Aggregation Behavior of a Series of Structurally Related Single-Chain Amphiphiles. Structural Effects on Aggregate Morphology as Studied by Electron Microscopy

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Seven novel single-chain amphiphiles have been prepared containing cationic *N*-methylpyridinium (**1–5**) or neutral quinoline (**6, 7**) head groups. The flexible tail is in all cases an *n*-hexadecyl moiety, connected to the head group by way of an ester (**1, 2, 4, 7**) or ether linkage (**3, 5, 6**), sometimes via a vinyl (**2**) or 4-vinylphenyl (**3, 5**) rigid segment. Sonicated aqueous dispersions of **1–7** have been examined by electron microscopy, with negative staining as well as freeze fracture techniques. Closed bilayer assemblies were observed for **1–2** (containing only one heteroaromatic ring in the rigid segment) and **4–5**. The thickness of the vesicle bilayers was dependent on the temperature at which sonication was performed. No stable vesicles are formed from **3**, presumably because of a too large size of the hydrogen belt. As expected, the quinoline detergents **6** and **7** do not form vesicles, but the molecular shape of **6** allows vesicle formation in the presence of 50% (w/w) cholesterol. It is emphasized that there is at present no comprehensive theory which explains the relation between the structure of a single-chain amphiphile and the morphology of the most stable aggregate in aqueous solution.

Recent pioneering work, particularly by Kunitake[1-3] and Fendler,[4] has shown that stable membrane assemblies are not only formed from phospholipid constituents but also from a wide variety of single-chain and double-chain fully synthetic amphiphiles.[5] These findings have disclosed an important area of membrane mimetic chemistry.[6] Even more recently, the stability of the bilayers has been further increased via polymerization of the detergent molecules within the aggregate.[7] In the case of double-chain amphiphiles and in particular phospholipids, the relation between chemical structure and morphology of the aggregate has been analyzed in terms of a shape concept, emphasizing a balance between the cross-sectional areas subtended by the polar and apolar regions in the amphiphile.[8]

For single-chain synthetic amphiphiles a large variety in aggregate morphology has been observed, including globules, rods, tubes, disks, as well as multi- and single-walled vesicles.[9] In a beautifully detailed study, Kunitake et al.[9] have proposed that three essential structural elements should be present in order to allow the formation of stable bilayer assemblies: (1) a flexible tail, (2) a rigid segment, and (3) a hydrophilic head group. These structural features, but also the presence of a spacer group and an additional interacting group, all affect the aggregate morphology.

Table I. Aggregation Behavior of the Amphiphiles 1-7

compd	mp, °C	T_c, °C (ΔH, kcal mol^{-1})	aggregate morphology[a] (diameter, Å)
1	102.4–104.0		A: vesicles (1400) B, FF: vesicles (170)
2	117.5–119.5		A: vesicles (1700) B, FF: vesicles (900)
3	190–210	92 (1.7), 123 (2.0), 135 (0.85)	A: non-closed bilayers (separation 40 ± 8 Å)
4	90–94.1	58 (1.0), 70 (2.0)	A: vesicles (220) B, FF: vesicles (100)
5	190–198		B, NS, and FF: vesicles (375)
6	93.0–96.0	44 (2.1)	A: vesicles (400)[b]
7	52.6–53.3		*c*

[a] Method A or B (see text). NS = negative staining method; FF = freeze fracture method. [b] In the presence of 50% (w/w) of cholesterol. [c] No bilayers are formed (method A).

Herein we compare the aggregation behavior, as studied by electron microscopy, of seven novel cationic and neutral single-chain amphiphiles (**1–7**, Figure 1). All amphiphiles contain an *n*-hexadecyl flexible tail which is linked with the hydrophilic part by way of an ester or ether linkage, sometimes separated by a vinyl or phenyl rigid segment. Amphiphiles **1–5** are single-chain analogues of some double-chain amphiphiles carrying an *N*-methylpyridinium head group which we prepared previously.[5] The latter compounds readily formed closed vesicles. These vesicles have been successfully used in the reconstitution of bovine rhodopsin, thereby establishing their potential use as membrane mimics.[10]

