^{1}H NMR Spectroscopic Investigation of the Mechanism of 2-Substituted-2-Oxazoline Ring Formation and of the Hydrolysis of the Corresponding Oxazolinium Salts

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Keywords: 2-Oxazolines / 2-Substituted-2-oxazolinium salts / Hydrolysis / Reaction mechanisms

Chlorination of 2-hydroxyethylamides containing electron-donor substituents such as alkyl, phenyl or alkyl- or alkyloxy-substituted phenyl at 23 °C with $SOCl_2$ proceeds *via* 2-substituted-2-oxazolinium hydrochlorides that can be transformed in situ into 2-substituted-2-oxazolines by neutralization with a weak base. The mechanism of neutral and base-assisted hydrolysis of 2-substituted-2-oxazolinium salts occurs by the nucleophilic attack at the C2 rather than the C5 position of the ring and yields the *N*-substituted-(2-hydroxyethyl)amide via the rearrangement of an amino ester intermediate. The elucidation of the mechanisms of these two reactions provides a one-pot, two-step method for the synthesis of the 2-substituted-2-oxazolines and clarifies the limitations of the functionalization of 2-substituted-2-oxazolinium salts by hydrolysis under neutral and basic conditions.

Introduction

Cyclic iminoethers[1] are used as ligands in catalysis,[2] protective groups for carboxylic acids,[3] local anesthetics,[4] monomers in cationic ring-opening polymerization,[5] in the synthesis of polymers with complex architecture,[6] etc. One method for their synthesis involves the chlorination of 2-hydroxyethylamides with $SOCl_2$ to yield 2-chloroethylamides which, upon dehydrohalogenation with a strong base, give 2-substituted-2-oxazolines. [1,7] A few publications have reported that chlorination of 2-hydroxyethylamides yields directly the 2-substituted-2-oxazolinium hydrochloride rather than the 2-chloroethylamide.[3,8] The 2-substituted-2-oxazolinium hydrochlorides form the corresponding 2-substituted-2-oxazolines upon neutralization with a weak base. These two different procedures to transform 2-hydroxyethylamides into 2-substituted-2-oxazolines via reaction with $SOCl_2$ imply that the mechanism of this reaction might be determined by the nature of the substituent attached to the 2-hydroxyethylamide. In addition, the reaction of the 2-substituted-2-oxazolinium salt with nucleophiles, including 2-substituted-2-oxazolines, H_2O, HO^-, etc., is usually considered to occur at the C5 position of the ring and is important for the living character of the propagation step and for the chain-end functionalization of poly(2-substituted-2-oxazoline)s.[1e,5b,5c,9,10] The reaction mechanism of the 2-substituted-2-oxazolinium salt with H_2O is not elucidated.[10,11] This publication presents a ^{1}H NMR spectroscopic investigation on the mechanism of 2-substituted-2-oxazoline ring formation as well as on the hydrolysis of the corresponding oxazolinium salt. The goal is to elucidate the mechanism of 2-substituted-2-oxazoline synthesis and of the neutral and base-assisted hydrolysis of 2-substituted-2-oxazolinium salts. The hydrolysis reaction represents a model for the functionalization of the 2-substituted-2-oxazolinium propagating chains frequently encountered during the cationic ring-opening polymerization of cyclic imino ethers.

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Results and Discussion

Formation of the 2-Substituted-2-Oxazoline Ring from Substituted 2-Hydroxyethylamides and $SOCl_2$

The reaction of $SOCl_2$ with **1a** and **1b** (Scheme 1)2 is too fast to be followed kinetically. Complete transformation of **1a** and **1b** into the oxazolinium salt **7** is achieved at 23 °C in 3 and 4 min, respectively. This is due to the electron-donating and resonance-stabilization effects of the substituent R which enhances the reactivity of the carbonyl in the intramolecular attack that leads to the formation of the oxazolinium ring. Compound **7** is stable in $CDCl_3$ solution at 23 °C for up to 1.5 h, when formation of **8** was first observed. Compound **8** also formed when the reaction temperature was raised from 23 °C to 50 °C for 35 min. Therefore, less-reactive 2-hydroxyethylamides were employed in order to follow the mechanism of the 2-substituted-2-oxazoline formation at 23 °C. For **1c**, which should be as reactive as **1a**, a conversion of 100% to **7** was achieved in 6 minutes, again too fast to be followed kinetically. When **1d** was employed, some reaction intermediates could be seen since complete conversion into **7** is achieved in 20 min at 23 °C.

The most successful experiment was with compound **1e**. Reaction of **1e** with $SOCl_2$ is complete at 23 °C in 100 min, and all intermediaries could be followed by monitoring the

