Dehydrobromination of 1,2-Dibromoethoxyethane Using Various Amine Bases

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1,2-Dibromoethoxyethane was treated with a number of basic reagents, mainly tertiary amines, to accomplish dehydrobromination to 1-bromo-2-ethoxyethene, a precursor to an acetaldehyde carbanion equivalent. The yield of this vinyl bromide and the other common byproducts of reaction varied markedly depending on the base and reaction conditions employed. Direct distillation of the product under reduced pressure from a tertiary amine solution was the method of choice, showing little if any effect of temperature and giving reproducible results. Following this procedure, *N,N*-dimethyldodecylamine was the preferred base for this reaction. This paper presents results of the dehydrobromination reaction using more than 30 different bases and conditions.

The compounds 1,2-dibromoethoxyethane, **1**, and 1-bromo-2-ethoxyethene, **2**, present interesting starting materials in organic syntheses. Compound **1** has been used extensively in the Boord synthesis and related reactions,[1] and compound **2** has been used widely as a precursor to ethoxyacetylene[2] and more recently in coupling reactions where its organometallic derivatives act as excellent acetaldehyde anion equivalents.[3] The synthesis of **1** from readily available ethyl vinyl ether has been easily accomplished by a number of researchers since Wisclencius first reported the reaction.[4] The synthesis of **2** from **1** was first reported by Favorskii in 1945 using *N,N*-diethylaniline as a dehydrobrominating agent.[5] Since that time a number of authors have synthesized **2**; but in most cases, changes in procedure were enacted in hopes of improving the mediocre yields that had been reported.[2c-f,h,3e,6] Our interest in **2**, first as an ethoxyacetylene precursor[7] and more recently as a two-carbon aldehyde homologation agent via various organometallic intermediates prompted us to study the dehydrobromination reaction of **1** to see if a high yielding, convenient, and reproducible synthesis of **2** could be found.[8]

The viability of tertiary amines such as triethylamine, pyridine, quinoline, and dimethylaniline as dehydrohalogenation agents has been demonstrated.[9] In most reports these amines are used interchangeably without marked changes in reaction products or yields. However, in certain cases, because of instability of the starting material or product, reactions have been reported to occur with only a specific amine.[10] The literature contains very few studies that compare the relative dehydrohalogenation yields for more than a few amine bases for any one system.[11]

This dehydrobromination study of **1** is an example where the starting material has a very labile α bromine that causes it to undergo side reactions which vary according to the base and conditions employed. As such, this system shows marked differences in product yield and composition depending on the base and conditions used to initiate reaction. In addition to the amine bases, a few non-amine bases were also employed; but in each of these cases the production of **2** was less than satisfactory.

Results and Discussion

A study of the literature methods for the dehydrobromination of **1** indicated that the Favorskii method using a tertiary amine base held the most promise (Scheme I).[5]

Scheme I

$$CH_2{=}CHOC_2H_5 + Br_2 \rightarrow \underset{\mathbf{1}}{BrCH_2CHBrOC_2H_5}$$

$$\mathbf{1} \xrightarrow{\text{base}} \underset{\mathbf{2}}{BrCH{=}CHOC_2H_5} + \underset{\mathbf{3}}{BrCH_2CH(OC_2H_5)_2}$$

Two general modifications to accomplish the reaction have been reported, and both of these were tried.[2d] In procedure A, **1** was heated with the base for a specified period of time

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Table I. Dehydrobromination Results via Procedure A

entry	base[a]	temp, °C	time, h	2, Z:E ratio	2, isolated yield (%)	3, yield (%)[b]
1	$C_6H_5N(C_2H_5)_2$	90–100	1.0	not reported	64–68[c]	not quantified
2	$C_6H_5N(C_2H_5)_2$	95–100	1.0	83:17	51	12
3	2,6-lutidine	91–96	1.5	85:15	26–74[d]	10–32[e]
4	2,6-lutidine	120–127	3.0	75:25	1	5
5	$(n\text{-}C_4H_9)_3N$	95–100	1.0	84:16	37	15

[a] The ratio of 1 to base was 1:2.5. [b] VPC yield. [c] Reference 2d. [d] Five runs were made with an average yield of 45%.

