NMR spectra were recorded with 8K data points with 5000 scans and zero-filling and run at ambient temperature. The amide samples were prepared at concentrations ranging between 0.2 and 0.25 M in 10-mm tubes.

The 300-MHz ^1H NMR spectra were recorded with 16K data points and 4 scans and run at temperatures ranging from 19 to 23 °C. The amide samples were prepared as 0.08 M stock solutions in CD_3OD and pipetted in 0.5-mL portions into 5-mm tubes.

KSCN was crushed and dried in a desiccator under vacuum prior to use. Measured portions of the salt (H20T Mettler balance) were placed in the sample tubes to which the amide solutions were added. All chemical shifts are referenced to internal Me_4Si.

3,6,9-Trioxatridecanoic Acid (7). Sodium metal (46 g, 2 mol) was added to 2-(2-*n*-butoxyethoxy)ethanol (335 mL, 2 mol) with heating and stirring. The reaction mixture was stirred at 80 °C for 41 h, until all sodium had reacted. When chloroacetic acid (94.5 g, 1 mol) was added at room temperature with stirring, a white precipitate, NaCl, formed immediately. The reaction mixture was allowed to stir overnight. The reaction mixture was diluted with water, and the unreacted alcohol was extracted from the basic water layer with diethyl ether. The aqueous layer was then acidified with 70 mL of 6.7% HCl, and the crude acid was extracted with diethyl ether. The ether layer was dried over $MgSO_4$ and filtered and the solvent removed in vacuo, yielding 264.3 g of crude brown oil. Vacuum distillation of the crude acid yielded 128.0 g (0.58 mol, 58.2%) of the colorless liquid **7**: bp 138–150 °C, 0.3 mmHg; IR (neat) 3500–2500, 1760, 1140 cm^{-1}.

***N*-Ethyl-3,6,9-trioxatridecanamide (8).** To 75 g (0.63 mol) of distilled thionyl chloride 37 g (0.168 mol) of acid **7** was added dropwise with stirring and heating. The reaction mixture was refluxed for 45 min, and the excess $SOCl_2$ was removed by distillation affording the acid chloride in 98% yield (39.4 g, 0.165 mol): IR (neat) 1800, 1150–1100 cm^{-1}.

The acid chloride was added dropwise to a chilled solution of 70% aqueous ethylamine (50 g, 0.776 mol). The mixture was stirred overnight at room temperature. The organic content of the basic aqueous reaction mixture was extracted with diethyl ether. The ether layer was washed with 6.7% HCl, saturated $NaHCO_3$, and brine and dried over magnesium sulfate. The solvent was removed in vacuo, affording 34.7 g (0.14 mol, 85%) of amide **8** as a light yellow oil with a purity of 96% by GC: bp 155–160 °C, 0.7 (mm Hg); IR (neat) 3360, 2960–2860, 1670, 1540, 1300, 1260, 1120 cm^{-1}; ^{13}C NMR (15 MHz, $CDCl_3$) δ 169.92 (C=O), 71.16, 70.90, 70.51, 70.31, 70.12, 69.99 (6 OCH_2), 33.63, 31.62, 19.21 (3 CH_2), 14.73, 13.82 (2 CH_3); mol wt 247 (m/e, $M^{+\cdot}$).

***N*-Ethyl-3,6,9-trioxatridecanamine (9).** A solution of amide **8** (34 g, 0.138 mol) in 150 mL of diethyl ether was added dropwise with stirring to a suspension of $LiAlH_4$ (10.5 g, 0.276 mol) in 300 mL of diethyl ether under argon. The reaction mixture was refluxed for 5 days and then cooled in an ice salt bath and ice water was added to neutralize the excess $LiAlH_4$. The reaction mixture was filtered and the ether layer dried over magnesium sulfate. The solvent was removed in vacuo, yielding 29.4 g (0.126 mol, 91.3%) of liquid amine **9**. The crude oil was distilled under vacuum, affording 23.4 g (0.100 mol, 72.8%) of the colorless amine **9**: bp 79–95 °C, 0.03 mmHg: IR (neat) 3300, 2960–2850, 1460, 1380, 1350, 1120 cm^{-1}; ^{13}C NMR (15 MHz, $CDCl_3$) δ 71.16, 70.96, 70.57, 70.31, 70.06 (6 OCH_2), 49.08, 44.02, 31.68, 19.28 (4 CH_2), 15.19, 13.89 (2 CH_3).

