The stock 1:10 imidazole/imidazolium ion buffer solution was prepared by dissolving the amount of imidazole (imidazole-*1-d*) to give 0.11 M imidazole in 0.1 M HCl(DCl). The ionic strength was maintained at 0.5 M with potassium chloride. Solutions of lower buffer concentration were prepared by dilution with 0.5 M potassium chloride solution. The atom fraction of deuterium was determined by Mr. Josef Nemeth.[34]

(34) Urbana, IL 61801.

Kinetics. The hydrolysis of *N*-acetylbenzotriazole was monitored by observing the decrease in absorbance at 300 nm, using a Cary 118C ultraviolet-visible spectrophotometer equipped with a constant-temperature cell compartment and interfaced with a computerized data acquisition system. The absorbance values at 1- or 10-s intervals were collected and analyzed by using a nonlinear-least-squares computer program. Plots of log $(A_t - A_\infty)$ vs. time were used in a confirmatory fashion.

Registry No. *N*-Acetylbenzotriazole, 18773-93-8.

Effect of Inverse Micelles on the Competition between Lactonization and Polymerization Reactions of an ω-Hydroxy Carboxylic Acid[1]

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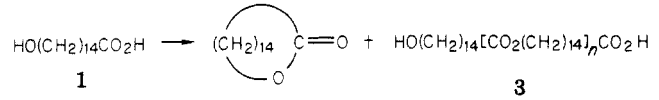
The ability of inverse micelles to influence the competition between carbodiimide-mediated lactonization and polymerization of 15-hydroxypentadecanoic acid (1), yielding pentadecanolide (2) and polymer (3), respectively, has been investigated by using inverse micellar systems in benzene based on di-*n*-dodecyldimethylammonium bromide (DDABr) and on bis(2-ethylhexyl) sodium sulfosuccinate (AOT) with and without water pools. Two ionic carbodiimides, 1-cyclohexyl-3-[2-(*N*-methylmorpholinio)ethyl]carbodiimide *p*-toluenesulfonate (4) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (5), were used. The inherent ability of carbodiimide 4 to effect lactonization of 1 is inhibited moderately by DDABr inverse micelles without water pools and completely by AOT inverse micelles without water pools. Carbodiimide 4 did not effect esterification when these inverse micellar systems contained water pools; carbodiimide 5 apparently did not do so under any of the conditions used.

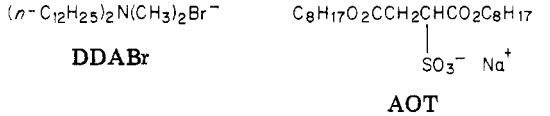
Under esterification conditions an ω-hydroxy carboxylic acid undergoes competing intra- and intermolecular reactions to yield lactone and polymer, respectively.[2] The formation of medium (8–11 membered) and large (12 membered and above) rings is entropically unfavorable,[3] and synthetic procedures have used high-dilution[2] and/or special activation techniques[4,5] to promote lactonization relative to polymerization. Inverse micelles in nonpolar aprotic solvents have been used to catalyze numerous reactions;[6] their catalytic ability is believed to result, in part, from the fact that they can bind substrates strongly in specific orientations.[6] We herein report the ability of inverse micelles to influence the competition between lactonization and polymerization for 15-hydroxypentadecanoic acid (1), yielding pentadecanolide (2) and



1 2 3

polymer 3, respectively, when mediated by carbodiimides. Carbodiimides have been used previously to effect esterification/lactonization in other systems.[7]

Several inverse micellar systems based on di-*n*-dodecyldimethylammonium bromide (DDABr) and on bis(2-ethylhexyl) sodium sulfosuccinate (AOT) in benzene



DDABr AOT

were used with and without dissolved water pools.[8] When 1 is solubilized by an inverse micelle containing a water pool, it is likely that its hydroxyl and carboxyl groups are hydrogen bonded to the pool. Within an inverse micelle even in the absence of a water pool it is assumed that these two functional groups are localized at the ionic core due to ion–dipole interactions.[8] Thus, association with an inverse micelle, with or without a water pool, should bring the hydroxyl and carboxyl groups of 1 closer together on a time-averaged basis than they would be otherwise in bulk solution. If a carbodiimide is also solubilized in an inverse micelle containing a single molecule of 1, it might be expected to effect lactonization as the result of the proximity of the hydroxyl and carboxyl groups. Two ionic carbodiimides, 1-cyclohexyl-3-[2-(*N*-methylmorpholinio)-ethyl]carbodiimide *p*-toluenesulfonate (4)[9a] and 1-[3-(di-

(1) Some of these results were presented at the International Symposium on Solution Behavior of Surfactants—Theoretical and Applied Aspects, June 30–July 3, 1980, Potsdam, NY.