prior to solvent extraction of the mixture. Compound **2** was isolated by distillation after removal of the extraction solvent.[2b,d] Table I shows the results obtained following procedure A. The yields varied markedly, not only when different bases were used but even between different runs using the same base, 2,6-lutidine (entry 3). Since the reaction is highly exothermic, it is difficult to keep the heated pot at an exact temperature. This undoubtedly led to some of the discrepancies found in our yields. Both Brandsma and Favorskii emphasized the importance of controlling the temperature during the reaction to decrease polymer formation.[2d,5] The reaction of 2,6-lutidine at 120–127 °C (entry 4) shows the importance of temperature control, as a greatly reduced yield occured when the temperature rose above 100 °C. The yield of **2** was only 1% while the competing acetal **3** had increased to five times that amount; the rest of the starting material was converted to tar. Since **1** decomposes in the gas chromatograph, it was difficult to measure its disappearance during reaction, a necessity for determining the ideal contact time between the base and **1** in order to maximize yield. We found that typical workup procedures converted **1** to **3**, so it was necessary to get complete conversion of **1** while minimizing the contact of **2** with the heated base which results in decomposition and polymerization.

An additional observation from Table I is that **2** is produced in two stereoisomeric forms, *Z* and *E*. In all of the cases listed (entries 2–5), it can be seen that the *Z* form predominates by at least a 3:1 ratio, a result consistent with that found in previous reports. Literature references show that this preference for "cis" products is common because of stabilization by stereoelectronic effects.[13] In the present case (*Z*)-**2** is the stabilized form which predominates as the thermodynamic product of reaction, with a theromdynamic *E* to *Z* ratio of 17:83.[14]

The observed adverse temperature effects on product yields prompted us to study the dehydrobromination reaction by procedure B where **2** was heated with a base while directly distilling the product at reduced pressure as formed. This procedure reduces the product contact time with the heated solution and thus is much less sensitive to reaction pot temperature changes. Table II shows the advantage of this modification using three different bases. The product yields remain almost identical in each case over the same temperature range that caused a considerable decrease in yield of **2** using procedure A. With quinaldine as base, an increase in yield of **2** was obtained when the temperature was raised from 100 to 130 °C; but some of this increase was quite likely to result of the change in base concentration (vide infra).

Table III lists our results using procedure B as the dehydrobromination method. Since it has been reported that below 85 °C the reaction is too slow to progress with

Table II. Temperature Effects Using Procedure B[a]

base (ratio)[b]	temp, °C	time,[c] h	2, Z:E ratio	2, isolated yield (%)	3, yield (%)
quinaldine (1:1.5)[d]	100	5.0	76:24	19	47
quinaldine	125	3.0	81:19	39	25
quinaldine	130	4.0	83:17	40	25
$C_6H_5N(C_2H_5)_2$	98	2.5	85:15	66	15
$C_6H_5N(C_2H_5)_2$	115	3.0	82:18	68	17
$(n\text{-}C_4H_9)_3N$	96	2.3	88:12	79	5
$(n\text{-}C_4H_9)_3N$	120	3.0	86:14	76	6

[a] The reaction scale was 0.25 mol 1, unless otherwise noted. [b] The ratio of 1 to base was 1:2.5 unless otherwise noted. [c] Time was measured from the addition of 1 until 2 no longer distilled. [d] The amount of 1 used was 0.43 mol.

these typical bases,[2d] our reactions were made at 90–130 °C with no noticeable adverse temperature effects. One of the requirements for procedure B is that the base have a boiling point high enough so that codistillation with the product will not occur. Table III shows two examples (entries 6 and 9) where base distillation was a problem at the reduced pressure used for the reaction.

The aromatic or cyclic bases (entries 1, 2, 5, and 10) all formed insoluble salts that either caked the side of the flask and distillation head or resulted in thick tars, both of which made efficient distillation of the product impossible. Similar amines are reported to have formed tetraalkylammonium halide salts in a competitive reaction with dehydrohalogenation which forms hydrobromide salts of the corresponding base.[9d] If both salts were formed, this could account for the excess solid that makes distillation difficult. The best previous yield (84%) of **2** had been reported[3e] with a 1:1 mixture of **1** and tributylamine. Our yield (entry 4) was much below that (61%) and there were again separation problems; the salts of reaction caused the solution to thicken and turn dark with some decomposition to polymer and bromo acetal, **3**. A marked improvement in yield was noted when the base ratio was increased 2.5-fold (entry 3). Under these conditions the distillation of product was clean but the darkening of the solution still indicated the formation of some polymer. In addition, about 2% ethyl bromide, a byproduct that usually indicates competing reactions, was isolated. In our work, the compound that yielded the best results was *N,N*-dimethyldodecylamine (entries 7 and 8), a base which upon reaction produced a clear yellowish solution with an orange salt precipitate. A 77% yield with only 3% **3** as a byproduct (entry 7) indicated a very clean reaction. When scaled up to 1.25 mol (entry 8), an 86% yield with still only a 3% impurity of **3** resulted. The *Z*:*E* ratio of 7.33:1.00 is about as high as a *Z* ratio as was found with any of the bases. Since (*Z*)-**2** is the form most often utilized in making the (ethoxyvinyl)lithium synthon, this provides a good preparation for it. In general, the higher the percentage of **2** produced, the fewer the byproducts of the reaction. Only the stereoisomers of **2** along with small amounts of acetal, **3**, were found in entries 6–8, while in the rest of the experiments other competing products were produced, most notably ethanol, ethyl bromide, bromo-