***N*-(2-Methoxyethyl)acetamide (13).** Acetyl chloride (26.0 g, 0.33 mol) was added dropwise with stirring to a cooled (0 °C) solution of 2-methoxyethylamine (22.6 g, 0.30 mol) and triethylamine (33.4 g, 0.33 mol) in 200 mL of benzene. The reaction mixture was refluxed overnight and filtered to remove the triethylamine hydrochloride. The salt was washed with benzene and the combined organic layers dried over sodium sulfate. The solvent was removed in vacuo, and the crude oil was distilled under vacuum, affording the colorless oil **13** (32.72 g, 94%): bp 75–90 °C, 0.1 mmHg; IR (neat) 3385, 1650, 1445, 1375, 1130 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 6.53 (br, 1 H, N*H*), 3.55 (m, 2 H, CH_2CH_2N), 3.51 (m, 2H, OCH_2), 3.43 (s, 3H, OCH_3), 2.07 (s, 3H, CH_3C=O). (Chemical shift assignments were made by using $Eu(fod)_3$ shifted spectra.)

***N*-(2-Methoxyethyl)ethylamine (14).** Acetamide **13** (10.0 g, 0.085 mol) was added dropwise with stirring to a cooled (0 °C) suspension of $LiAlH_4$ (3.90 g, 0.10 mol) in 200 mL of diethyl ether under nitrogen and the reaction mixture refluxed overnight. Excess $LiAlH_4$ was neutralized with ice water, and the solid was removed by vacuum filtration and washed with ether. The ether layer was dried over sodium sulfate and the solvent removed by distillation. Distillation of the crude oil yielded the colorless amine **14** (5.25 g, 60%): bp 20–24 °C, 10 mmHg; IR (neat) 3310, 1455, 1380, 1115 cm^{-1}; ^{13}C NMR (15 MHz, $CDCl_3$) δ 72.25 (CH_2OCH_3), 58.80 (OCH_3), 49.32 ($NHCH_2CH_2OCH_3$), 44.18 (NCH_2CH_3), 15.33 (CH_2CH_3).

***N*-Ethyl-*N*-(3,6,9-trioxatridecyl)-3,6,9-trioxatridecanamide (3).** 3,6,9-Trioxatridecanoyl chloride (10 g, 0.042 mol) in 25 mL of benzene was added dropwise with stirring to a solution of amine **9** (8 g, 0.034 mol) and triethylamine (3.5 g, 0.035 mol) in 75 mL of benzene at room temperature. The reaction mixture was warmed at 35 °C with stirring for 1 h and then filtered to remove the triethylamine salt. The slightly acidic reaction mixture was washed with saturated $NaHCO_3$ and water and dried over magnesium sulfate. The solvent was removed in vacuo, affording 13.7 g of crude **3** as a light yellow oil (0.031 mol, 92.6%). TLC on silica gel with ethyl acetate gave one spot with an rf of 0.18. Purification was accomplished by MPLC on silica gel (230–400 mesh) with ethyl acetate as the eluting solvent: IR (neat) 2950–2850, 1640, 1455, 1350, 1115 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 4.31, 4.27 (2 s, 2 H, CH_2C=O), 3.67–3.41 (m, 26 H), 1.55 (quintet, 4 H, $CH_3CH_2CH_2CH_2O$–), 1.38 (sextet, 4 H, $CH_3CH_2CH_2CH_2O$–), 1.19, 1.12 (2 t, 3 H, NCH_2CH_3), 0.928 (t, 6 H, $CH_3CH_2CH_2CH_2O$–); ^{13}C NMR (15 MHz, $CDCl_3$) δ 169.07, 168.91 (C=O); 71.09, 70.57, 70.06, 69.50, 69.25; 46.45, 45.38 (NCH_2CH_2O–); 42.82, 41.06 (NCH_2CH_3); 31.71, 19.28, 13.92, 12.75; mol wt 435.3196 (m/e, $M^{+\cdot}$).