(2) Stoll, M.; Rouvé, A. *Helv. Chim. Acta* **1935**, *18*, 1087.

(3) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; p 198.

(4) For reviews, see: (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (b) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (c) Back, T. G. *Ibid.* **1977**, *33*, 3041.

(5) For specific pertinent examples, see: (a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. (b) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49. (c) Rastetter, W. H.; Phillion, D. P. *J. Org. Chem.* **1980**, *45*, 1535.

(6) (a) Fendler, J. H.; Fendler, E. J. "Catalysis in Micellar and Macromolecular Systems"; Academic Press: New York, 1975; Chapter 10. (b) Fendler, J. H. *Acc. Chem. Res.* **1976**, *9*, 153.

(7) For examples, see: (a) Neelakantan, S.; Padmassani, R.; Seshadri, T. R. *Tetrahedron* **1965**, *21*, 3531. (b) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Ibid.* **1958**, *2*, 1.

(8) (a) For a general discussion of the ability of inverse micelles in nonpolar solvents to dissolve water and polar solubilizates, see ref 6. (b) Even without added water there were certainly traces present. It is apparently impossible to prepare *completely* anhydrous inverse micellar solutions even with due care (Eicke, H. F.; Christen, H. *Helv. Chim. Acta* **1978**, *61*, 2258. Djermouni, B.; Ache, H. J. *J. Phys. Chem.* **1979**, *83*, 2476).

(9) (a) Sheehan, J. C.; Hlavka, J. J. *J. Org. Chem.* **1956**, *21*, 439. (b) Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. L. *Ibid.* **1961**, *26*, 2525.

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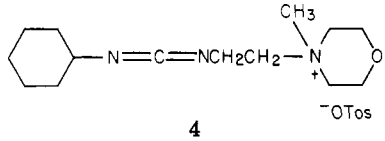
Table I. Carbodiimide-Mediated Reactions of 1 in Benzene Containing Inverse Micelles with and without Water Pools at 20 °C

		surfactant			carbodiimide		
run	10^3[1], M	nature	10^3[micelle], M	10^3[water], M	nature	10^3(concn), M	% yield of 2
1	2.89	DDABr	15	0	4	16.5	22
2	2.89	DDABr	15	0	4	16.8	21
3	2.90	DDABr	15	0	4	16.6	20
4	1.45	DDABr	15	0	4	16.7	24
5	2.89	DDABr	15	0	5	16.3	0
6	2.86	AOT	18	0	4	16.6	0
7	2.87	AOT	18	0	5	16.3	0
8	2.89	DDABr	15	306	4	16.4	0
9	2.89	DDABr	15	306	5	16.5	0
10	2.91	AOT	15	361	4	16.7	0

methylamino)propyl]-3-ethylcarbodiimide hydrochloride (**5**),[9b] were used. Both **4** and **5** are insoluble in benzene



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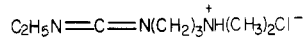

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alone but soluble in inverse micellar solutions of DDABr and AOT with and without water pools. Therefore, the solubilization site of the ionic carbodiimide in an inverse micellar solution is an inverse micelle.

Runs 1–7 were performed with inverse micellar solutions of DDABr and AOT without water pools, and the results are summarized in Table I. In runs 1–5, the DDABr concentration was 9.07×10^{-2} M, which corresponds to an approximate micelle concentration of 1.5×10^{-2} M, based on a critical micelle concentration (cmc) of 1.5×10^{-3} M and an assumed aggregation number of 6.[10] In runs 6 and 7, the AOT concentration was 0.180 M, which corresponds to an approximate micelle concentration of 1.8×10^{-2} M, based on a cmc of 7×10^{-4} M and an assumed aggregation number of 10.[11] Runs 8–10 were performed with water pools, and the results are likewise summarized in Table I. In runs 8 and 9, the overall DDABr concentration, cmc, and aggregation number of runs 1–5 were employed to give the same approximate micelle concentration in the presence of the indicated amount of water.[10] In run 10, the AOT concentration was 0.180 M, which corresponds to an approximate micelle concentration of 1.5×10^{-2} M, based on a cmc of 7×10^{-4} M and an aggregation number of 12 in the presence of the indicated amount of water.[11] If all of the added water is in the form of pools, then the water to micelle ratio is 20:1 for runs 8 and 9 and 24:1 for run 10. Other pertinent concentration ratios are as follows: micelle to **1**, 5:1 for runs 1–3, 5, and 8–10 and 10:1 for run 4, and 6:1 for runs 6 and 7; carbodiimide to **1**, 6:1 for runs 1–3 and 5–10 and 12:1 for run 4; carbodiimide to micelle, 1:1 for runs 1–10. Thus, on the average, an individual molecule of **1** is statistically isolated in an inverse micelle containing one molecule of ionic carbodiimide.

