with addition funnel, Hershberg stirrer, reflux condenser, and nitrogen pad was added 1 L of xylene. A coarse sodium dispersion was prepared by first heating the mixture until the sodium melted and then rapidly stirring to break up the molten sodium. The flask was cooled to room temperature and 90 mL (ca. 2.2 mol) of anhydrous methanol was added. When all signs of gas evolution stopped, 217.2 g (2.0 mol) of chlorotrimethylsilane was added over 3 h. The mixture was stirred overnight at room temperature. After the reflux condenser was replaced by a Claisen head and condenser, the product was distilled (bp 45–58 °C (760 mm)) under nitrogen. Redistillation through a 1 m Vigreaux column under nitrogen gave 129 g (1.24 mol, 62%) of methoxytrimethylsilane, bp 57–58 °C (760 mm).

Ethoxytrimethylsilane (6b) was prepared using the same procedure.

Benzyloxytrimethylsilane (9b), 2-propyloxytrimethylsilane (11b), ethylene glycol bis(trimethylsilyl) ether (4) glyceroltris(trimethylsilyl) ether (5), and 2,3-butanediol bis(trimethylsilyl) ether (7) were prepared using established literature procedures.[23] **Dihydrobenzoin (8)** was prepared by the PtO_2-catalyzed hydrogenation of benzoin.[24]

Coupling of Methoxytrimethylsilane (3b). To a 300-mL Parr autoclave was added 26.0 g (250 mmol) of methoxytrimethylsilane and 3.65 g (25 mmol) of di-*tert*-butyl peroxide. The autoclave was pressured to 200 psig with nitrogen and heated and stirred at 145 °C for 16 h and cooled and the products were analyzed by GLC. GLC analyses were carried out on a Varian Model 2800 gas chromatograph using a 3.1 m × 1.5 mm 3% SE-30 on Chromosorb W column programmed from 75 °C (isothermal for 1 min) to 260 °C at 10 °C/min using dodecane as an internal standard. At a flow rate of 12 mL/min, retention times were: ethylene glycol bis(trimethylsilyl) ether (4), 3.8 min; dodecane, 7.5 min; and glycerol tris(trimethylsilyl) ether (5), 8.5 min. A third, unidentified, component (~2%) had a retention time of 14 min. The yield of ethylene glycol bis(trimethylsilyl) ether was 11.6 mmol (46%), while that of the glycerol derivative was 1.7 mmol (10%).

A second identical reaction was worked up to isolate ethylene glycol. Methoxytrimethylsilane was distilled from the reaction mixture and methanol was added to the residue. The mixture was brought to reflux and the methoxytrimethylsilane was slowly distilled off. The syrupy residue (0.83 g, 98% recovery) was treated with benzoyl chloride/pyridine.[25] The isolated solid was recrystallized from methanol–water to yield ethylene glycol dibenzoate, mp 71.6–72 °C. The mixture melting point with an authentic sample showed no depression. The NMR spectra of the two samples were superimposable.

Coupling of Ethoxytrimethylsilane (6b). Ethoxytrimethylsilane (82 g, 750 mmol) and di-*tert*-butyl peroxide (11 g, 75 mmol) were combined in a 300-mL Parr autoclave and stirred and heated at 145 °C for 16 h. The autoclave was cooled and the reaction mixture distilled to recover unreacted starting material. The residue was distilled through a 15-cm Vigreaux column to yield 7.4 g (32 mmol, 43%) of a 1:1 mixture of *meso*- and *dl*-2,3-butane diolbis(trimethylsilyl) ether (7), bp 36 °C (10 mm), and 2.4 g of a higher boiling mixture of several components (bp 95–105 °C (10 mm)).[26]

By comparison with an authentic sample, the dimer 7 was shown to consist of a 1:1 meso/*dl* mixture by GLC (2 m × 3 mm 3% SE-30 on Chromosorb W, 100 °C). After ethanolysis of **7**, the NMR spectrum of the dioxolanes prepared from the diols and formaldehyde confirmed the 1:1 meso/*dl* mixture.[27]

Coupling of Benzyloxytrimethylsilane (9). To 18.1 g (100 mmol) of benzyloxytrimethylsilane in a 100-mL round-bottomed flask equipped with magnetic stirrer and air condenser was added, under nitrogen, 1.46 g (10 mmol) of di-*tert*-butyl peroxide. The mixture was heated at 145 °C under nitrogen for 16 h. The reaction mixure was fractionally distilled through a 15-cm Vigreaux column to recover unreacted starting material. The distillate (bp 90–92 °C (15 mm)) contained a trace of benzaldehyde by NMR.