***N*-Ethyl-*N*-(3,6,9-trioxatridecyl)acetamide (1).** An excess of acetyl chloride in 5 mL of benzene was added dropwise with stirring to a heated mixture of amine **9** (0.8 g, 0.0034 mol) and triethylamine (0.38 g, 0.0037 mol) in 20 mL of benzene. A white vapor formed, succeeded by for-

mation of the white triethylamine salt. After 1 h of refluxing and stirring at room temperature overnight, the reaction mixture was filtered. The acidic benzene layer was washed with saturated $NaHCO_3$ (3 × 7 mL) and water (10 mL) and dried over magnesium sulfate. The solvent was removed in vacuo, yielding 0.55 g of amide **1** (0.002 mol, 58.8%) as a pale green oil, 95.4% pure by GC. The crude amide was distilled under vacuum, affording colorless **1**: bp 133–135 °C, 0.05 mmHg; IR (neat) 2950–2850, 1640, 1450, 1370, 1260, 1115 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 3.65–3.39 (m, 17 H), 2.11, 2.09 (2 s, 2 H, $CH_3C{=}O$), 1.55 (quintet, 2 H, $CH_3CH_2CH_2CH_2O$–), 1.38 (sextet, 2 H, $CH_3CH_2CH_2CH_2O$–), 1.19, 1.10 (2 t, 3 H, NCH_2CH_3), 0.928 (t, 3 H, $CH_3CH_2CH_2CH_2O$–); ^{13}C NMR (15 MHz, $CDCl_3$) δ 170.62 (C=O), 71.28, 70.69, 70.11, 69.59, 69.46; 48.15, 45.42 (NCH_2CH_2O–); 44.70, 40.93 (NCH_2CH_3); 31.71, 19.30, 13.97, 12.93.

***N*-Ethyl-*N*-(2-methoxyethyl)acetamide (4).** Acetyl chloride (8.0 g, 0.10 mol) was added dropwise with stirring to a cooled (0 °C) solution of *N*-(2-methoxyethyl)ethylamine (9.0 g, 0.087 mol) and triethylamine (10.0 g, 0.099 mol) in 150 mL of benzene. The mixture was refluxed overnight. The triethylamine salt was removed by vacuum filtration and washed with benzene. The benzene layer was dried over sodium sulfate, and the solvent was removed in vacuo. Vacuum distillation of the crude oil afforded the colorless amide **4**: bp 55–59 °C, 0.15 mmHg (10.95 g, 87%); IR (neat) 2960–2800, 1650, 1430, 1370, 1125 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 3.52, 3.50 (2 s, 3 H), 3.45, 3.39 (2 qt, 2 H, NCH_2CH_3), 3.35, 3.32 (**4** H), 2.09 (s, 3 H, $CH_3C{=}O$), 1.18, 1.10 (2 t, 3 H, NCH_2CH_3); ^{13}C NMR (15 MHz, $CDCl_3$) δ 170.62, 170.42 (C=O), 71.02, 70.76 (CH_2OCH_3), 58.93, 58.67 (OCH_3), 48.02, 45.29 ($NCH_2CH_2OCH_3$), 44.57, 40.80 (NCH_2CH_3), 21.64, 21.18 ($CH_3C{=}O$), 13.84, 12.73 (CH_2CH_3).

***N*-Ethyl-*N*-(2-methoxyethyl)methoxyacetamide (5).** Methoxyacetic acid (6.62 g, 0.074 mol) was added dropwise with stirring to distilled thionyl chloride (37 g, 0.296 mol). The reaction mixture was stirred at 50–60 °C for 30 min. The excess $SOCl_2$ was removed by distillation, yielding 6.10 g of crude methoxyacetyl chloride: IR (neat) 1840 (m), 1780 (s) cm^{-1}. The crude methoxyacetyl chloride was added dropwise with stirring to a cooled (0 °C) solution of *N*-(2-methoxyethyl)ethylamine (**14**) (5.0 g, 0.049 mol) and triethylamine (5.45 g, 0.054 mol) in 200 mL of benzene. The reaction mixture was refluxed overnight. The triethylamine salt was filtered from the solution and the filtrant dried over sodium sulfate. The solvent was removed in vacuo, and the crude oil was distilled under vacuum, yielding the colorless oil **5**: bp 74–76 °C, 0.12 mmHg (4.75 g, 55.4%); IR (neat) 2960–2810, 1650, 1455, 1365, 1190, 1115, 1015 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 4.18, 4.15 (2 s, 2 H, $-CH_2C{=}O$), 3.52–3.32 (m, 12 H), 1.18, 1.12 (2 t, 3 H, NCH_2CH_3); ^{13}C NMR (15 MHz, $CDCl_3$) δ 169.00, 168.80 (C=O), 71.47, 71.21, 70.89, 70.82, 59.06; 46.38, 45.29 (NCH_2CH_2O–); 42.75, 41.00 (NCH_2CH_3); 13.97, 12.80.