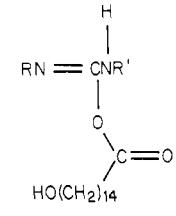
Table II. Carbodiimide-Mediated Reactions of 1 without Surfactant at 20 °C

run	10^3[1], M	solvent	carbodiimide[a]	% yield of 2
11	2.88	C_6H_6	DCC	0
12	2.88	CH_2Cl_2	4	44
13	3.03	CH_2Cl_2	4	46

[a] The concentration was 1.66×10^{-2} M in every case.

The general reaction procedure for runs 1–10 was as follows. Water, if used, and **1** were added to a benzene solution of the surfactant. Immediately they dissolved, and then the ionic carbodiimide was added. It dissolved within 5 min, and the resultant homogeneous mixture was stirred for 24 h at room temperature. In all runs but 5 and 7–10, the mixture eventually became turbid, presumably due to formation of insoluble polymer **3**. For example, in run 1, turbidity developed after 3 h, and after 24 h a white precipitate was present. The reaction mixture was filtered through silica gel, *n*-hexyl laurate as an internal standard was added to the resultant residue of neutral organic materials, and the mixture was analyzed quantitatively by high-performance liquid chromatography.

As indicated in Table I, only the combination of carbodiimide **4** and DDABr without water pools in runs 1–4 yielded modest amounts of lactone **2**.[12] Since carbodiimides can function as coupling agents in neutral aqueous solution,[13] the lack of formation of **2** in run 8 with **4**, DDABr, and water pools is probably not due to hydrolysis of the carbodiimide to the corresponding urea before attack by the carboxylate of **1** forms *O*-acylisourea intermediate **6** (R and R′ = substituents of **4**).[14] Indeed, unreacted



6

(10) (a) Kitahara and Kon-no have reported (Kitahara, A.; Kon-no, K. *J. Colloid Interface Sci.* **1979**, *29*, 1) that at 50 °C in benzene for DDABr the apparent aggregation number is 6 for a 0.10 *m* (0.088 M) solution and the cmc is 0.0017 *m* (0.0015 M). The calculation of the micelle concentration neglects the difference in temperature and the presence of solubilizates and, when added, water. (b) However, Hunter and Younis have found (Hunter, T. F.; Younis, A. I. *J. Chem. Soc., Faraday Trans. 1* **1979**, *75*, 550) that additives increase the aggregation number of DDABr in benzene. Therefore, the calculated micelle concentration represents a maximum value.

(11) Herrman and Schelly have reported (Herrman, U.; Schelly, Z. A. *J. Am. Chem. Soc.* **1979**, *101*, 2665) that for AOT in benzene the cmc is 7×10^{-4} M at 25 °C, and that at 37 °C the mean aggregation number is 10 over the concentration range of 2×10^{-3} to 4×10^{-2} M and increases to 12 in the presence of five water molecules per AOT molecule. The calculations of micelle concentrations neglect the difference in temperature and presence of solubilizates.

(12) Dilactone and trilactone are other potential neutral products formed by cyclization of **3** with $n = 1$ and 2, respectively. They have been obtained previously with **1** (e.g., ref 5a), but only traces, if any, of these materials were detected in the present study.

(13) (a) Sheehan and Hlavka reported[9a] that **4** is stable in water at 25 °C for 7 h. (b) For an example with carbodiimide **5**, see: Royer, G. P.; Anantharmaiah, G. M. *J. Am. Chem. Soc.* **1979**, *101*, 3394.

(14) It is not known which double bond of **4** reacts to give **6**.

Table III. Carbodiimide-Mediated Reactions of 1 in Benzene[a] without Surfactant at 20 °C

run	10^3[1], M	carbodiimide nature	carbodiimide amt, mmol	% yield of 2
14	2.85	4	0.167	35
15	2.88	4	0.163	31
16	2.89	5	0.157	0

[a] The volume of each reaction mixture was 10 mL.

carbodiimide 4 was detected by infrared spectroscopy (N=C=N band) at the end of a control corresponding to run 8. If 6 is in fact formed in run 8, attack of its hydroxyl group at the carbonyl carbon of its protonated form to give 2[15] apparently cannot compete with that of other nucleophiles present such as water.