The NMR spectrum of the residue (3.2 g, 8.9 mmol, 89%) was consistent with a 1:1 meso/*dl* mixture of dihydrobenzoin bis(trimethylsilyl) ethers (**10**). The product was treated with ethanolic sodium hydroxide to cleave it to dihydrobenzoin (**8**). GLC analysis on the isolated dihydrobenzoin (2 m × 3 mm 3% SE-30 on Chromosorb W, 140–200 °C at 20 °C/min) showed that it consisted of a 1:1 mixture of meso and *dl* diastereomers by comparison with authentic samples.

Attempted Coupling of 2-Propyloxytrimethylsilane (11). 2-Propyloxytrimethylsilane (92g, 697 mmol) and di-*tert*-butyl peroxide (10.4g, 70 mmol) were heated at 145 °C in the 300-mL autoclave for 16 h. After the mixture was cooled, unreacted starting material was distilled off. The distillation residue (2.2 g) showed at least six components by GLC. Treatment of this residue with methanol and reexamination of the product mixture by GLC showed that pinacol (**12**) was a minor component of the mixture by spiking with an authentic sample.

Registry No.—**3b,** 1825-61-2; **6b,** 1825-62-3; **9b,** 14642-79-6; **11b,** 1825-64-5; **4,** 7381-30-8; **5,** 6787-10-6; *meso*-**7,** 53229-15-5; *dl*-**7,** 53274-85-4; *meso*-**10,** 6186-14-7; *dl*-**10,** 6186-15-8; chlorotrimethylsilane, 75-77-4; methanol, 67-56-1; ethanol, 64-17-5; DTBP, 110-05-4.

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Neutral Hydrolysis of Ketene Bis(2-methoxyethyl) Acetal in Water in the Presence of *tert*-Butyl Alcohol, Tetra-*n*-butylammonium Bromide, and Potassium Bromide. Effects of Hydrophobic Hydration

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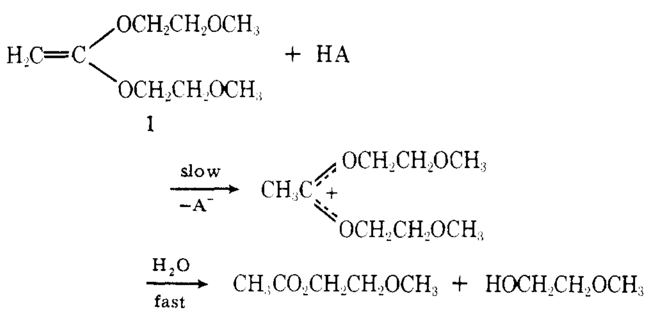
The study of solvation of organic molecules in water is hampered by the lack of a general and quantitative theory for the aqueous liquid state.[1] However, both experiment and theory have provided unequivocal evidence for the occurrence of hydrophobic hydration which is associated with the peculiar water ordering process around apolar groups in the molecule.[2]

In addition to nuclear magnetic relaxation studies,[3] these "water structure" effects are directly revealed in characteristic standard thermodynamic functions of solvation including large, negative entropies and large, positive heat capacities. In kinetic studies using binary aqueous solvent systems, hydrophobic hydration effects may be indicated by the manifestation of extrema in the thermodynamic quantities of activation (e.g., $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, $\Delta V^{\ddagger}$, or $\Delta C_p{}^{\ddagger}$)[4] in the water-rich region. More insight into the cause for these extrema has been obtained through separation of solvent effects on the activation parameters into changes in initial state and transition state solvation.[5] One reaction which has been investigated in some detail is the pH-independent hydrolysis of arylsulfonylmethyl perchlorates.[6,7] This reaction proceeds via rate-determining proton transfer from the α-sulfonyl carbon atom to a water molecule and exhibits pronounced cosolvent and electrolyte effects.[6] In this communication we present evidence for the effects of hydrophobic hydration on a neutral hydrolysis reaction involving rate-determining proton transfer *from water to carbon,* i.e., hydrolysis of ketene bis(2-methoxyethyl) acetal (1).