Results and Discussion

The solutions of **1–7** employed in electron microscopy (EM) studies were prepared by two procedures. Method A involved treatment of a dilute aqueous solution of **1–7** with a sonifier cell disruptor for 30 min at 0 °C. Micrographs were then prepared by the two-step droplet method using a 1% solution of uranyl acetate for staining. In method B, the solutions of **1–7** were ultrasonicated for 20 min in an ultrasonic bath at 45 °C. After removing undissolved material, micrographs were taken with the two-step droplet method as in method A (but now using 1%

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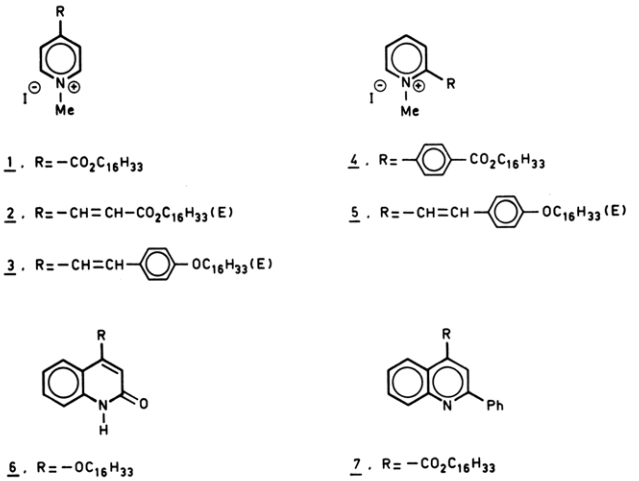

Figure 1. Structures of the amphiphiles.

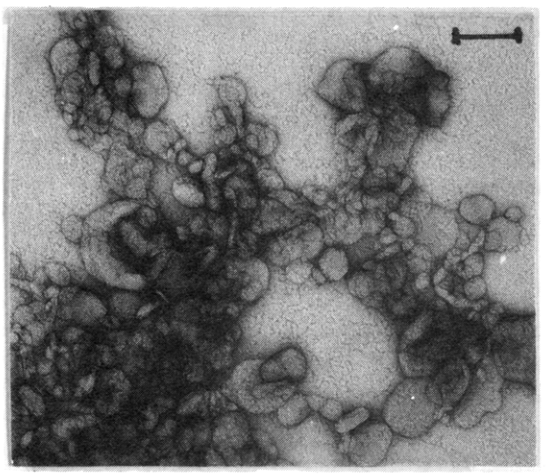

Figure 2. Electron micrograph of amphiphile **4**, sonication at 0 °C, negative staining (uranyl acetate), initial magnification ×26000. The marker line represents 1200 Å.

(w/w) ammonium molybdate as negative stain) or the freeze fracture technique. Table I records the observed morphologies as well as solid-state phase-transition temperatures T_c (and accompanying enthalpy changes) as detected by differential scanning calorimetry (DSC).

The micrographs of the specimens prepared by the two-step droplet method closely resemble the patterns previously found for liposomes and for vesicles formed from other synthetic amphiphiles (Figure 2). Sonication of solutions of **1**, **2**, and **4–6** containing the staining agent afforded micrographs showing lamellae of curved, parallel hydrocarbon layers. Upon sonication at 0 °C, the thickness of the bilayers (35 ± 5 Å), as estimated from the corresponding negatives, corresponds with the value of ca. 37 Å expected for twice a fully extended *n*-hexadecyl hydrocarbon chain. However, if sonication was performed at 45 °C, the thickness of the bilayer shrank to 20 ± 5 Å (Figure 3), presumably mainly as a result of interlacing of the hydrophobic tails. These results might explain the previously observed increase in stability of vesicles in entrapment experiments using structurally related double-chained amphiphiles at elevated temperatures.[5] This temperature dependent effect has also been observed for phospholipid vesicles[11] and is usually ascribed to the formation of unannealed vesicles when sonication is performed below the phase transition temperature.

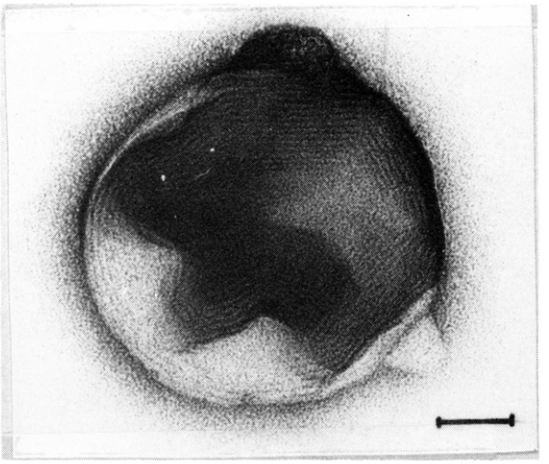

Figure 3. Electron micrograph of amphiphile **1**, sonication at 45 °C in the presence of 1% (w/w) of ammonium molybdate, initial magnification ×85000. The marker line represents 390 Å.