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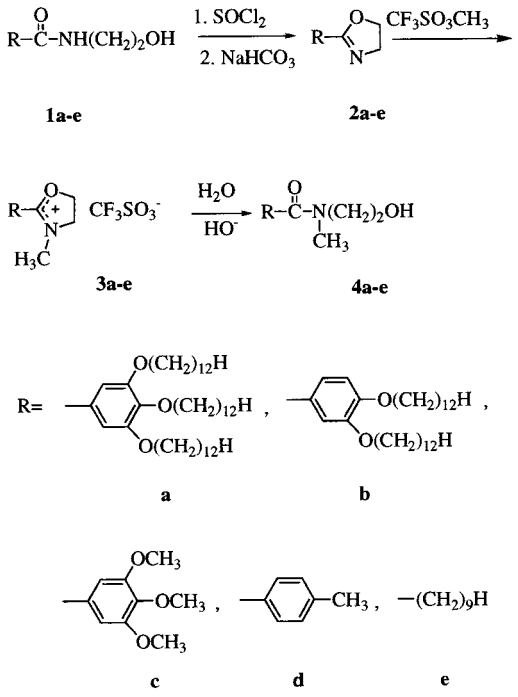
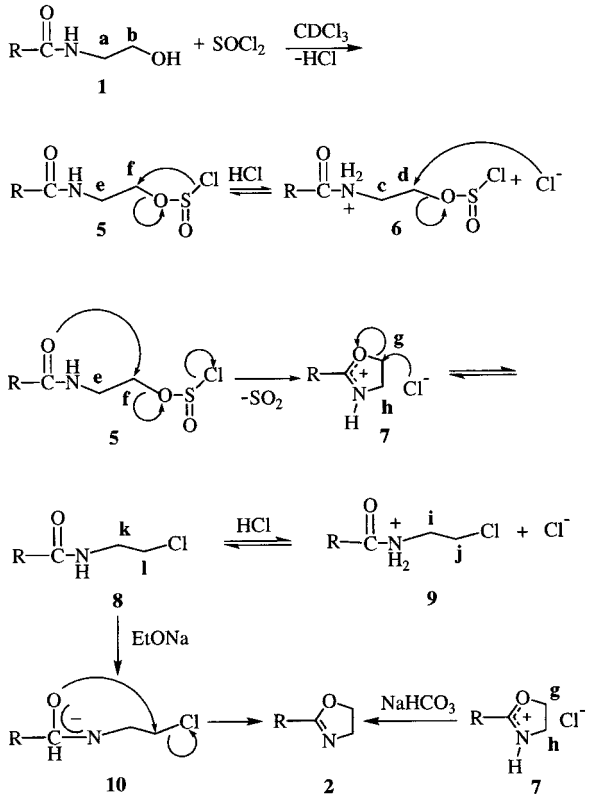
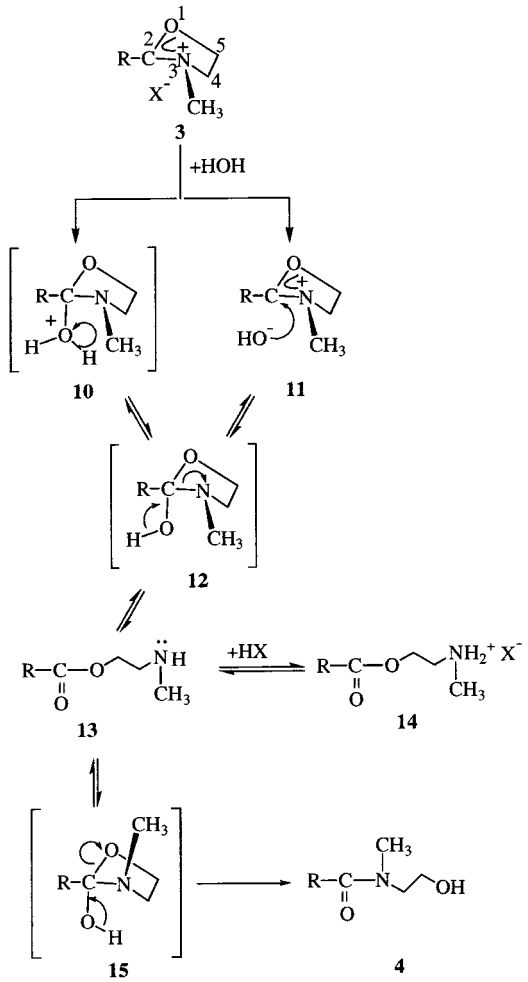


Scheme 1. Synthesis and hydrolysis of 2-substituted-2-oxazolinium triflates **3a–e**



Scheme 2. The mechanism of 2-substituted-2-oxazoline formation from the respective 2-hydroxyethylamides and $SOCl_2$ via the 2-substituted-2-oxazolinium hydrochloride

chemical shifts of the ethylene bridge protons by ^1H NMR spectroscopy in $CDCl_3$ (Figure 1, Scheme 2). The reaction starts with the nucleophilic attack of the hydroxyl group of



Scheme 3. The mechanism of the neutral and base-assisted hydrolysis of the 2-substituted-2-oxazolinium salts **3a–e**

1e on the $SOCl_2$. After 1 min, compound **5** is observed at equilibrium with its hydrochloride salt **6** (protons **e**, **f** and **c**, **d**, respectively). The formation of the salt **6** is thermodynamically favored and therefore prevails in subsequent spectra, while the kinetically favored **5** is quickly consumed both in this equilibrium and in the formation of the oxazolinium ring. Usually, in the reaction of alcohols with $SOCl_2$, the formation of the sulfite ester **5** is followed by an internal nucleophilic substitution (S_Ni) with retention of configuration to form a halide derivative of type **8**.[12] This is not the case here, since **7** is observed together with **5** and **6** beginning with spectra taken after 1 min, while **8** is formed only subsequently. Most probably, the nucleophilicity of oxygen and the positive partial charge on the carbon induced by the electron-withdrawing effect of the OSOCl group favor the attack of the carbonyl oxygen at the carbon next to the OSOCl group instead of the usual S_Ni displacement of SO_2. Moreover, because this reaction is an intramolecular attack with a five-membered ring transition state, it is also kinetically favored compared to the attack of other nucleo-