Results and Discussion

The mechanism of the hydrolysis of ketene acetal 1 has been investigated by Kankaanperä et al.[8] The reaction shows the features of general acid catalysis and involves rate-determining proton transfer from a Brønsted acid (HA) to the C-2 carbon atom of the olefinic bond ($k_{HA}/k_{DA} \approx$ 7–10, Brønsted $\alpha = 0.56 \pm 0.02$). At sufficiently high pH (10^{-2} M NaOH) there



HA = Brønsted acid

is a conveniently fast water-catalyzed process (HA = H_2O; k_{H_2O}/k_{D_2O} = 7.2)[8] in which water takes the role of the Brønsted acid. We have studied this pH-independent hydrolysis in the presence of t-BuOH, n-Bu_4NBr, and KBr. The first two additives may be characterized as water structure promoting agents due to dominating hydrophobic hydration of the butyl groups.[2,9] KBr is a structure-breaking electrolyte.[2,9]

Isobaric thermodynamic quantities of activation ($\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$) for hydrolysis of 1 in t-BuOH–H_2O in the solvent composition range n_{H_2O} = 0.85–1.00 (n_{H_2O} = mole fraction of water) are shown graphically in Figure 1. Since the rate of solvolysis of 1 in pure t-BuOH is small as compared with the rate of hydrolysis, the data pertain only to the water reaction. If a solvent operator,[10] δ_m, is defined which measures the change in a thermodynamic activation parameter on changing the reaction medium from pure water to water containing the additive, then it follows from Figure 1 that $\delta_m\Delta G^{\ddagger}$ is positive for n_{H_2O} = 1.00–0.85. This has also been found for dioxane-water mixtures.[8] In t-BuOH–H_2O there exists no simple relation between log k_{obsd} and solvent polarity parameters[11] like $(\epsilon - 1)/(2\epsilon + 1)$, and E_T or log a_{H_2O}. Figure 1 also portrays the more complex behavior of the functions $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ which pass through extrema around n_{H_2O} = 0.95. We note that in the region n_{H_2O} = 1.00–0.95 the sign of $\delta_m\Delta G^{\ddagger}$ is governed by the contribution of $T\delta_m\Delta S^{\ddagger}$, whereas the function $\delta_m\Delta H^{\ddagger}$ dominates the behavior of $\delta_m\Delta G^{\ddagger}$ from n_{H_2O} = 0.95 to 0.85. This phenomenon has been encountered previously for pH-independent proton transfer reactions.[5c,12] Since it is well known[1] that the most pronounced solvent heterogeneity occurs near n_{H_2O} = 0.95, it is likely that the extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ primarily stem from hydrophobic hydration effects. Hence, we suggest that the solvent dependence of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ reflects the net loss of hydrophobic hydration upon transfer of the reactants into the polar transition state, which reaches a maximum around the solvent composition of maximum solvent structural ordering.[12,13] Since the hydrophobicity of 1 appears to be relatively low,[14] the extrema in $\delta_m\Delta H^{\ddagger}$ and $\delta_m\Delta S^{\ddagger}$ are rather modest and do not allow a critical test for the existence of an isokinetic temperature.[15]