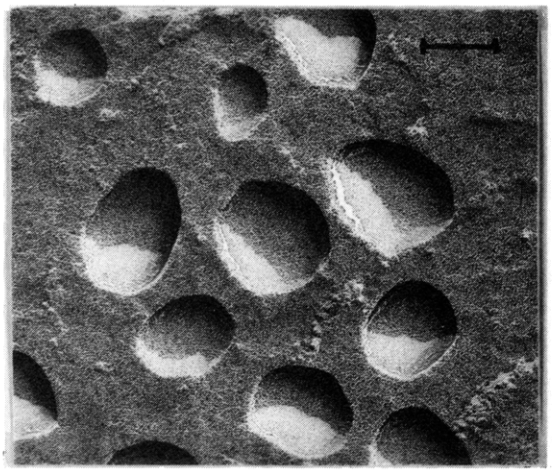

Figure 4. Electron micrograph of amphiphile **5**, sonication at 45 °C, freeze fracture replica, initial magnification ×111500. The marker line represents 300 Å.

Recently it has been suggested[12] that the morphology of vesicular systems is not preserved at the stage of the EM observation under high vacuum and that staining agents can give rise to "bilayered structures" even in systems which are molecular or micellar solutions in their original states. Therefore we also employed freeze fracture EM, where the specimen is prepared by instantaneous freezing of the aqueous sample. The results were fully consistent with those obtained with the negative staining technique (for an example, see Figure 4).

Returning to the morphologies listed in Table I, we note that the monoaryl detergents **1** and **2** form stable vesicles. This observation is not in agreement with one of the Kunitake's rules[9] that states that in single-chain amphiphiles the presence of at least two benzene rings in the rigid segment is necessary for the formation of bilayer assemblies. Indeed, the formation of stable vesicles from **1** and **2** is surprising since the corresponding amphiphiles with R = $-C_8H_{17}$, $-C_{12}H_{25}$, and $-C_{17}H_{35}$ only form micelles.[13] The presence of the dipolar ester groups in **1** and **2** might help vesicle formation, but usually such effects are more

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pronounced when the dipolar moiety is situated at the end of the *n*-alkyl chain.[9]

Secondly we see that an increase of the size of the "hydrogen belt" (i.e., the part of the molecule situated between the head group and the *n*-alkyl chain)[14,15] leads to an increase of the mean diameter of the vesicle (1 → 2) and ultimately prevents the formation of stable vesicular aggregates (3). Interestingly, amphiphile 5 containing the same substituent R as 3 readily forms stable vesicles. In this case the presence of a bent rigid system facilitates molecular ordering in the vesicle bilayer, possibly because the pyridinium dipole now induces more dipolar character in the "hydrogen belt", thereby helping a more favorable alignment of the molecules.

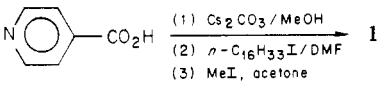
The uncharged detergents 6 and 7 posses head groups which are less hydrated than those of 1–5 and will form micellar aggregates. In the case of 6 the molecular shape will resemble an inverted cone which, in combination with the cone-shaped cholesterol,[16] can form a closed bilayer structure (Table I). The formation of bilayers was not observed for 7, neither pure nor in combination with cholesterol (up to 50% by weight), probably as a result of the presence of the bulky substituent in the ortho position of the quinoline head group.

We conclude that we are only at the initial stages of understanding the relation between the structure of a single-chain amphiphile and its aggregation behavior in aqueous solution.

Experimental Section

Melting points were measured with a Mettler FP-1 melting point apparatus. ^{1}H NMR spectra were taken on a Hitachi-Perkin-Elmer R24B spectrometer at 60 MHz. ^{13}C NMR spectra were obtained by using a Varian XL 100/15 spectrometer. Elemental analyses were performed by H. Draayer, J. Ebels, and J. E. Vos of the analytical section of this department.