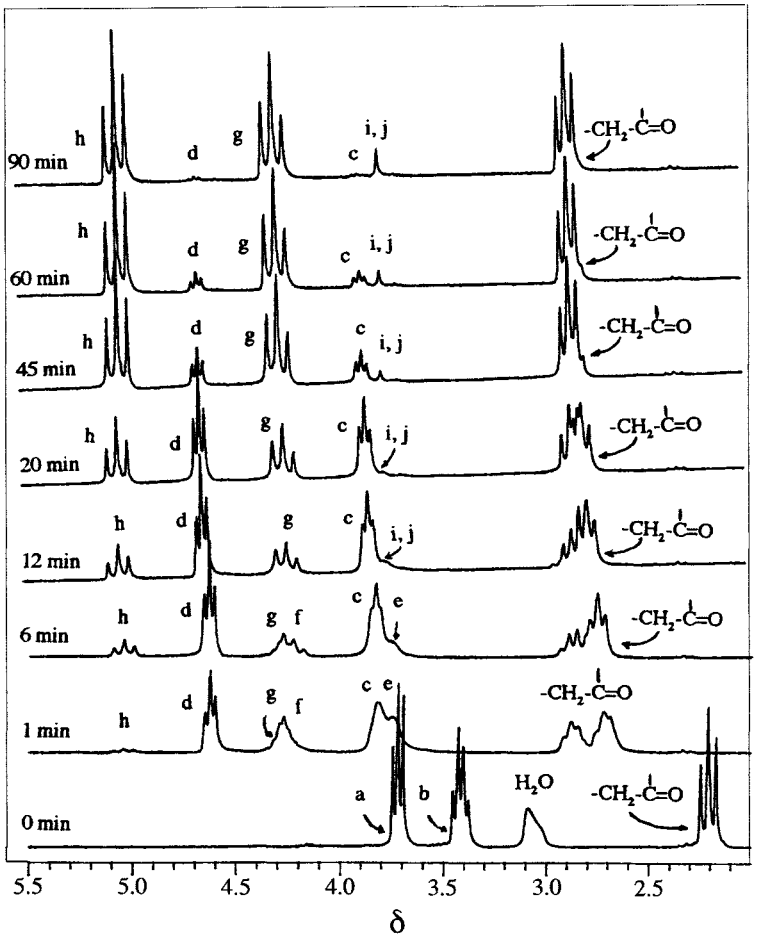


Figure 1. ^1H NMR (200 MHz) spectra for the reaction of **1e** with $SOCl_2$ in dry $CDCl_3$ at 23 °C; the reaction time is marked on each spectrum; protons are labeled according to Scheme 2

philes in the system, such as Cl^-, and therefore **8** is observed only later in the mechanism. Spectra taken after 20 min show **6** along with the oxazolinium ring formation (protons **c**, **d** yield protons **h**, **g**, respectively). Nevertheless, formation of the oxazolinium ring from **6** is less probable, since the carbonyl group is not so nucleophilic in the tertiaryamide. Therefore, compound **5** is consumed to form **7** as soon as it is obtained from **6**. Formation of **8** by the nucleophilic attack of Cl^- at the 5-position of **7**, followed by neutralization to **9**, is demonstrated from spectra taken after more than 30 min (protons **i**, **j**).

A similar experiment was performed in the presence of traces of H_2O. This created traces of HCl from the very beginning. Compound **9** was observed in the early stages of the reaction along with the formation of **5** and **6**, due to the competition of intramolecular attack of oxygen with the intermolecular attack of Cl^-.

Reaction of **7** with $NaHCO_3$ at 23 °C yields instantaneously the 2-substituted-2-oxazoline **2**. This reaction has been reported previously.[8] Compound **2** could be also prepared from **9** in the presence of EtONa/EtOH.[13] This reaction gives complete conversion of **9** to **2** within 2.5 min.

Neutral and Base-Assisted Hydrolysis of the Oxazolinium Triflate Salts

The positive charge of oxazolinium salts makes them susceptible to nucleophilic attack by the counteranion X^- at their C5 position (**7** to **8** in Scheme 2 and Scheme 3).[11] However, the most reactive nucleophilic 2-substituted-2-oxazolines (i.e., those containing electron-donating substituents) produce the most unreactive 2-oxazolinium salts. In addition, the oxazolinium triflates are even more stable since the triflate counteranion is a very weak nucleophile which is unable to attack the oxazolinium ring.[14] Compounds **3a** and **3b** are stable in dry deuterated solvents for up to seven days. However, upon mixing **3a** and **3b** with [D_6]DMSO containing traces of H_2O, chemical changes occur and the reaction could be followed by time-resolved ^1H NMR spectroscopy (Figure 2). For **3b**, several protons were used to identify the products: the bridging CH_2O and CH_2N, the CH_3N or the aromatic protons. For example, the resonances for the ethylene protons in the oxazolinium salt yields triplets **d** and **e** at δ = 4.28 and δ = 5.01, respectively. Hydrolysis leads to the correspondent formation of triplets **d′** and **e′** at δ = 3.22 and δ = 4.58, respectively, and

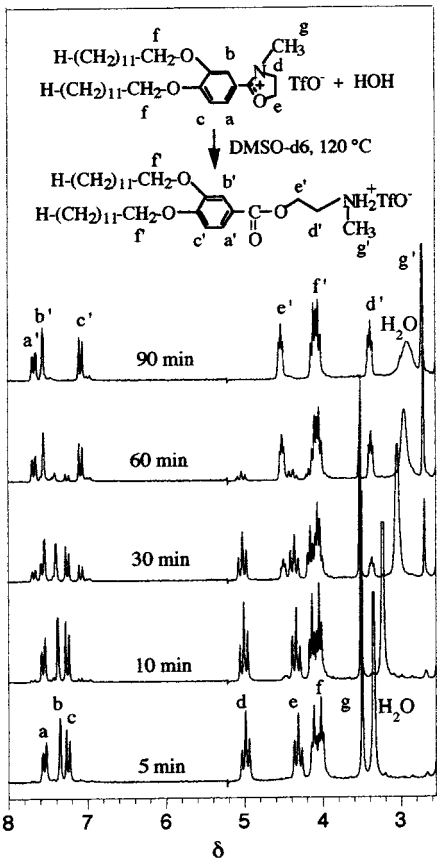


Figure 2. Time-resolved ^{1}H NMR (200 MHz) spectra for the reaction of **3b** with H_2O in [D_6]DMSO at 120 °C; the reaction time is marked on each spectrum

complete consumption of the 2-oxazolinium salt is observed in 1.5 h at 120 °C. The final spectrum is characteristic of the aminoethyl ester **13**. This is stable in solution for up to 48 h at 23 °C. Further addition of KOH (saturated solution in D_2O) leads to rapid formation of the hydroxylamide **4**, with the corresponding triplets at $\delta = 3.55$ (CH_2OH) and $\delta = 3.80$ (CH_2NHCO). Parallel experiments in which base was added from the beginning showed that **4** is formed within 16 min at 23 °C. No intermediaries could be seen due to the broadening of the peaks.