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Table III. Dehydrobromination Results via Procedure B[a]

entry	base (ratio)[b]	temp, °C	time,[c] h	2, Z:E ratio	yield (%) 2[d]	yield (%) 3[e]	major byproducts[e,f]
1	$C_6H_5N(C_2H_5)_2$	98	2.5[g]	85:15	66	15	EA, 2; EB, 6; EE, 1
2	quinaldine	120	4.0[h]	83:17	40	25	BA, 1; EA, 13; EB, 3; EE, 1
3	$(n\text{-}C_4H_9)_3N$	96	2.3[i]	88:12	77	5	EB, 2
4	$(n\text{-}C_4H_9)_3N$ (1:1)	100	2.3[g]	83:17	61	12	EA, 2; EB, 2; EE, 6
5		120	2.7[h]	84:16	42	4	BA, 1; EA, 1; EB 1
6	$c\text{-}C_6H_{11}N(C_2H_5)_2$	95	3.0[j]	84:16	62	3	
7	$n\text{-}C_{12}H_{25}N(CH_3)_2$	99	2.5[k]	88:12	77	3	
8	$n\text{-}C_{12}H_{25}N(CH_3)_2$[l]	95	3.0[k]	88:12	86	3	
9	$C_6H_5CH_2N(CH_3)_2$	98	2.3[j]	89:11	45	21	
10	$(c\text{-}C_6H_{11})_2NCH_3$	98	2.3[h]	86:14	71	7	BA, 1; EB, 1; EE, 1

[a] The reaction scale was 0.25 mol 1, unless otherwise noted. [b] The ratio of 1 to base was 1:2.5, unless otherwise noted. [c] Time was measured from the addition of 1 until 2 no longer distilled. [d] Isolated yield. [e] VPC yield. [f] Notation: BA = bromoacetaldehyde; EA = ethyl alcohol; EB = ethyl bromide; EE = ethoxyethyne. [g] Dark solution with thick tar formed. [h] Insoluble salt formed. [i] Dark solution formed. [j] Base codistills with the product. [k] A clear solution with an orange precipitate formed. [l] The amount of 1 used was 1.25 mol.

Table IV. Dehydrobromination Results Using Base–Solvent and Related Systems

entry	procedure	system	ratio[a,b]	temp, °C	time, h	2, Z:E ratio	yield (%) 2[c]	yield (%) 3[c]	major byproducts[d,e]
1	B	$C_6H_5N(C_2H_5)_2$–mineral oil	1:1.0[f]	100	2.0		5	36	
2	A	$C_6H_5N(C_2H_5)_2$–benzene	1:1.5[f]	80	1.0	83:17	36	12	
3	A	$(C_2H_5)_3N$–ether	1:1.0	35	19.5	83:17	30	28	
4	B	P2VP–HMPA[g]	1:1.3	103	2.5	75:25	14	39	EA, 1; EB, 5
5	A	t-BuOK–HMPA	1:1.0	50	1.5				EE, 43[c]
6	B	Li_2CO_3, LiCl–HMPA	1:2.0[h]	98	3.0			30	AC, 1; BA, 1; CA, 13; EA, 13; EB, 3; EC, 2
7	B	Li_2CO_3, LiF–HMPA	1:2.0[h]	96	2.5	67:33	3	70	AC, 1; BA, 2; EA, 14; EB, 9
8	B	DBU-neat[i]	1:2.5[j]	95	2.5	52:48	4	4	
9	A[k]	DBU-neat	1:1.0	40	2.0	47:53	1	16	EA, 1
10	A[k]	DBU–ether	1:1.0	−78	3.0	90:10	4	16	EA, 1; EB, 1
11	A[l]	$(C_2H_5)_3N$-neat	1:2.5	3	30.0	94:6	44	10	
12	A[m]	$(C_2H_5)_3N$–CH_2Cl_2	1:1.5	−78	30.0	93:7	74	6	