Materials. The amphiphiles 1–7 were synthesized by the methods given below. No attempts were made to optimize yields. Amphiphile 1 was prepared from 4-pyridinecarboxylic acid.



***n*-Hexadecyl 4-Pyridinecarboxylate.** A mixture of 4-pyridinecarboxylic acid (3.35 g, 27.2 mmol) and dicesium carbonate (4.44 g, 13.6 mmol) in anhydrous methanol (150 mL) was refluxed for 30 min. After removal of the solvent, the dry cesium salt was dissolved in DMF (20 mL), cetyl iodide (9.60 g, 27.2 mmol) was added, and the mixture was stirred for 48 h at 80 °C. Then the solvent was removed in vacuo, and the residue taken up in chloroform (200 mL) and filtered. Again the solvent was evaporated and the crude ester was crystallized from anhydrous acetone. The yield was 7.56 g (79.8%): mp 49.5–50.8 °C; ^{1}H NMR ($CHCl_3$) δ 0.9 (t, 3 H), 1.3 (m, 28 H), 4.3 (t, 2 H), 7.75 (d, 2 H), 8.7 (d, 2 H). Anal. Calcd for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73; N, 4.03. Found: C, 75.80; H, 10.70; N, 4.12.

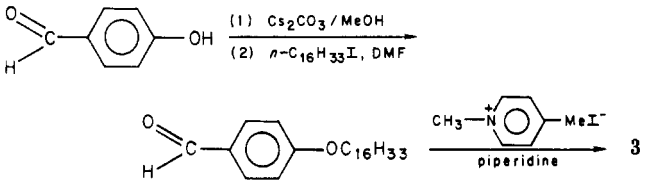
1-Methyl-4-((*n*-hexadecyloxy)carbonyl)pyridinium Iodide (1). A mixture of *n*-hexadecyl 4-pyridinecarboxylate (5.0 g, 14.4 mmol) and methyl iodide (10.0 g, 70.4 mmol) in acetone (150 mL) was refluxed for 48 h. The solvent was removed in vacuo and the residue was crystallized from acetone–ethyl acetate (1:3) to give yellow needles of 1 (6.2 g, 88.7%): mp 102.4–104.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.25 (m, 28 H), 4.35 (t, 2 H), 4.70 (s, 3 H), 8.35 (d, 2 H), 9.35 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 126.92 (d), 146.75 (d), 146.68 (s), 161.02 (s), 67.36 (t), 31.48, 28.81, 27.99, 25.38, 22.25, 13.68 (q), 49.83 (q). Anal. Calcd for $C_{23}H_{40}NO_2I$: C, 56.44; H, 8.24; N, 2.86; I, 25.93. Found: C, 56.40; H, 8.23; N, 2.86; I, 25.71.

Amphiphile 2 was prepared from 2-(4-pyridinyl)acrylic acid via esterification and N-alkylation as carried out in the preparation of 1.

(*E*)-2-(4-Pyridinyl)acrylic acid was prepared following the procedure of Leonard et al.[17] starting from pyridine-4-carboxaldehyde: yield 83.6%; mp 277–279 °C. Anal. Calcd for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.21; H, 4.93; N, 9.23.

(*E*)-1-((*n*-Hexadecyloxy)carbonyl)-2-(*N*-methyl-4-pyridinio)ethene iodide (2): yield 90.2%; yellow needles; mp 117.5–119.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H), 1.25 (m, 28 H), 4.2 (t, 2 H), 4.65 (s, 3 H), 6.8 (d, 1 H, J = 16 Hz), 7.6 (d, 1 H, J = 16 Hz), 8.1 (d, 2 H), 9.25 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 125.82 (d), 145.98 (d), 150.08 (s), 129.91 (d), 136.80 (d), 164.45 (s), 65.78 (t), 31.75, 29.16, 28.37, 25.70, 22.51, 13.94 (q), 49.29 (q). Anal. Calcd for $C_{25}H_{42}NO_2I$: C, 58.25; H, 8.21; N, 2.72; I, 24.62. Found: C, 57.81; H, 8.25; N, 2.70; I, 24.04.

Amphiphile 3 was prepared according to the following sequence.



4-(*n*-Hexadecyloxy)benzaldehyde. Following standard procedures, the yield was 95.1%: mp 45–48 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H), 1.5 (m, 28 H), 4.0 (t, 2 H), 6.9 (d, 2 H), 7.8 (d, 2 H), 9.9 (s, 1 H). Anal. Calcd for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05; O, 9.23. Found: C, 79.39; H, 11.03; O, 9.15.