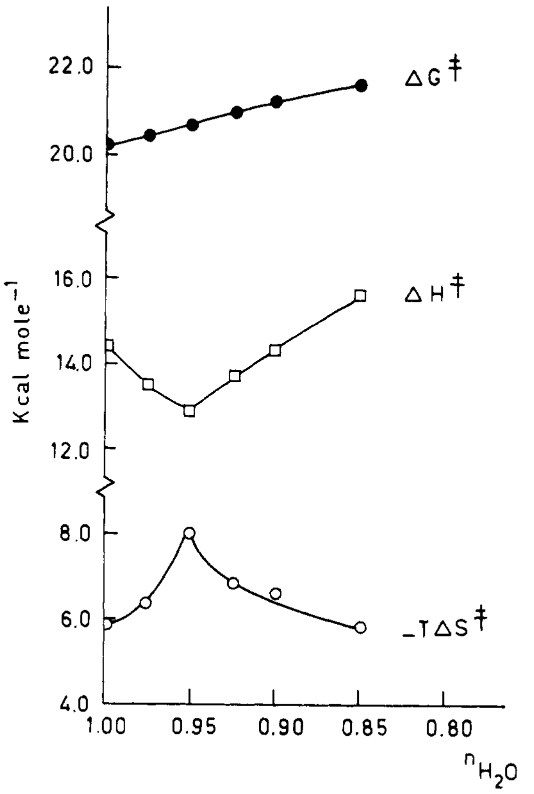


Figure 1. Plot of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $-T\Delta S^{\ddagger}$ vs. n_{H_2O} for the neutral hydrolysis of 1 in t-BuOH–H_2O containing 10^{-2} M NaOH (25 ± 0.04 °C).

The solvent dependence of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $-T\Delta S^{\ddagger}$ for hydrolysis of 1 in aqueous n-Bu_4NBr is shown in Figure 2. The small increase of $\Delta G^{\ddagger}$ by 0.5 kcal mol^{-1} going from water to 1.0 M electrolyte is again the result of mirror image behavior of larger changes in $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$. As for t-BuOH–H_2O, the initial decrease of $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ should be attributable to the water structure promoting effect of n-Bu_4NBr. Extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are observed at ~0.35 M n-Bu_4NBr. This concentration coincides almost exactly with the concentration of n-Bu_4NBr for which $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the neutral hydrolysis of p-nitrophenyl dichloroacetate pass through extrema.[12] It is likely that at electrolyte concentrations above 0.35 M the hydrocarbon residues of the cations will be occupying most of the cavities between hydrogen-bonded waters which would otherwise be void and that the hydration spheres of distinct cations will be subject to mutual overlap.[16] In this connection, it is of interest to note that recent NMR studies have shown that the water resonance of aqueous n-Bu_4NBr solutions passes through an extremum around the same concentration.[17]

Activation parameters for hydrolysis of 1 in 0–1.0 M KBr

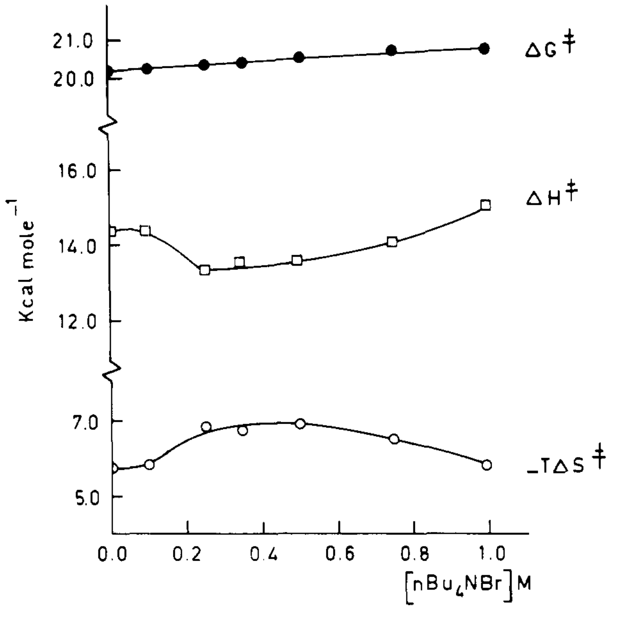


Figure 2. Plot of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $-T\Delta S^{\ddagger}$ vs. the molarity of n-Bu_4NBr for the neutral hydrolysis of 1 (10^{-2} M NaOH, 25 ± 0.04 °C).