It is impossible to perform the most appropriate control on the influence of DDABr inverse micelles on the lactonization of 1 with 4 because 4 is completely insoluble in benzene alone. However, less satisfactory alternative controls are summarized in Table II, and the results of heterogeneous reactions of 1 with 4 and 5 in benzene without a surfactant are given in Table III. The reaction procedures used for runs 11–16 were analogous to those for the runs of Table I. In run 11, *N,N'*-dicyclohexylcarbodiimide (DCC) was employed under homogeneous conditions in benzene without a surfactant; lactone 2 was not produced. In runs 12 and 13, 4 was used under homogeneous conditions in dichloromethane without a surfactant, and significant yields of 2 resulted. Apparently, 4 inherently promotes lactonization. Although an absolute statement still cannot be made on the basis of these controls, it is probable that in benzene the DDABr inverse micelles function only to solubilize 4 without significant catalysis of lactonization. In fact, to the extent that possible solvent effects on going from dichloromethane to benzene can be neglected, the DDABr inverse micelles moderately *inhibit* lactonization. These conclusions are supported by the results of runs 14 and 15, since even under heterogeneous conditions 4 yields lactone 2. The AOT inverse micelles *completely inhibited* the lactonization but not the polymerization of 1 with 4 in benzene. The complete lack of lactone 2 formation with carbodiimide 5 under all conditions used may simply be due to its inability to effect esterification.[16] Even without water pools in runs 5 and 7 the formation of insoluble polymer 3 was not observed.

The ability of 4 to effect lactonization could be due to a weak intramolecular ion–dipole interaction between the quaternary ammonium ion and the hydroxyl group of *O*-acylisourea intermediate 6 derived from carbodiimide 4. Such an interaction would bring the hydroxyl group into proximity with the carbonyl carbon where attack results in lactone 2. Perhaps the structural and electronic character of an AOT inverse micelle completely precludes this ion–dipole interaction. In other methods[4,5] used for lactonization of ω-hydroxy carboxylic acids, similar intramolecular interactions may play an organizational role.

It should be noted that the respectable yield of 2 obtained with 4 in dichloromethane was not maximized. We plan to do so and to investigate the ability of 4 to promote lactonization of other ω-hydroxy carboxylic acids under these very mild conditions.

(15) The formation of 2 may proceed from 6 directly and/or from the anhydride of 1 formed by attack of 1 on 6. The latter route is perhaps unlikely in view of the 5:1 ratio of micelle to 1, however. For a discussion of intermediates in carbodiimide-mediated reactions, see: Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* **1973**, *95*, 4052.

(16) Carbodiimide 5 can form a cyclic isomer.[9b]

Experimental Section

General Methods. All melting and boiling points are uncorrected. The ^{1}H NMR spectra were recorded with a Varian HA-100 spectrometer, and $CDCl_3$ was used as the solvent with Me_4Si as an internal standard. Infrared (IR) spectra were obtained on Perkin-Elmer Model 621 and Beckman Model IR-10 spectrophotometers. Ultraviolet (UV) spectra were recorded on a Hitachi Model 100–80 spectrophotometer with matched 1-cm quartz cuvettes, and mass spectra were recorded on a Varian MAT CH-5 spectrometer with an ionizing voltage of 70 eV and direct insertion. Gas–liquid chromatography (GLC) was performed on a Varian Model 2700 instrument with a 6 ft × $^1/_4$ in. aluminum column packed with 4% SE-30 on 60–80-mesh AW-DMCS Chromosorb W. High-performance liquid chromatography (HPLC) was performed on a Beckman Model 332 chromatograph fitted with a 25 cm × 4.6 mm (i.d.) stainless-steel column packed with 10-μm LiChrosorb RP-18 and a Schoeffel Model 770 variable-wavelength ultraviolet detector. For quantitative measurements by HPLC, the cut-and-weigh integration method was used with Keuffel and Esser Co. Albanene tracing paper. All weighings of starting materials and internal standards to ±0.02 mg were performed with aluminum pans on a Cahn Model RM-2 electrobalance with the readout on a Keithley Model 171 digital voltmeter or on a Cahn Model 7500 electrobalance.