(*E*)-1-(4-(*n*-Hexadecyloxy)phenyl)-2-(*N*-methyl-4-pyridinio)ethene iodide (3) was prepared following the procedure of Donchi et al.[18] starting from 4-methylpyridine. The yield of pure 3, after crystallization from anhydrous ethanol, was 34.5%: mp 190–210 °C; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H), 1.5 (m, 28 H), 4.0 (t, 2 H), 4.5 (s, 3 H), 6.9 (d, 2 H), 7.0 (d, 1 H, J = 14 Hz), 7.5 (d, 2 H), 7.7 (d, 1 H, J = 14 Hz), 8.0 (d, 2 H), 8.9 (d, 2 H). Anal. Calcd for $C_{30}H_{46}NOI$: C, 63.93; H, 8.23; N, 2.49. Found: C, 63.32; H, 8.20; N, 2.44.

Amphiphile 4 was prepared from 2-(4-carboxyphenyl)pyridine[19] via esterification (Cs_2CO_3/MeOH) and N-methylation (MeI, acetone) using the procedure described for 1.

1-Methyl-2-(4-((*n*-hexadecyloxy)carbonyl)phenyl)-pyridinium iodide (4): yield 63.5%; mp 90–94.1 °C; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H), 1.33 (m, 28 H), 4.44 (t, 3 H), 4.83 (d, 3 H, at elevated temperatures a singlet at 4.75), 7.4–8.5 (m, 8 H). Anal. Calcd for $C_{29}H_{44}NO_2I \cdot H_2O$: C, 59.68; H, 7.94; O, 8.22. Found: C, 58.88; H, 7.95; O, 8.32.

Amphiphile 5 was synthesized following a procedure analogous to that given for 3.

(*E*)-1-(4-(*n*-Hexadecyloxy)phenyl)-2-(*N*-methyl-2-pyridinio)ethene Iodide (5). The yellow ochre product was crystallized from acetone: yield 18.5%; mp 190–198 °C dec; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H), 1.5 (m, 28 H), 4.1 (t, 2 H), 4.5 (s, 3 H), 7.0–8.3 (m, 10 H). Anal. Calcd for $C_{30}H_{46}NOI \cdot 1/2H_2O$: C, 62.93; H, 8.27; N, 2.45; O, 4.19. Found: C, 62.88; H, 8.26; N, 2.47; O, 3.88.

2(1*H*)-Oxo-4-(*n*-hexadecyloxy)quinoline (6) was prepared by reaction of the monosodium salt of 2,4-dihydroxyquinoline with *n*-hexadecyl iodide in DMF: yield 3.9 g (46.2%); light green needles; mp 93.0–96.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H), 1.3 (m, 28 H), 4.0 (t, 2 H), 5.8 (m, 1 H), 7.5 (m, 5 H); IR 3350, 1650 cm^{-1}. Anal. Calcd for $C_{25}H_{39}NO_2 \cdot H_2O$: C, 77.37; H, 10.24; N, 3.47. Found: C, 77.42; H, 10.32; N, 3.36.

2-Phenyl-4-((*n*-hexadecyloxy)carbonyl)quinoline (7). A mixture of atophane (Aldrich, 8 g, 32 mmol) and dicesium carbonate (5.23 g, 16 mmol) in anhydrous methanol (200 mL) was heated till a clear solution was obtained. The solvent was

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evaporated in vacuo and the residue was suspended in DMF (500 mL). Then *n*-hexadecyl iodide (11.28 g, 32 mmol) was added and the mixture was stirred for 72 h at 80 °C. The solvent was removed in vacuo and the residue was taken up in chloroform and filtered. The solvent was slowly evaporated and the light yellow precipitate was filtered off and crystallized from anhydrous ethanol. The crystals were dried over $CaCl_2$ in vacuum desiccator: yield 10.49 g (70.1%); mp 52.6–53.3 °C; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.3 (m, 28 H), 4.46 (t, 2 H), 7.3–8.7 (m, 10 H). Anal. Calcd for $C_{32}H_{43}NO_2$: C, 81.14; N, 9.15; N, 2.96. Found: C, 81.22; H, 8.98; N, 3.23.

Differential Scanning Calorimetry (DSC). These experiments were carried out by using a Perkin-Elmer DSC-2 apparatus as described previously.[20] The T_c values were reproducible to within 2 °C.