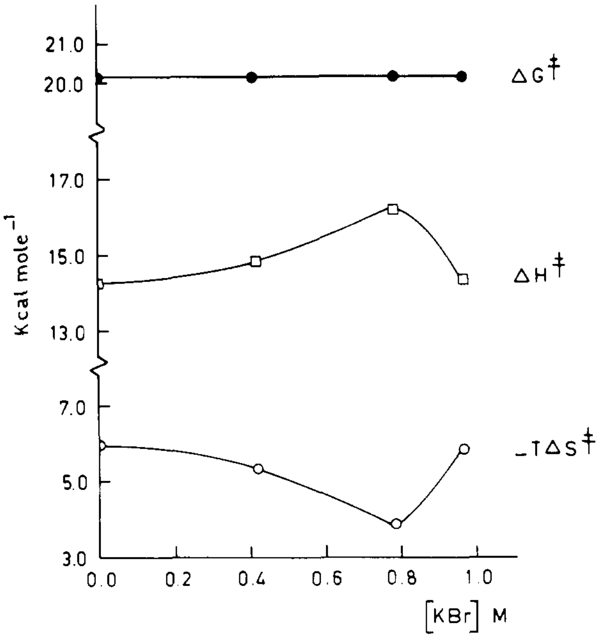


Figure 3. Plot of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $-T\Delta S^{\ddagger}$ vs. the molarity of KBr for the neutral hydrolysis of 1 (10^{-2} M NaOH, 25 ± 0.04 °C).

are shown in Figure 3. Over the whole concentration range, $\delta_m\Delta G^{\ddagger}$ shows only a very small variation. The functions $\delta_m\Delta H^{\ddagger}$ and $T\ \delta_m\Delta S^{\ddagger}$ show larger changes and, more significant, they vary in an *opposite* manner compared with those for hydrolysis in aqueous t-BuOH and n-Bu_4NBr solutions. Presumably, the decrease in water structure ensuing from the outer hydration spheres (class II_{sb} solvation shells)[18] of both the K^+ and Br^- ions hampers the formation of an ordered transition state (increase of $\Delta H^{\ddagger}$ and increase of $\Delta S^{\ddagger}$ relative to hydrolysis in the absence of KBr). Extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are observed around 0.8 M KBr, just as for the neutral hydrolysis of p-nitrophenyl dichloroacetate.[12] Above 0.8 M KBr, the II_{sb} hydration envelopes of K^+ and Br^- seriously interfere with each other,[19] leading to a negative entropy change because the freedom of movement of water molecules will then be primarily restricted by the electrostatic fields of the ions. The same explanation has been suggested[17] to account for the strong attenuation of the upfield shift of the water chemical shift if the KBr concentration is increased above 0.8 M.

In conclusion, the present results indicate that slow proton transfer from water to carbon in highly aqueous media is subject to specific $\Delta H^{\ddagger}$-$\Delta S^{\ddagger}$ compensation effects and appears to respond to changes in the structural integrity of the solvent.

Experimental Section

Materials. Ketene bis(2-methoxyethyl) acetal (1) was prepared according to Kankaanperä et al.[8] The product was purified by distillation: bp 98–102 °C (5 mm) [lit.[20] bp 92 °C (760 mm)]; NMR ($CDCl_3$) δ 3.13 (2 H, s), 3.32 (6 H, s), 3.66 (8 H, m); IR 1650 cm^{-1} (C=C); UV (cyclohexane) λ_{max} 220 nm. The water used in the kinetic measurements was demineralized and distilled twice in an all-quartz distillation unit. t-BuOH and KBr were of the highest grade available (UCB) and were used without further purification. n-Bu_4NBr was obtained from Fluka AG and was crystallized twice from ethyl acetate–diethyl ether (3:1). The solvent mixtures were all made up by weight.

Reaction Products. NMR and IR spectral evidence indicates quantitative hydrolysis of 1 to give 2-methoxyethyl acetate and 2-methoxyethanol.