Materials. The 1-cyclohexyl-3-[2-(*N*-methylmorpholinio)-ethyl]carbodiimide *p*-toluenesulfonate [4, mp 113–115 °C (lit.[9a] mp 113–115 °C)] and *N,N'*-dicyclohexylcarbodiimide (DCC) were used as received (Aldrich). Likewise, 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride [5, mp 104–109 °C (lit.[9b] mp 108–112.5 and 113.5–114.5 °C)] was used as received (Aldrich); its IR spectrum (Nujol) was consistent with that reported by Sheehan and co-workers.[9b] The di-*n*-dodecyldimethylammonium bromide (DDABr, Eastman) was purified by recrystallization from ethyl acetate to give material with a melting point of 169–171 °C (sealed tube; lit.[10a] mp 169–170 °C), and bis(2-ethylhexyl) sodium sulfosuccinate (AOT, Fisher) was purified according to a standard procedure[17] to give material that was dried at 50 °C (0.01 mmHg) for 60 h.

Solvents. The HPLC-grade solvents H_2O, CH_3CN, CH_3OH, and tetrahydrofuran (THF) were used for HPLC analyses as received (J. T. Baker and Burdick and Jackson). Spectral quality C_6H_6 (Mallinckrodt and J. T. Baker, 0.03% H_2O) and CH_2Cl_2 (Burdick and Jackson, 0.003% H_2O) were used as received. For silica gel column chromatography, HPLC-grade hexanes (J. T. Baker) and distilled reagent-grade ether (J. T. Baker) were used.

15-Hydroxypentadecanoic Acid (1). A mixture of 10.0 g (41.7 mmol) of pentadecanolide (2, California Aromatics and Flavors), 8.5 g (0.15 mol) of KOH, 50 mL of H_2O, and 500 mL of CH_3OH was refluxed under N_2 for 5.5 h and rotary evaporated to near dryness. Then 450 mL of 10% (w/v) sulfuric acid was added, and the resultant solid was collected to give 10.59 g (99%) of 1, which was recrystallized from C_6H_6 to give 1, mp 85–86 °C (lit.[18] mp 84–84.5 °C).

***n*-Hexyl Laurate.**[19] Under a $CaCl_2$-filled drying tube, a solution of 19.0 g (87.0 mmol) of lauroyl chloride[20] in 25 mL of anhydrous ether was added dropwise to a stirred mixture of 10.4 g (0.102 mol) of *n*-hexyl alcohol (Aldrich), 20 mL of pyridine, and 60 mL of anhydrous ether at 0 °C. The reaction mixture was refluxed for 1.5 h, stirred overnight at 25 °C, and added to a mixture of H_2O and ether. The ether layer was washed with four 100-mL portions of 3% hydrochloric acid and 100 mL of H_2O and dried over Na_2SO_4. Rotary evaporation left an oil which was fractionally distilled to give 12.2 g (49%) of *n*-hexyl laurate, bp 133–135 °C (0.5 mmHg). Under the HPLC conditions used for quantitative analysis of 2 and by GLC analysis this material was homogeneous.

Reactions of 15-Hydroxypentadecanoic Acid with Carbodiimides 4 and 5 in Benzene Solutions of DDABr with and without Water Pools. In a typical reaction corresponding

(17) Menger, F. M.; Saito, G. *J. Am. Chem. Soc.* **1978**, *100*, 4376.
(18) Mathur, H. H.; Bhattacharyya, S. C. *J. Chem. Soc.* **1963**, 3505.
(19) Rheinboldt, H.; König, O.; Otten, R. *Justus Liebigs Ann. Chem.* **1929**, *473*, 249.
(20) Adams, R. A.; Ulrich, L. H. *J. Am. Chem. Soc.* **1920**, *42*, 599.

to runs 1–3, 10 mL of a 0.0907 M solution of DDABr in C_6H_6 was added by volumetric pipet to a round-bottomed flask containing a magnetic stirring bar followed by 7.46 mg (0.0289 mmol) of 1 to give a homogeneous solution. Then 70.0 mg (0.165 mmol) of 4 was added, and the mixture was stirred at room temperature for 24 h. It became homogeneous within 5 min, and then turbidity developed after 3 h. At the end of the reaction a white solid, presumably polymer 3, was present. In run 4, the same procedure was used with 3.74 mg (0.0145 mmol) of 1.

In run 8, the same procedure was used except that 55 μL (55 mg, 3.06 mmol) of HPLC-grade H_2O was added by microsyringe before the addition of 1. The reaction mixture remained clear and homogeneous during the 24-h run.

For runs 5 and 9, procedures analogous to those of runs 1–3 and 8, respectively, were used with the substitution of 5 for 4. In both runs 5 and 9 the reaction mixtures remained clear and homogeneous during the 24 h.