The conformation of **3** is exclusively *anti* imposed by the cycle. Previous studies carried out on imidate salts have shown that this conformation is responsible for a specific mechanism of ring opening upon attack of a suitable anion.[11b,11c]

When **3b** comes in contact with traces of H_2O in [D_6]DMSO, H_2O acts as a nucleophile (Scheme 3) and attacks the positively charged C2 to form **10**. Rapid release of proton leads to the formation of the hemiorthoamide intermediate **12**. This has a lone pair orbital on OCH_2 and the lone pair orbital on N oriented antiperiplanar to the C−OH bond and thus the OH group is susceptible to be expelled. On the other hand, the lone pair orbital of OH and a lone pair orbital of OCH_2 are oriented antiperiplanar to the C−N bond, and this creates a low energy barrier for the fragmentation of the C−N bond. Consequently, under kinetically controlled conditions the aminoalkyl ester **13** is obtained. Compound **13** is further stabilized by neutralization with acid and forms **14**.

It is conceivable that the triflate anion of **3** exchanges with H_2O to form **11**. The nucleophilic attack of HO^- at C2 leads to the formation of **12**. This hypothesis was tested by addition of a small quantity of triflic acid to a solution of **3b** in [D_6]DMSO at 120 °C. After 1 h, compounds **13** and **15** were not observed and decomposition was observed after 1.5 h. This could be due either to the neutralization of HO^- or to the impeded release of a proton from **10**. Consequently, the attack at the C2 carbon could not be assigned specifically, although it is probable that both the H_2O and HO^- present in solution are responsible for the nucleophilic attack.

Addition of KOH to the solution irreversibly traps the H^+X^- formed earlier by neutralization, thus impeding the stabilization of **13** to **14**. A nucleophilic attack of N at the ester fragment is kinetically favored and leads to the formation of the tetrahedral intermediate **15**. This has the lone electron pairs of O and N aligned in an antiperiplanar orientation to the C−O bond, hence the ring opens with the formation of the thermodynamically stable **4**.

In conclusion, the nature of the intermediates and the succession of reaction steps involved in the oxazolinium ring formation and hydrolysis were elucidated. It was established that the formation of the 2-oxazolinium salt **7** is an intermediary step in the formation of 2-chloroethylbenzamides **8**. When the R group of **1** is phenyl, alkyl- and alkyloxy-substituted phenyl or alkyl the 2-substituted-2-oxazolinium chloride **7** is obtained during the chlorination of the 2-hydroxyethylamide 1 with $SOCl_2$ at 23 °C. Compound **7** can be transformed into **2** by neutralization with a weak base such as $NaHCO_3$. The reaction of 2-oxazolinium triflates with H_2O follows an orbital-assisted mechanism of ring opening similar to that observed in the imidate salts.[11b,11c] Hydrolysis of 2-substituted-2-oxazolinium triflates in neutral conditions results in the formation of the aminoalkyl ester **13**, while addition of a base leads to the formation of the hydroxylamide **4**. Thus, while most nucleophiles, including 2-substituted-2-oxazolines and counteranions, attack the C5 position of the oxazolinium ring, H_2O and HO^- attack the C2 position. These results confirm the experiments reported by Nuyken et al.[10] The reaction of the electrophilic 2-oxazolinium rings with H_2O and HO^- is quantitative. However, in the case of the hydrophobic polyoxazolines, the selectivity of the reaction of HO^- or H_2O with the 2-oxazolinium chain end of the polymer decreases with the increase of the polymer hydrophobicity, i.e. with the increase of its molecular weight. The elucidation of these two reaction mechanisms facilitates both a simplified and more direct approach (i.e., two-step, one-pot reaction at room temperature) to the synthesis of 2-substituted-2-oxazolines from 2-hydroxyethylamides and clarifies the synthetic capabilities for the chain-end functionalization of their polymers.

Experimental Section

Materials: THF and Et_2O were refluxed over sodium ketyl and distilled before use. CH_2Cl_2 was refluxed over CaH_2 and distilled before use. Benzene was shaken with H_2SO_4, washed with H_2O, dried with $MgSO_4$ and distilled over sodium ketyl. $SOCl_2$ (97%), ethanolamine (99+%) and methyl trifluoromethanesulfonate (MeOTf) (≥97%) were vacuum distilled. $CDCl_3$ (99.9%) and [D_6]DMSO (99.9%) were passed through $MgSO_4$ and distilled under vacuum over molecular sieves.

General Methods: ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Varian Gemini 200 spectrometer. Chemical shifts are reported as δ values. Purity was determined by thin layer chromatography (TLC) on silica gel plates (Kodak) with fluorescent indicator, and high pressure liquid chromatography (HPLC). HPLC measurements were carried out with a Perkin−Elmer Series 10 high pressure liquid chromatograph equipped with an LC-100 column oven, Nelson Analytical 900 Series integrator data station and two Perkin−Elmer PL gel columns of 5×10^2 and 1×10^4 Å in THF at 40 °C and UV detection at 254 nm. Elemental analysis were carried out at MHV Laboratories, Phoenix, Arizona.

Syntheses: The 2-hydroxyethylamides **1a−e** were obtained from the corresponding acid chlorides, which were synthesized at 23 °C in CH_2Cl_2 by the DMF-catalyzed reaction of the respective acids with an excess of $SOCl_2$ (5:1), followed by distillation of the solvent and $SOCl_2$ under vacuum. The acid chlorides were used in the next step without purification.