Vesicle solutions were prepared using method A[5] or B (see text). Ultrasonic irradiation was carried out by using a Branson Sonifier Cell Disruptor B15 and/or a Bransonic 220 water bath.

Electron Microscopy. Micrographs were obtained by using negative staining as well as freeze-fracture techniques. The negative stained samples were prepared as described previously,[5,10] using 1% (by weight) solutions of uranyl acetate or ammonium molybdate as negative stain. The freeze-fracture replicas were obtained as in previous studies.[10] All samples were examined by using a Philips 300 electron microscope at 80 kV and photographed by using Kodak 4463 sheets.

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Registry No. 1, 90990-83-3; 2, 91002-39-0; 3, 90990-84-4; 4, 90990-85-5; 5, 90990-86-6; 6, 90990-87-7; 7, 90990-88-8.

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Selective Reductions. 36. Reaction of Lithium 9-Boratabicyclo[3.3.1]nonane with Selected Organic Compounds Containing Representative Functional Groups

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The approximate rates, stoichiometry, and products of the reaction of lithium 9-boratabicyclo[3.3.1]nonane with selected organic compounds containing representative functional groups were examined under standard conditions (tetrahydrofuran, room temperature) in order to explore the reducing characteristics of this reagent and to establish the utility of the reagent as a selective reducing agent. Primary alcohols, phenols, and thiols evolve hydrogen rapidly and quantitatively. However, the reaction of 3-hexanol and 3-ethyl-3-pentanol is very slow. *n*-Hexylamine is inert to this reagent. Aldehydes and ketones are reduced rapidly and quantitatively to the corresponding alcohols. Even the highly hindered ketone, 2,2,4,4-tetramethyl-3-pentanone, is reduced within 30 min. Reduction of camphor gives 91% isoborneol and 9% borneol, respectively. Cinnamaldehyde is rapidly reduced to the cinnamyl alcohol quantitatively without attacking the double bond. Carboxylic acids liberate hydrogen rapidly and quantitatively, but further reduction is very slow. Anhydrides consume 2 equiv of hydride without further hydride uptake, corresponding to reduction to an equimolar mixture of carboxylic acid and alcohol. Acid chlorides, esters, and lactones are rapidly reduced to the corresponding alcohols. Epoxides utilize 1 equiv of hydride at a moderate rate. In the case of unsymmetrical epoxides, the Markovnikov ring opening is predominant. Acetal, ketal, and ortho esters are inert to this reagent. Primary amides liberate hydrogen slowly. Caproamide undergoes slow reduction, but benzamide is not reduced. Tertiary amides consume 2 equiv of hydride slowly, undergoing reduction to the corresponding amines. Benzonitrile is reduced to the amine stage within 12 h; however, an aliphatic nitrile, capronitrile, is reduced only sluggishly. 1-Nitropropane rapidly liberates 1 equiv of hydrogen, but further reduction is very slow. Nitrobenzene utilizes 2.5 equiv of hydride, 1 for hydrogen evolution and 1.5 for reduction. Azobenzene is inert and azoxybenzene is reduced very sluggishly. Cyclohexanone oxime rapidly evolves 1 equiv of hydrogen, but no reduction is observed. Phenyl isocyanate consumes only 1 equiv of hydride to proceed to the formanilide stage. Pyridine is reduced very slowly. However, pyridine *N*-oxide undergoes rapid reduction with this reagent. Disulfides are rapidly reduced to the thiol stage, whereas, sulfoxides, sulfones, sulfonic acids, and sulfides are inert to this reagent. Cyclohexyl tosylate is also inert, but *n*-octyl tosylate undergoes reduction within 3.0 h. This hydride is inert to a typical *n*-alkyl chloride but reacts moderately with an *n*-alkyl bromide and rapidly with an *n*-alkyl iodide. A secondary alkyl bromide is almost inert to this hydride.

In contrast to the mild reducing characteristics of lithium borohydride,[1] its derivative lithium trialkylborohydride[2-5] is a remarkably powerful and selective reducing agent. The introduction of three alkyl groups changes the hydride donor activity tremendously. Therefore, it appeared of interest to explore monoalkyl- and dialkylborohydrides for their reducing characteristics.

Recently preparative procedures for various alkali metal alkylborohydrides have been reported.[6-11] Because of the

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