Reactions of 15-Hydroxypentadecanoic Acid with Carbodiimides 4 and 5 in Benzene Solutions of AOT with and without Water Pools. For runs 6 and 7, the procedures of runs 1–3 and 5, respectively, were used with the substitution of a 0.180 M solution of AOT in C_6H_6 for the solution of DDABr in C_6H_6. In run 10, the procedure of run 8 was used with 65 μL (65 mg, 3.61 mmol) of HPLC-grade H_2O and the substitution of the above AOT solution for the DDABr solution. In run 6, the initially homogeneous reaction mixture became turbid, and after 24 h, a white solid, presumably polymer 3, was present. In runs 7 and 10, the reaction mixtures remained clear and homogeneous during the 24 h.

Reaction of 15-Hydroxypentadecanoic Acid with DCC in Benzene. In run 11, 7.43 mg (0.0288 mmol) of 1 followed by 34.2 mg (0.166 mmol) of DCC was added to 10.0 mL of C_6H_6 in a round-bottomed flask containing a magnetic stirring bar. The resultant clear, homogeneous mixture was stirred at room temperature and became turbid; at the end of the 24-h reaction period a white solid, presumably polymer 3, was present.

Reaction of 15-Hydroxypentadecanoic Acid with Carbodiimide 4 in Dichloromethane. In a typical reaction corresponding to runs 12 and 13, 70.3 mg (0.166 mmol) of 4 and 10.0 mL of CH_2Cl_2 were added to a round-bottomed flask containing a magnetic stirring bar. The mixture was stirred for 5 min until the 4 completely dissolved, and then 7.43 mg (0.0288 mmol) of 1 was added to give a clear, homogeneous mixture which remained so while being stirred at room temperature for 24 h.

Reactions of 15-Hydroxypentadecanoic Acid with Carbodiimides 4 and 5 in Benzene without Surfactants. In a typical reaction corresponding to runs 14 and 15, 68.9 mg of 4 and 10.0 mL of C_6H_6 were added to a round-bottomed flask containing a magnetic stirring bar; the 4 did not dissolve on stirring. Then 7.43 mg (0.0288 mmol) of 1 was added, and the resultant heterogeneous mixture was stirred at room temperature for 24 h with no change in appearance. For run 16, the same procedure was used with the substitution of 5 for 4.

Workup and Analysis of Runs 1–16. The reaction mixture was added to a 1.7 (i.d.) × 30 cm column of 60–200-mesh silica gel which was packed in hexane and washed with 150 mL of 1:1 (v/v) ether–hexane. The column was eluted with 250 mL of 1:1 (v/v) ether–hexane. The single fraction collected was rotary evaporated, and to the residue an approximately equal amount of the internal standard, *n*-hexyl laurate, was added along with the aluminum pan on which it was weighed. Then ca. 0.5 mL of HPLC-grade THF was added, and the resultant solution was analyzed by HPLC with 85% (v/v) CH_3CN–H_2O as eluant at a flow rate of 2.0 mL/min. Detection was at 214 nm with 0.04 absorbance units as full scale. The retention times for lactone 2 and *n*-hexyl laurate under these conditions are 8.25 and 24.5 min, respectively. The identity of 2 as produced in the carbodiimide-mediated reactions was confirmed by comparison of its retention time with that of authentic material under a second set of HPLC conditions: 89% (v/v) CH_3OH–H_2O at a flow rate of 1.0 mL/min. The retention times for 2 and *n*-hexyl laurate under these conditions are 12.1 and 28.0 min, respectively. For detection of di- and trilactones the following HPLC conditions were used: 90% (v/v) CH_3OH–THF at a flow rate of 2.0 mL/min. The retention times for *n*-hexyl laurate and di- and trilactones under these conditions are 3.1, 5.6, and 13.8 min, respectively. Molar extinction coefficients measured at 214 nm which were used in quantitation of the HPLC analyses are as follows: 2, 81.7 (CH_3CN); *n*-hexyl laurate, 74.5 (CH_3CN); dilactone, 100.4 (THF).

The filtration procedure described above through the silica gel column removed unreacted 1 (as determined by a control), polymer 3, surfactants, unreacted ionic carbodiimides, and resultant ionic ureas. In run 11, analysis of the residue after filtration indicated the probable presence of unreacted DCC along with several other unidentified materials. Thus in all runs except 11, only 2 and di- and trilactones, if formed, were isolated from the reaction mixture.

Control on the Product Isolation Procedure. In the HPLC analyses for 2 in runs with and without surfactant, a peak with a retention time of 14.5 min consistently appeared with the same relative size and shape. A 1.7 (i.d.) × 30 cm column of silica gel was prepared as above and eluted with 250 mL of 1:1 (v/v) ether–hexane. The eluate was rotary evaporated, and HPLC-grade THF was added as in runs 1–16. Analysis of the resultant solution by HPLC yielded the peak of interest and confirmed that the impurity resulted from the silica gel chromatography procedure.