[a] Ratio of 1 to base used. [b] Reaction scale was 0.20 mol 1, unless otherwise noted. [c] Isolated yield. [d] VPC yield. [e] Notation: AC = acetaldehyde; BA = bromoacetaldehyde; CA = chloroacetaldehyde diethyl acetal; EA = ethyl alcohol; EB = ethyl bromide; EC = ethyl chloride; EE = ethoxyethyne. [f] The amount of 1 used was 0.30 mol. [g] Poly(2-vinylpyridine) in hexamethylphosphoramide. [h] The amount of 1 used was 0.25 mol. [i] 1,8-Diazabicyclo[5.4.0]undec-7-ene. [j] The amount of 1 used was 0.40 mol. [k] Modified workup eliminated the acid wash step. [l] Modified workup: added 100 mL of pentane, followed by suction filtration, rotary evaporation, product distillation. [m] See: Zembayashi, M.; Tamao, K.; Kumada, M. *Synthesis* **1977**, 422, for procedure.

acetaldehyde, and ethoxyacetylene.

A summary of our observations on the dehydrobrominations indicates that at higher temperatures, or with other conditions conducive to polymer formation, ethanol formation increases along with that of ethyl bromide. The ethyl bromide undoubtedly is a product from the reaction of ethanol and hydrogen bromide. The unstable bromoacetaldehyde probably is formed from **3** when traces of water are present, and it most likely cyclizes quickly to its more stable trimer form.[15] The ethoxyacetylene is produced in minor amounts when the base is able to remove a second equivalent of HBr from the **2** initially formed in the reaction, a process known to occur quite readily with stronger bases.[2b,d,f,h]

Dehydrobromination reactions are most often accomplished by reacting bromides in base–solvent systems.[16] Since Favorskii's original paper reported the use of diethylaniline as a base in Vaseline oil,[5] we wanted to compare the results obtained in some base–solvent systems with those obtained by the nonsolvent systems described above. The bases that could be used in these systems are limited since it is known that alkoxide bases when added to **1** produce the corresponding α-bromo acetals and those in turn, when reacted with *tert*-butoxide, give ketene acetals.[17] One of the recurring problems in the dehydrobromination of **1** is the occurrence of **3** as an undesirable coproduct. This is known to be formed by the reaction of **1** or **2** with ethoxide or ethanol, which, if supplied externally as a base or solvent or internally as a decomposition product, results in a lower yield of **2**.[18]

Table IV illustrates our results using base–solvent systems for reaction. In most cases where an amine was used in a solvent (entries 1–4, 10) the yields did not approach those of the better bases listed in Table III, and excess amounts of **3** formed. A sterically bulky alkoxide base, *t*-BuOK in HMPA (entry 5), was used to see if this would promote elimination over substitution. The product of reaction, in relatively good yield, was ethoxyacetylene, indicating that this base did favor elimination and proceeded to remove 2 equiv of HBr. Two notably mild non-amine base systems that sounded promising were also tried.[19] In the first of these (entry 6) lithium carbonate and lithium chloride in HMPA gave a variety of products, many caused by chlorine–bromine exchange, but none of the desired **2**. In a similar reaction (entry 7) using a salt unlikely to give exchange, lithium fluoride and lithium carbonate with powdered glass in HMPA, a narrower

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spectrum of products resulted. But even though some **2** was found, the reaction did not appear that it could be made competitive with previous methods.

The case of 1,8-diazobicyclo[5.4.0]undec-7-ene, DBU, is interesting as it has been touted as a good nonnucleophilic base that gives higher yields than the more typically used bases.[11b,c] When DBU was used without a solvent (entry 8) following general procedure B, it appeared too reactive, resulting in smoking, spattering of the solution, and immediate formation of a black insoluble precipitate. The small amount of product that did distill contained a high proportion of **3** and a low ratio of (*Z*)- to (*E*)-**2**. It has been reported that (*Z*)-**2** is four times more reactive than the *E* form, so presumably more *Z* than *E* was consumed in the formation of byproducts.[12] A second trial using only an equivalent amount of DBU at a lower temperature (entry 9) gave a similar result. In this case the reaction mixture was taken up in water and extracted. The entire solid black precipitate dissolved in water but the amount of product produced was even lower than before. Finally, in hopes of finding conditions where DBU would initiate dehydrobromination without causing side reactions, a trial was made (entry 10) at −78 °C in an ether solvent. The reaction appeared promising as voluminous amounts of white salt precipitated and the solution remained light yellow until finally turning to a white solid mass when warmed to room temperature. Even though all of the solid dissolved in water and an ether layer separated, analysis of the product after solvent evaporation showed a low yield again containing mostly **3**. It was noteworthy that at this low temperature the ratio of (*Z*)- to (*E*)-**2** increased to 9:1, a ratio higher in *Z* than any of the bases produced at elevated temperatures.