General Procedure for the Synthesis of Compounds 1a−e. − 3,4,5-Tris(dodecanyloxy)-*N*-(2-hydroxyethyl)benzamide (1a):[15] 3,4,5-Tris(dodecanyloxy)benzoyl chloride[16] (17.6 g, 25.5 mmol) was dissolved in CH_2Cl_2 (400 mL) and slowly added to ice-cooled ethanolamine (25.0 mL) with vigorous stirring. The mixture was stirred at 0 °C for 1 h and the temperature was then raised to 40 °C for another 4 h. The solution was then poured into a separatory funnel and washed three times with H_2O, dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation and the crude product was recrystallized twice from acetone at 0 °C to yield 16.1 g (87.6%) of a white powder, m.p. 68−70 °C. Purity (HPLC), 99+%. − TLC (1:1 hexanes/EtOAc), R_f = 0.42. − ^{1}H NMR ($CDCl_3$, TMS): δ = 0.88 (t, J = 6.3 Hz, 9 H, CH_3), 1.27−1.65 [m, 54 H, $CH_3(CH_2)_9$], 1.78 (m, 6 H, CH_2CH_2OAr), 2.68 (br. s, 1 H, OH), 3.62 (q, J = 4.5 Hz, 2 H, CH_2OH) 3.83 (t, J = 4.8 Hz, 2 H, NHCH_2), 3.99 (overlapped t, 6 H, CH_2OAr), 6.53 (m, 1 H, CONH), 6.97 (s, 2 H, Ar). − ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 22.7 (CH_3CH_2), 26.1 ($CH_2CH_2CH_2O$), 29.4, 29.6 ($CH_3CH_2CH_2(CH_2)_6$), 30.3 (CH_2CH_2OAr), 31.9 ($CH_3CH_2CH_2$), 43.0 (NHCH_2), 62.5 (CH_2OH), 69.3 (CH_2OAr, 4-position), 73.4 (CH_2OAr, 3,5-position), 105.7 (*ortho* to O), 128.9 (*ipso* to CONH), 140.8 (*para* to CONH), 153.1 (*meta* to CONH), 168.4 (CONH).

3,4-Bis(dodecanyloxy)-*N*-(2-hydroxyethyl)benzamide (1b):[15] From 3,4-bis(dodecanyloxy)benzoyl chloride[16] (18.9 g, 37.0 mmol) and ethanolamine (25.0 mL, excess) in CH_2Cl_2 (125 mL), following the procedure outlined above, 17.2 g (87.2%) of a white powder was obtained after two recrystallizations from acetone, m.p. 86−88 °C Purity (HPLC), 99+% TLC (1:1 hexanes/EtOAc): R_f = 0.26. − ^{1}H NMR ($CDCl_3$, TMS): δ = 0.88 (t, J = 6.3 Hz, 6 H, CH_3), 1.26−1.68 [overlapped peaks, 36 H, $CH_3(CH_2)_9$], 1.87 (m, 4 H, CH_2CH_2OAr), 2.75 (br. s, 1 H, OH) 3.63 (q, J = 5.0 Hz, 2 H, CH_2OH), 3.85 (t, J = 5.1 Hz, 2 H, NHCH_2), 4.04 (overlapped t, 4 H, CH_2OAr), 6.55 (br. s, 1 H, NH), 6.88 (d, J = 8.2 Hz, 1 H, *meta* to CONH), 7.28 (dd, J = 8.2 Hz, J = 2.4 Hz, 1 H, *ortho* to CONH), 7.40 (d, J = 2.4 Hz, 1 H, *ortho* to CONH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3), 22.6 (CH_3CH_2), 26.0 ($CH_2CH_2CH_2O$), 29.1, 29.2, 29.3, 29.4, 29.6 ($CH_3CH_2CH_2(CH_2)_6$), 30.2 (CH_2CH_2O), 31.9 ($CH_3CH_2CH_2$), 42.9 (NHCH_2), 62.3 (CH_2OH), 69.1, 69.4 (CH_2OAr), 112.3, 112.8 (*meta* to CONH, *ortho* to CONH and O), 119.8 (*ortho* to CONH), 126.4 (*ipso* to CONH), 148.9, 152.1 (*meta* to CONH, *ipso* to O and *para* to CONH), 168.4 (CONH).

***N*-(2-Hydroxyethyl)-3,4,5-trimethoxybenzamide (1c):** From 3,4,5-trimethoxy benzoyl chloride (11.5 g, 49.9 mmol) and ethanolamine (10.0 mL, 16.6 mmol) in CH_2Cl_2 (50 mL), a brown oil was obtained which was extracted three times with warm CH_2Cl_2 and recrystallized from CH_2Cl_2/hexane to yield 8.6 g (67.4%) of white needles, m.p. 118−120 °C. Purity (HPLC), 99+%. − TLC (1:1 hexanes/EtOAc): R_f = 0.35. − ^{1}H NMR ($CDCl_3$, TMS): δ = 3.05 (br. s, 1 H, OH), 3.62 (q, J = 5.6 Hz, 2 H, NHCH_2), 3.80 (m, 2 H, CH_2OH), 3.90 (overlapped s, 9 H, CH_3OAr), 6.72 (br. s, 1 H, NH), 7.07 (s, 2 H, Ar). − ^{13}C NMR ($CDCl_3$, δ) 39.6 (CH_2NH), 56.1 (CH_3OPh, 3,5 position), 60.2 (CH_3OPh, 4 position), 61.6 (CH_2OH), 105.5 (Ar, *ortho* to CONH), 128.9 (Ar, *ipso* to CONH), 142.8 (Ar, *para* to CONH), 155.8 (Ar, *meta* to CONH), 168.2 (CONH).

***N*-(2-Hydroxyethyl)-4-methylbenzamide (1d):** 4-Methyl benzoyl chloride (7.7 g, 49.9 mmol) was dissolved in C_6H_6 (50 mL) and added dropwise to an ice-cooled mixture of ethanolamine (20.0 mL, excess) and C_6H_6 (5 mL) with vigorous stirring. After addition was complete, the mixture was heated to 70 °C for 5 h. The solvent was removed under vacuum and the resulting oil was washed with H_2O and extracted three times with Et_2O/CH_2Cl_2 (2:1). The combined solutions were dried over $MgSO_4$ and the solvent distilled under vacuum to yield 6.7 g (75.7%) of pure product, m.p. 78−80 °C. Purity (HPLC), 99+%. − TLC (1:1 hexanes/EtOAc): R_f = 0.50. − ^{1}H NMR ($CDCl_3$, TMS): δ = 2.39 (s, 3 H, CH_3), 3.61 (q, J = 6.0 Hz, 2 H, NHCH_2), 3.80 (t, J = 6.0 Hz, 2 H, CH_2OH), 6.72 (br. s, 1 H, NH), 7.22 (d, J = 8.0 Hz, 2 H, 2,6-Ar), 7.68 (d, J = 8.0 Hz, 2 H, 3,5-Ar).