Control on the Purity of AOT. In the HPLC analyses for 2 in runs using AOT, a peak with a retention time of 9.4 min consistently appeared with the same relative size and shape. A 10-mL aliquot of the 0.180 M solution of AOT in C_6H_6 was added to a 1.7 (i.d.) × 30 cm column of silica gel prepared as above and eluted with 250 mL of 1:1 (v/v) ether–hexane. The eluate was rotary evaporated, and HPLC-grade THF was added to the residue. Analysis of the resultant solution by HPLC yielded the peak of interest and confirmed that it was due to an impurity in the AOT [perhaps bis(2-ethylhexyl)maleate].

Solubility of Carbodiimide 4 in Benzene. As a qualitative test to see if any 4 dissolves in C_6H_6 alone, 72.5 mg (0.171 mmol) of 4 was added to 10 mL of C_6H_6 in a round-bottomed flask containing a magnetic stirring bar. The mixture was stirred for 16 min at room temperature and the 4 allowed to settle. A 1.0-mL aliquot was then removed by volumetric pipet and placed on a NaCl plate drop by drop, allowing the C_6H_6 to evaporate between drops. By IR analysis (N=C=N band) no 4 was detected on the plate. As another test, a 1.0-mL aliquot of the above mixture, excluding solid 4, was added to a tared round-bottomed flask and rotary evaporated. There was no increase in the weight of the flask.

Control on the Stability of Carbodiimide 4 in a Benzene Solution of DDABr with Water Pools. A reaction mixture comparable to that of run 8 was analyzed by IR for the presence of unreacted 4 after a 24-h period. About 20 drops of the reaction mixture were placed on a NaCl plate 3 drops at a time, allowing for evaporation of C_6H_6 between additions. Analysis of the resultant film on the plate yielded a band at 2105 cm^{-1} (N=C=N), indicating that some unreacted 4 remained at the end of the run.

1,17-Dioxacyclodotriacontane-2,18-dione (Dilactone) and 1,17,33-Trioxacyclooctatetracontane-2,18,34-trione (Trilactone). A mixture of 203 mg (0.787 mmol) of 1, 70 mg (0.37 mmol) of *p*-toluenesulfonic acid monohydrate, and 100 mL of C_6H_6 was refluxed for 21 h under a Dean–Stark trap fitted with a reflux condenser equipped with a $CaCl_2$-filled tube; the side arm of the trap was initially filled with C_6H_6. The reaction mixture was washed with three 15-mL portions of 5% aqueous $NaHCO_3$ and 15 mL of saturated aqueous NaCl and dried over Na_2SO_4. Rotary evaporation left 184 mg of a white solid that was dissolved in 10 mL of C_6H_6 in a volumetric flask. Rotary evaporation of 1 mL of this solution withdrawn by volumetric pipet left 18 mg of a solid to which was added 8.60 mg of *n*-hexyl laurate. This mixture was dissolved in HPLC-grade THF and analyzed by HPLC to give yields of 36% and 22% for 2 and dilactone, respectively. Since pure trilactone was not obtained, its molar extinction coefficient was not available for quantitation. However, the area (weight) ratio of the tri- to dilactone peaks was 0.43:1. The remaining 9 mL of C_6H_6 solution was chromatographed on a 3 × 45 cm column of silica gel packed in hexane. The column was eluted sequentially with 200-mL portions of 10%, 20%, 30%, and 40% (v/v) ether–hexane, and 75 mL fractions were collected; 1 eluted with the 10%, dilactone with the 20%, and trilactone with the 40% eluant. Dilactone was recrystallized from ether to give hexagonal platelets: mp 88–88.5 °C (lit.[2] mp 88 °C); mass spectrum, *m/e* 480 (M^+·); ^1H NMR δ 4.06 (t, *J* = 6 Hz, 4 H, CH_2O),

2.28 (t, J = 7 Hz, 4 H, CH_2CO), 1.22–1.80 (m, 48 H, CH_2). The multiplet at δ 1.22–1.80 contained an intense singlet at 1.28. Trilactone was not isolated in pure form, but its presence was indicated by an $M^{+\cdot}$ signal at m/e 720 in its mass spectrum.