Kinetic Measurements. The rate of hydrolysis of 1 was determined spectrophotometrically by following the disappearance of the ketene band at 235 nm. The reactions were carried out in 2-cm quartz cells which were placed in the adequately thermostated (±0.04 °C) cell compartment of a Zeiss PMQII spectrophotometer. A concentrated solution (~5 μL) of 1 in anhydrous dioxane was added to the aqueous reaction medium in the cuvette (6 mL) by means of a capillary pipet and under vigourous magnetic stirring.[21] The conversions were followed to greater than 75% completion, and infinity points were taken after 10 half-lives. Pseudo-first-order rate constants (k_{obsd}) were reproducible to within 3%. All hydrolyses were carried out in the presence of 10^{-2} M NaOH to suppress catalysis by the hydronium ion. Rate measurements in dilute NaOH showed that k_{obsd} values were essentially constant between at least pH 10–12. Solvolysis of 1 in pure t-BuOH ($k_{obsd} = 4.81 \times 10^{-5}\ s^{-1}$, 26.5 °C) is slow as compared with hydrolysis ($k_{obsd} = 9.67 \times 10^{-3}\ s^{-1}$, 25.0 °C).

Activation parameters were calculated from k_{obsd} values obtained at 3–5 different temperatures in the range 15–35 °C. Excellent Eyring plots were obtained in all cases. The estimated error in $\Delta H^{\ddagger}$ is ±0.3 kcal mol^{-1} and in $\Delta S^{\ddagger}$ ±1 eu. The error in $\Delta G^{\ddagger}$ is ~0.03 kcal mol^{-1}.

Registry No.—**1**, 5130-02-9; *tert*-butyl alcohol, 75-65-0; tetra-n-butylammonium bromide, 1643-19-2; potassium bromide, 7758-02-3.

Supplementary Material Available: Rate constants at different temperatures and activation parameters for hydrolysis of 1 in t-BuOH–H_2O are listed in Table I and for hydrolysis in aqueous solutions of n-Bu_4NBr and KBr in Table II (3 pages). Ordering information is given on any current masthead page.

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Alkylation of 1-Cyanocyclohexene[1]

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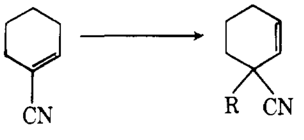
The alkylation of extended enolates derived from conjugated acids, esters, and ketones is an important part of synthetic methodology.[2] We report here some useful observations on the alkylation of a conjugated nitrile and some of its relatives.

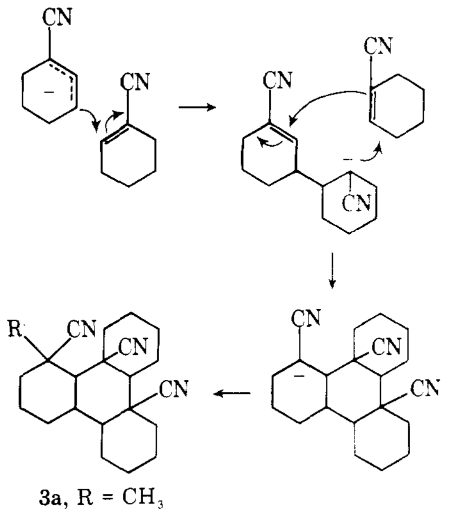
1-Cyanocyclohexene (1)[3] was converted into the corresponding anion by the action of LDA in THF containing HMPA, and the resulting anion was quenched with excess alkylating agent. Under these conditions products **2a–c** were obtained in yields of 78, 63, and 55%, respectively. Methyl cyclohexene-3-carboxylate[4] was converted into methyl 3-methylcyclohexene-3-carboxylate in 72% yield under these conditions. Lower yields of **2** and considerable amounts of polymeric material were obtained when ether, DME, or THF containing no HMPA were used as solvents; however, when HMPA was replaced with tetramethyl-12-crown-4 (in THF), a crown ether known to form complexes with lithium ions,[5] methylatin of **1** gave **2a** in 72% yield.