2-(*N*-Decanoyl)aminoethanol (1e): *n*-Decanoyl chloride (4.9 g, 26.0 mmol) was dissolved in 40 mL CH_2Cl_2 and added slowly to an ice-cooled mixture of ethanolamine (20.0 mL, excess) in CH_2Cl_2 (25 mL) with vigorous stirring. The mixture was then warmed to 23 °C for 16 h. The CH_2Cl_2 layer was separated and the solvent distilled under vacuum. The residue was washed with $NaHCO_3$ (5% in H_2O) and filtered. The precipitate was dissolved in CH_2Cl_2 and dried with $MgSO_4$. The solvent was removed under vacuum and final recrystallization from acetone yielded 5.1 g (92.3%) of a white powder, m.p. 56−59 °C Purity (HPLC), 99+%. − TLC (1:1 hexanes/EtOAc): R_f = 0.50. − ^{1}H NMR ($CDCl_3$, TMS): δ = 0.87 (t, 3 H, CH_3), 1.20−1.56 (m, 12 H, CH_2), 1.50−1.77 (m, 2 H, CH_2-CH_2-CO) 2.20 (t, 2 H, CH_2-CO), 3.1 (br. s, 1 H, −OH), 3.41 (q, J = 6.2 Hz, 2 H, NHCH_2), 3.72 (t, J = 6.2 Hz, 2 H, CH_2OH).

General Procedure for the Synthesis of Compounds 2a−d. − 2-[3,4,5-Tris(dodecanyloxy)phenyl]-2-oxazoline (2a):[15] Compound **1a** (15.0 g, 21.0 mmol) was dissolved in CH_2Cl_2 (270 mL) and $SOCl_2$ (5.0 mL, 70.0 mol) was added dropwise at 23 °C. After 10 min, ^{1}H NMR spectroscopy and TLC (1:1 hexanes/EtOAc) analysis indicated complete conversion. The reaction was neutralized by addition of a saturated $NaHCO_3$ solution (300 mL) accompanied by vigorous stirring of the two-phase system for 0.5 h. The organic layer was separated, washed three times with H_2O (200 mL), dried with

$MgSO_4$ and filtered. The solvent was removed on a rotary evaporator and the product was recrystallized twice from hexanes at 0 °C to yield 12.7 g (87.8%) of a white solid, m.p. 50−52 °C. Purity (HPLC), 99+%. − TLC (CH_2Cl_2), R_f = 0.30. − ^{1}H NMR ($CDCl_3$, TMS): δ = 0.88 (t, J = 6.3 Hz, 9 H, CH_3), 1.26 [m, 54 H, $CH_3(CH_2)_9$], 1.77 (m, 6 H, CH_2CH$_2$OAr), 4.00 (t, J = 6.5 Hz, 6 H, CH_2OAr), 4.04 (t, J = 10.0 Hz, 2 H, OCH$_2$CH_2N), 4.42 (t, J = 9.5 Hz, 2 H, OCH_2CH$_2$N), 7.15 (s, 2 H, Ar). − ^{13}C NMR ($CDCl_3$): δ =14.1 (*C*H$_3$), 22.7 (CH$_3$*C*H$_2$), 26.1 (*C*H$_2$CH$_2$CH$_2$OAr), 29.3, 29.6 [CH$_3$CH$_2$CH$_2$(*C*H$_2$)$_6$], 30.3 (*C*H$_2$CH$_2$OAr), 31.9 (CH$_3$CH$_2$*C*H$_2$), 54.9 (N*C*H$_2$), 67.6 (=CO*C*H$_2$), 69.1 (*C*H$_2$OAr, 4-position), 73.4 (*C*H$_2$OAr, 3,5-position), 106.6 (*ortho* to O), 122.4 (*ipso* to C), 140.9 (*para* to C), 152.9 (*meta* to C), 164.6 (*C*=N). − $C_{45}H_{81}NO_4$ (700.1): calcd. C 77.19, H 11.66; found C 76.97, H 11.76.

2-[3,4-Bis(dodecanyloxy)phenyl]-2-oxazoline (2b): From **1b** (16.8 g, 31.5 mmol) in CH_2Cl_2 (750 mL) and $SOCl_2$ (6.56 mL, 0.09 mol), neutralized by 750 mL of saturated $NaHCO_3$ was obtained 13.3 g (82.3%) of a white solid, m.p. 52−54 °C. Purity (HPLC), 99+%. − TLC ($CHCl_3$), R_f = 0.48. − ^{1}H NMR ($CDCl_3$, TMS): δ = 0.88 (t, J = 6.6 Hz, 6 H, CH_3), 1.26−1.70 [m, 36 H, CH$_3$(CH_2)$_9$], 1.78 (m, 4 H, CH_2CH$_2$OAr), 4.00 (overlapped t, 6 H, CH_2OAr, OCH$_2$CH_2N), 4.42 (t, J = 9.0 Hz, 2 H, OCH_2CH$_2$N), 6.87 (d, J = 9.2 Hz, 1 H, *meta* to CON), 7.47 (d, J = 2.6 Hz, 1 H, *ortho* to CON) 7.49 (dd, J = 9.2 Hz, J = 2.6 Hz, 1 H, *ortho* to CON). − ^{13}C NMR ($CDCl_3$): δ = 14.1 (*C*H$_3$), 22.7 (CH$_3$*C*H$_2$), 26.0 (*C*H$_2$CH$_2$CH$_2$O), 29.2, 29.3, 29.6 [CH$_3$CH$_2$CH$_2$(*C*H$_2$)$_6$], 30.2 (*C*H$_2$CH$_2$O), 31.9 (CH$_3$CH$_2$*C*H$_2$), 54.7 (N*C*H$_2$), 67.6 (OCN*C*H$_2$), 69.1, 69.3 (*C*H$_2$OAr), 112.5, 113.1 (*meta* to OCN, *ortho* to OCN), 119.8 (*ipso* to CON) 121.6 (*ortho* to OCN), 148.7 (*meta* and *para* to CON), 164.8 (O*C*=N). − $C_{33}H_{57}NO_3$ (515.8): calcd. C 76.84, H 11.14; found C 76.65, H 10.94.