Isolation of Pentadecanolide from a Large-Scale Run with Carbodiimide 4 in Benzene. A large-scale run similar to run 14 was performed with 73.6 mg (0.285 mmol) of 1, 0.721 g (1.70 mmol) of 4, and 150 mL of C_6H_6 by using the same procedure. The reaction mixture was added to a 3 × 30 cm column of silica gel packed in hexane and eluted with 400 mL of 1:1 (v/v) ether–hexane. The eluate was rotary evaporated to give an oil which was dissolved in 1 mL of HPLC-grade THF. Preparative GLC (180 °C) yielded 2 [retention time 10.8 min, mp 34–34.5 °C (lit.[2] mp 32 °C)], whose ^1H NMR spectrum was identical with that of authentic lactone 2: δ 4.04 (t, J = 6 Hz, 2 H, CH_2O), 2.27 (t, J = 6 Hz, 2 H, CH_2CO), 1.18–1.80 (m, 24 H, CH_2). The multiplet at δ 1.18–1.80 contained an intense singlet at δ 1.30. Likewise, the IR (neat film on NaCl) and mass spectra of the GLC-collected 2 were identical with those of authentic material, including a strong band at 1735 cm^{-1} (C=O) and a signal for $M^{+\cdot}$ at m/e 240, respectively.

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Reduction of the *N*-Propargyl Group with Tritium. General Procedure for the Preparation of *N*-[2,3-^{3}H]Allyl Opiate Ligands at High Specific Activity[1]

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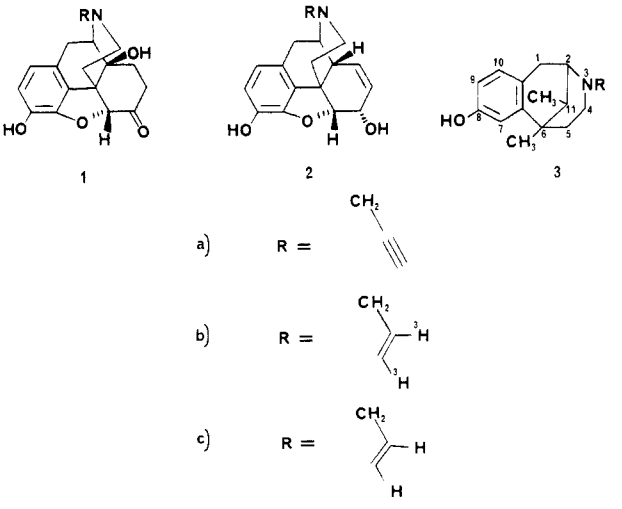
Radiolabeled neurotransmitter receptor ligands are exceedingly valuable substances for obtaining information about their respective receptors, and a number of them possess the *N*-allyl group. A method is outlined to prepare (−)-*N*-([2,3-^{3}H]allyl)naloxone (**1b**), (−)-*N*-([2,3-^{3}H]allyl)nalorphine (**2b**), and (±)-*N*-([2,3-^{3}H]allyl)normetazocine (**3b**) from their respective *N*-propargyl precursors. Triton nuclear magentic resonance studies confirm labeling specificity. This labeling strategy affords the highest specific activities for such ligands reported to date and possesses a number of other advantages over previous methods. Utilization of such tritiated ligands for receptor binding assay will undoubtedly lead to a more comprehensive mapping of and increased information about their respective receptors.

By means of generally labeled (−)-[^{3}H]naloxone (6.1 Ci/mmol), a potent opiate receptor antagonist, the existence of a specific opiate receptor was first demonstrated by Snyder and Pert[2] in 1973. Since then, a number of investigators have tried to improve the utility of this valuable tritiated ligand for receptor binding assay by preparing it specifically labeled and at higher (greater than 30 Ci/mmol) specific activity. A synthesis of (−)-[7,8-^{3}H]naloxone was reported[3] but suffered from the disadvantage of introducing tritium into a chemically labile position. Subsequently, a route to (−)-[15-^{3}H]naloxone was described[4] but yielded material of very low (4 Ci/mmol) specific activity. The lack of a satisfactory preparation of specifically tritiated (−)-naloxone at high specific activity prompted our interest in this compound.

A structural feature present in (−)-naloxone (**1c**) and common to a number of other useful receptor ligands is the *N*-allyl group. It seemed altogether reasonable to expect that the reduction of an *N*-propargyl group (A, Scheme I) with tritium gas to an *N*-[2,3-^{3}H]allyl group (B, Scheme I) would occur at high specific activity and thereby



constitute a useful strategy to prepare specifically tritiated (−)-naloxone and other *N*-allyl ligands. To demonstrate the utility of this methodology, we now describe the preparation of (−)-*N*-([2,3-^{3}H]allyl)naloxone (**1b**), (−)-*N*-([2,3-^{3}H]allyl)nalorphine (**2b**), a mixed opiate receptor agonist–antagonist,[5] and (±)-*N*-([2,3-^{3}H]allyl)nor-

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