Since (*Z*)-**2** is the only form reported to be convertible to its lithium salt,[3e] it was of interest to note that one article made reference to producing this isomer in 100% purity using triethylamine.[3f] Having used this base previously in refluxing ether without much success (entry 3), we decided to try again using different conditions. Performing the reaction in a cold room at 3 °C using a 2.5-fold excess of base and no solvent (entry 11) resulted in only a moderate yield, but the best *Z*:*E* ratio (94:6) obtained in the study. Unfortunately, a 10% yield of **3** was also isolated. Using conditions as close to those of Tamao's as possible (entry 12), we were able to get our best yield in a solvent system, 72%, but did not find exclusive formation of (*Z*)-**2**, as has been reported. In fact, we did find a high ratio, 93:7, but it was still contaminated with 6% of **3**. In our opinion this is a good alternate synthesis, but it suffers the drawbacks of having a long reaction time and the inconvenience of a solvent workup procedure. Since the separation of the isomers of **2** by distillation is just as easy as the separation of (*Z*)-**2** from **3**, it seems that the advantage of the small increase in *Z*:*E* ratio formed is outweighed by the overall lower product yield when compared to entry 8, table III.

In summary, a comprehensive study of the dehydrobromination reaction of 1,2-dibromoethoxyethane, **1**, has been accomplished. All of the nonpolymeric products of the reaction have been identified and quantified. From this a simple, reproducible, and high yielding synthesis of 1-bromo-2-ethoxyethene, **2**, has been found. This should make the title compound readily available for studies of its organometallic derivatives as acetaldehyde homologation agents.

Experimental Section

Instrumentation and Methods. ^{1}H NMR spectra were obtained on a Perkin-Elmer R-24B 60-MHz spectrometer and are reported in parts per million (δ) from the internal standard Me_4Si. IR spectra were recorded neat on a Beckman Acculab 4 spectrometer. Gas chromatographic analyses were performed on a Hewlett-Packard Model 5791 chromatograph equipped with an FID and a 60 m × 0.25 mm J&W Carbowax 20M wall coated, fused silica, open tubular capillary column which was programmed to hold at 50 °C for 8 min and then to increase 4°/min to a maximum of 220 °C. The chromatogram was recorded and integrated on a Hewlett-Packard Model 3390A reporting integrator. Peak identification was based on retention time matching with known standards and by mass spectra obtained on a Hewlett-Packard HP-5980 spectrometer. The amine bases[20] and solvents of reaction were commercial products of the highest purity available and were dried over CaH_2 or molecular sieves before distillation in vacuo onto molecular sieves.

1,2-Dibromoethoxyethane (1). A 1-L, three-necked round-bottomed flask equipped with a mechanical stirrer, a pressure-equalizing funnel, and a condenser topped with a drying tube ($CaCl_2$) was half immersed in a dry ice–isopropyl alcohol bath after the addition of 90 g (1.25 mol) of ethyl vinyl ether and 300 mL of dry CH_2Cl_2. The addition funnel was filled with a solution of 200 g (1.25 mol) bromine in 150 mL of dry CH_2Cl_2. Addition was started and continued at the rate of 2–3 drops/s until all the solution was added in about 2 h. The reaction mixture remained colorless until the last 15 min at which time it became clear red-orange. The flask was removed from the dry ice bath and stirring stopped as the solution was allowed to stand overnight at room temperature. The resulting clear yellow liquid was concentrated by vacuum rotary evaporation in a bath maintained at 35–40 °C. The crude dibromide, 282.8 g (98%), was a clear deep yellow oil. Product purity was determined by ^{1}H NMR (CCl_4) [δ 5.99 (t, 1 H), 3.87 (d, 2 H), 3.69 (t, 2 H), 1.32 (t, 3 H)]; an additional peak at δ 5.32 indicated the CH_2Cl_2 impurity of about 2%. Distillation of 1,2-dibromoethoxyethane into a receiver immersed in a dry ice–isopropyl alcohol bath was performed at reduced pressure to yield 264 g (91%) of a clear, colorless, fuming liquid, bp 44–47 °C/1.8 mm, lit.[5] bp 76 °C/16 mm.