2-[3,4,5-Trimethoxyphenyl]-2-oxazoline (2c): From **1c** (1.3 g, 5.0 mmol) and $SOCl_2$ (1.1 mL, excess) in CH_2Cl_2 (50 mL) at 23 °C for 20 min was obtained 1.1 g (88.9%) of a white solid after sublimation at reduced pressure, m.p. 64−66 °C. Purity (HPLC), 99+%. − TLC ($CHCl_3$), R_f = 0.65. − ^{1}H NMR ($CDCl_3$, TMS): δ = 3.87 (s, 9 H, CH_3OAr), 4.03 (t, J = 9.0 Hz, 2 H, OCH$_2$CH_2N), 4.42 (t, J = 9.0 Hz, 2 H, OCH_2CH$_2$N), 7.22 (s, 2 H, Ar). − ^{13}C ($CDCl_3$): δ =55.6 (*C*H$_2$N), 56.3 (*C*H$_3$OPh, 3, 5 position), 60.2 (*C*H$_3$OPh, 4 position), 67.5 (*C*H$_2$O), 105.2 (Ar, 2,6 position), 128.7 (Ar, 1 position), 143.0 (Ar, 4 position), 153.2 (Ar, 3, 5 position), 164.5 (O*C*N).

2-[4-Methylphenyl]-2-oxazoline (2d):[1b] From **1d** (6.5 g, 36.0 mmol) and $SOCl_2$ (8.0 mL, excess) in CH_2Cl_2 (100 mL) for 35 min, 3.2 g (72.4%) of a white solid was obtained after sublimation at reduced pressure. Purity (HPLC), 99+%. − m.p. 67−69 °C (ref.[1b] m.p. 67−68 °C). − TLC ($CHCl_3$) R_f = 0.52. − ^{1}H NMR ($CDCl_3$, TMS): δ = 2.39 (s, 3 H, CH_3Ar), 4.05 (t, J = 9.0 Hz, 2 H, OCH$_2$CH_2N), 4.42 (t, J = 9.0 Hz, 2 H, OCH_2CH$_2$N), 7.21 (d, J = 8.2 Hz, 2 H, 3,5-Ar), 7.84 (d, J = 8.2 Hz, 2 H, 2,6-Ar).

General Procedure for the Preparation of Compounds 3a−b. − 3-Methyl-2-[3,4,5-tris(dodecanyloxy)phenyl]-2-oxazolinium Triflate (3a): Compound **3a** was prepared by the addition of MeOTf to **2a** according to a literature procedure.[17] In a two-neck, pear-shaped flask equipped with a septum, magnetic stirrer and Ar inlet/outlet **2a** was dissolved (0.35 g, 0.50 mmol) in 5 mL anhydrous Et_2O under Ar. MeOTf (0.078 μL, 0.714 mmol) was added from a syringe after which time a precipitate formed over several minutes. After 3 h, the sealed flask was cooled to 4 °C in a refrigerator and allowed to stand for 2 h. The white precipitate was filtered under N_2 and rinsed with cold, anhydrous Et_2O. After drying on the filter under a stream of N_2, 0.41 g (95.1%) of a white powder was obtained, m.p. 56−58 °C. − TLC (2:1 hexanes/EtOAc) R_f = 0.2. − ^{1}H NMR ($CDCl_3$, TMS): δ = 0.88 (t, J = 6.2 Hz, 9 H, CH_3CH$_2$), 1.20−1.70 [m, 54 H, CH$_3$(CH_2)$_9$], 1.78 (m, 6 H, CH_2CH$_2$O), 3.61 (s, 3 H, CH_3N$^+$), 4.00 (t, J = 6.5 Hz, 4 H, CH_2OAr, 3,5-position), 4.09 (t, J = 6.6 Hz, 2 H, CH_2OAr, 4-position), 4.56 (t, J = 10.0 Hz, 2 H, CH_2N$^+$), 5.13 (t, J = 10.0 Hz, 2 H, CH_2O$^+$), 7.02 (s, 2 H, Ar). − ^{13}C NMR ($CDCl_3$): δ = 14.1 (*C*H$_3$), 22.6 (CH$_3$*C*H$_2$), 26.0 (*C*H$_2$CH$_2$CH$_2$OAr), 28.9, 29.0, 29.3 [CH$_3$CH$_2$CH$_2$(*C*H$_2$)$_6$], 29.6 (*C*H$_3$N$^+$) 31.8 (CH$_3$CH$_2$*C*H$_2$), 39.5 (*C*H$_2$CH$_2$OAr), 53.8 (N$^+$*C*H$_2$), 69.5 (*C*H$_2$OAr, 3,5-position), 69.8 (O$^+$*C*H$_2$), 73.7 (*C*H$_2$OAr, 4-position), 108.0 (*ortho* to C), 114.3 (*ipso* to C), 143.6 (*para* to C), 155.5 (*meta* to C), 170.7 (O−*C*$^+$−N). − $C_{47}H_{84}F_3NO_7S$ (864.2): calcd. C 65.32, H 9.80, N 1.62; found C 65.21, H 9.89, N 1.63.