***N*-Ethyl-*N*-(2-methoxyethyl)-3,6,9-trioxatridecanamide (6).** Acid **7** (4.27 g, 0.0194 mol) was added dropwise with stirring to refluxing thionyl chloride (9.24 g, 0.078 mol). The reaction mixture was refluxed for 30 min, and the excess thionyl chloride was distilled off with 50 mL of benzene. The crude acid chloride was added dropwise with stirring to a cooled solution (0 °C) of amine **14** (2.0 g, 0.0194 mol) and triethylamine (2.5 g, 0.025 mol) in 50 mL of benzene and the reaction mixture refluxed overnight. The slightly basic reaction mixture was filtered to remove the triethylamine salt, washed with water, 7% HCl, and brine, and then dried over sodium sulfate. The solvent was removed in vacuo, yielding 6.27 g of crude **5**, a dark brown liquid. The crude oil was chromatographed on a 40-g silica gel (230–400 mesh) gravity column, with ethyl acetate as the eluting solvent, affording 4.71 g (79.5%) of yellow oil. A fraction of 1.51 g was further purified in the same manner, yielding 0.754 g (0.0025 mol) of colorless amide **5**: IR (neat) 2960–2850, 1640, 1460, 1350, 1120 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 4.29, 4.27 (2 s, 2 H, $CH_2C{=}O$), 3.67–3.32 (m, 19 H), 1.53 (quintet, 2 H, $CH_3CH_2CH_2CH_2O$), 1.38 (sextet, 2 H, $CH_3CH_2CH_2CH_2O$), 1.18, 1.11 (2 t, 3 H, NCH_2CH_3), 0.927 (t, 3 H, $CH_3CH_2CH_2CH_2O$); ^{13}C NMR (15 MHz, $CDCl_3$) δ 169.19 (C=O), 71.21, 70.69, 70.17, 58.87; 46.52, 45.42 ($NCH_2CH_2OCH_3$); 42.88, 41.26 (NCH_2CH_3); 31.84, 19.30, 13.90, 12.99.

***N*-Ethyl-*N*-(3,6,9-trioxatridecyl)methoxyacetamide (2).** Methoxyacetic acid (1.16 g, 0.013 mol) was added dropwise with stirring to refluxing thionyl chloride (6.13 g, 0.052 mol), and refluxing was continued until the evolution of gas was completed. The excess thionyl chloride was removed by distillation. The crude acid chloride was added dropwise with stirring to a cooled (0 °C) solution of amine **9** (3.0 g, 0.013 mol) and triethylamine (1.3 g, 0.013 mol) in 30 mL of benzene. The reaction mixture was refluxed for 1 h. The salt was removed by vacuum filtration and washed with benzene. The slightly acidic reaction mixture was washed with water, saturated $NaHCO_3$ (2 × 5 mL), and saturated NaCl and dried over sodium sulfate. The solvent was removed in vacuo, yielding 2.88 g (73.3%) of crude **2** as an orange-brown oil. The crude amide was chromatographed on a 40-g silica gel (230–400 mesh) gravity column with ethyl acetate as the eluting solvent, yielding 1.96 g of a pale yellow oil. The purification procedure was repeated, affording 0.732 g (0.0024 mol, 18.5%) of colorless amide **2**: IR (neat) 2950–2850, 1640, 1460, 1350, 1120 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 4.22, 4.15 (2 s, 2 H, $CH_2C{=}O$), 3.61–3.38 (m, 19 H), 1.55 (quintet, 2 H, $CH_3CH_2CH_2CH_2O$), 1.38 (sextet, 2 H, $CH_3CH_2CH_2CH_2O$), 1.19, 1.12 (2 t, 3 H, NCH_2CH_3), 0.928 (t, 3 H, $CH_3CH_2CH_2CH_2O$); ^{13}C NMR (15 MHz, $CDCl_3$) δ 168.95 (C=O), 71.49, 71.23, 70.64, 70.13, 69.41 (8 C), 59.02; 46.43, 45.52 (NCH_2CH_2O–); 42.85, 41.10 (NCH_2CH_3); 31.75, 19.28, 13.89.

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