1

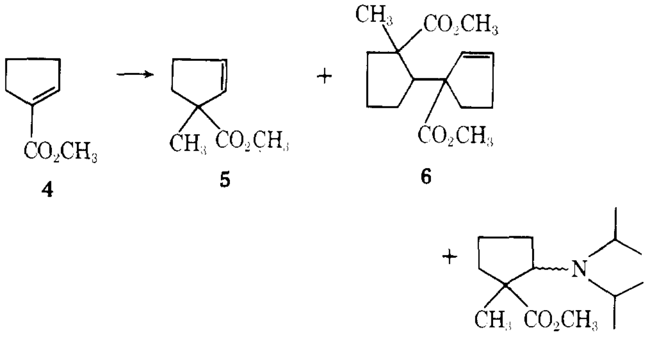
2a, R = CH_3
b, R = $CH(CH_3)_2$
c, R = $CH_2CH{=}C(CH_3)_2$

When DME containing TMEDA was used as solvent, methylation of **1** gave **2a** (45%) and a small amount of a mixture of trimers **3a,b**, the structures of which rest on spectral data (Experimental Section). Quenching of the anion (in DME–TMEDA) with water led to recovery of **1** (49%) and of pure trimer **3b**. These trimers are thought to arise as shown below.



3a, R = CH_3
b, R = H

Attempts to alkylate 1-cyanocylopentene[6] under the above conditions (THF–HMPA–LDA) were fruitless; thus, methylation of ester **4**[7] gave **5** (27%), **6**[8] (9%), and **7** (8%). On the other hand, the use of trityllithium as the base for the methylation of **4**, or its acid as the dianion, gave **5** in 45–55% yield.



4 5 6 7

Experimental Section[8]

Typical Procedure for Alkylations. To a solution of 41.0 mmol of lithium diisopropylamide in 50 mL of THF (N_2) containing 47.0 mmol of HMPA at −78 °C was added 40.0 mmol of **1** in 10 mL of THF. After 10 min, excess methyl iodide was added (syringe). The resulting solution was stirred at −78 °C for 10 min, allowed to warm to 25 °C, and quenched with ice water. The product was extracted into hexane, washed with saturated NH_4Cl and 10% aqueous HCl, dried, and concentrated. The crude product was passed through a short column of alumina to remove HMPA and distilled to yield 3.78 g (78%) of **2a:** bp 88–91 °C (20 torr); IR (CCl_4) 2225 cm^{-1}; NMR (CCl_4) δ 6.02–5.38 (m, 2), 2.22–1.58 (m, 6), 1.40 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 121 (26), 54 (100).

Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.30; H, 9.29; N, 11.54.

Reaction of 1 in DME Containing TMEDA. The anion of **1** (47 mmol) in 50 mL of DME containing 50 mmol of TMEDA was generated as above. When the anion was quenched with water and worked up as above **1** (49%) and 50 mg of a solid were recovered. Recrystallization of the solid from toluene gave pure **3b:** mp 298–299 °C; IR (KBr) 2220 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 321 (100), 295 (48), 268 (30), 254 (29), 214 (42), 108 (43).

Anal. Calcd for $C_{21}H_{27}N_3$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.35; H, 8.43; N, 13.22.

When the anion above was quenched with methyl iodide, **2a** (45%), and 550 mg of **3a** containing 10% of **3b** (two spots on TLC, Alumina/benzene), mp 218–220 °C was obtained: IR (CCl_4) 2225 cm^{-1}; NMR (CCl_4) δ 1.65 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 335 (100), 321 (10), 309 (46), 282 (40), 254 (11), 229 (83), 202 (43), 109 (44).

3-Isopropyl-3-cyanocyclohexene (2b) has bp (Kugelrohr) 100–120 °C (18 torr): IR (CCl_4) 2225 cm^{-1}; NMR (CCl_4) δ 6.10–5.40 (m, 2), 2.20–1.50 (m, 7), 1.10 (d, 3, CH_3, J = 6.5 Hz), 1.02 (d, 3, CH_3, J = 6.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 150 (1), 149 (4), 108 (11), 107 (100), 106 (15), 92 (6), 80 (22), 79 (11), 77 (7).

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