3-Methyl-2-[3,4-bis(dodecanyloxy)phenyl]-2-oxazolinium Triflate (3b): From **2b** (0.367 g, 0.714 mmol) and MeOTf (78.3 μL, 0.714 mmol) in 10 mL anhydrous Et_2O 0.47 g (97.2%) of a white powder was obtained, m.p. 88−89 °C. − TLC (2:1 hexanes/EtOAc) R_f = 0.35. − ^{1}H NMR ($CDCl_3$, TMS): δ = 0.88 (t, J = 6.2 Hz, 6 H, CH_3CH$_2$), 1.25−1.75 [m, 36 H, CH$_3$(CH_2)$_9$], 1.78 (m, 4 H, CH_2CH$_2$O), 3.63 (s, 3 H, CH_3N$^+$), 4.05 (overlapped t, J = 6.5 Hz, 4 H, CH_2OAr), 4.54 (t, J = 10.0 Hz, 2 H, CH_2N$^+$), 5.11 (t J = 10.0 Hz, 2 H, CH_2O$^+$,), 6.99 (d, J = 8.2 Hz, 1 H, *meta* to CNO), 7.30 (d, J = 2.2 Hz, 1 H, *ortho* to CNO), 7.45 (dd, J = 8.2 Hz, J = 2.2 Hz, 1 H, *ortho* to CNO). − ^{13}C NMR ($CDCl_3$): δ = 14.1 (*C*H$_3$), 22.7 (CH$_3$*C*H$_2$), 26.0 (*C*H$_2$CH$_2$CH$_2$OAr), 28.8, 29.0, 29.3 [CH$_3$CH$_2$CH$_2$(*C*H$_2$)$_6$], 29.6 (*C*H$_3$N$^+$), 30.2 (*C*H$_2$CH$_2$O), 31.9 (CH$_3$CH$_2$*C*H$_2$), 36.4 (*C*H$_2$CH$_2$OAr), 53.8 (N$^+$*C*H$_2$), 69.3 (O$^+$*C*H$_2$), 69.6 (*C*H$_2$OAr, 4-position), 70.3 (*C*H$_2$OAr, 3-position), 111.0 (*ipso* to C) 112.3, 114.1 (*ortho* to C), 125.1 (*meta* to C), 149.32 (*para* to C), 152.9 (*meta* to C), 171.5 (O−*C*$^+$−N). − $C_{35}H_{60}F_3NO_6S$ (679.9): calcd. C 61.83, H 8.89, N 2.06; found C 61.66, H 8.96, N 2.08.

Reactions Followed by ^{1}H NMR Spectroscopy: All reactions were carried out directly in the NMR sample tube.

Reaction of 1a with $SOCl_2$: Compound **1a** (20.0 mg, 0.027 mmol) was dissolved at 23 °C under N_2 in 0.6 mL dry $CDCl_3$ and $SOCl_2$ (2.7μL, 0.033 mmol) was added. Conversion into **7a** was complete in 3 min and no changes were observed during 1 h. Compound **9a** was observed in a spectrum taken at 1.5 h reaction time. The same experiment was repeated at 50 °C, when formation of **9a** was observed in 35 min.

Reaction of 1b with $SOCl_2$: Compound **1b** (20.0 mg, 0.037 mmol) was dissolved at 23 °C under N_2 in 0.5 mL dry $CDCl_3$ and distilled $SOCl_2$ (7.91μL, 0.110 mmol) was added. Conversion into **7b** was complete in 4 min and no changes were observed during 0.5 h.

Reaction of 1c with $SOCl_2$: Compound **1c** (20.0 mg 0.078 mmol) was dissolved at 23 °C under N_2 in 0.6 mL dry $CDCl_3$ and distilled $SOCl_2$ (18.0 μL, 0.231 mmol) was added. Conversion into **7c** was complete in 6 min after which formation of **9c** was observed.

Reaction of 1d with $SOCl_2$: Compound **1c** (17.9 mg, 0.110 mmol) was dissolved at 23 °C under N_2 in 0.6 mL dry $CDCl_3$ and distilled $SOCl_2$ (8.1 μL, 0.110 mmol) was added. Conversion into **7d** and **9d** was complete in 20 min. Compound **9d** could be observed beginning with the spectrum taken at 0.5 h.

Reaction of 1e with $SOCl_2$: *N*-decanoyl-2-aminoethanol (16.2 mg, 0.075 mmol) was dissolved at 23 °C under N_2 in 0.8 mL dry $CDCl_3$ and distilled $SOCl_2$ (7.0 μL, 0.09 mmol) was added. Conversion into **7e** and **9e** was complete in 100 min. Compound **9e** could be

observed beginning with the spectrum taken at 12 min (Figure 1). After 24 h, only **9e** was observed in the system. The experiment was repeated with traces of H_2O; compound **9e** was observed at 6 min reaction time .

Neutral Hydrolysis of 3a: Compound **3a** (22.1 mg, 0.025 mmol) was dissolved in 0.8 mL [D_6]DMSO containing traces of H_2O and heated to 120 °C for 2 h. The results were similar to the neutral hydrolysis of **3b**, described below.

Neutral Hydrolysis of 3b: Compound **3b** (17.5 mg, 0.025 mmol) was dissolved in 0.7 mL [D_6]DMSO containing traces of H_2O and heated to 120 °C for 2 h. Compound **13b** was observed in the spectrum taken at 10 min and **3b** was completely converted into **13b** after 1.5 h (Figure 2). Compound **13b** is stable for up to 48 h in solution.

Basic Hydrolysis of 3b: Compound **3b** (17.5 mg, 0.025 mmol) was dissolved in 0.7 mL [D_6]DMSO containing traces of H_2O and heated to 120 °C for 2 h then cooled to 23 °C. After 48 h, KOH (3.0 mg, 0.053 mmol) in D_2O (0.3 mL) was added under N_2 to the solution of **3b** at 23 °C and stirred. Complete conversion into **4b** was obtained after 15 min. A similar experiment was performed adding the KOH solution at 80 °C from the beginning; formation of **4b** was observed after 16 min.

Reaction of 3b With H_2O in the Presence of Triflic Acid: In an NMR tube, compound **3b** (15.2 mg, 0.021 mmol) was dissolved in 0.7 mL [D_6]DMSO containing traces of H_2O and 3.2 μL of triflic acid . The sample was heated to 120 °C for 2 h. No change in the ^{1}H NMR spectrum was observed during the first 1.5 h, followed by progressive decomposition into unknown products.

Acknowledgments

Financial support from the National Science Foundation (DMR-97−08581) is gratefully acknowledged.

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Received January 9, 2000
[O00018]