1-Bromo-2-ethoxyethene (2) by Procedure A. The procedure described in the literature[3d] was followed except that a three-necked, round-bottomed flask equipped with a mechanical stirrer, a condenser, and an additional funnel was used.

1-Bromo-2-ethoxyethene (2) by Procedure B. The following method utilizing *N*,*N*-dimethyldodecylamine is representative. The reaction apparatus consisted of a 300-mL three-necked round-bottomed flask equipped with a mechanical vacuum stirrer assembly, a 125-mL pressure-equilizing addition funnel, and a simple one-piece vacuum distillation apparatus including a Claisen adapter, thus allowing the insertion of a thermometer to measure the pot temperature. To the flask was added 133.1 g (0.63 mol) of dried, distilled *N*,*N*-dimethyldodecylamine. The freshly distilled 1,2-dibromoethoxyethane (58 g, 0.25 mol) was added to the addition funnel before the preheated oil bath was raised. The temperature of the oil bath was adjusted to 110–120 °C so as to maintain a pot temperature close to 100 °C thoughout the course of the reaction and a vacuum of 20 mm was applied. When the pot temperature reached 99 °C, the addition of the dibromide was started at 1 drop/s and the solution turned to a light yellow with a fine orange precipitate. Within 0.5 h, a colorless product began distilling at 42 °C/22 mm. This was collected in a receiver cooled in a dry ice–isopropyl alcohol bath. The addition was completed within 1 h. The reaction was allowed to proceed for an additional 1 h before the final amounts of product were brought over by dramatically increasing the stirrer speed and by heating the pot and head with a heat gun until no more liquid distilled. The main fraction, 31.5 g, and the 2.4 g collected in the gas trap were analyzed by VPC and shown to be almost pure 1-bromo-2-ethoxyethene (**2**) in a crude yield of 90%. The combined fractions were redistilled through a 30-cm Vigreaux column to give the following fractions: 12.7 g, bp 43–47 °C/40 mm (*Z*:*E* = 83:17); 14.2 g, bp 47–50°/37 mm (*Z*:*E* = 96:4); and 2.6 g, bp 50–58 °C/38 mm (*Z* = 81%, acetal = 19%) (lit.[2d] bp 28–47 °C/12 mm).

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The combined weight of the clear and colorless distilled fractions was 29 g (77%). Separation of pure isomers was accomplished by VPC and their identities were confirmed by ^{1}H NMR (CCl_4): *Z* isomer, δ 6.65 (d, 1 H), 5.10 (d, 1 H), 4.02 (q, 2 H), 1.36 (t, 3 H); *E* isomer, δ 6.78 (d, 1 H), 5.38 (d, 1 H), 3.82 (q, 2 H), 1.31 (t, 3 H); bromoacetaldehyde diethyl acetal, δ 4.60 (t, 1 H), 3.60 (t, 4 H), 3.27 (d, 2 H), 1.19 (t, 6 H).

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Registry No. 1, 2983-26-8; (*Z*)-2, 23521-49-5; (*E*)-2, 16339-88-1; 3, 2032-35-1; $C_2H_5OC{\equiv}CH$, 927-80-0.

Molecular Receptors. Synthesis and X-ray Crystal Structure of a Calix[4]arene Tetracarbonate–Acetonitrile (1:1) Clathrate

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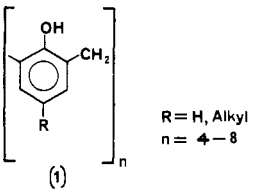
Treatment of *p-tert*-butylcalix[4]arene with ethyl chloroformate and sodium hydride produces tetraethyl *p-tert*-butylcalix[4]arene tetracarbonate, which forms a crystalline inclusion complex with acetonitrile. The crystal and molecular structure have been determined by X-ray diffraction. The crystals are tetragonal, space group $P4/ncc$ (no. 130) with four molecules in the unit cell of dimensions $a = b = 14.836$ (5) Å, $c = 26.720$ (8) Å. The macrocycle has fourfold crystallographic symmetry, and the benzene rings are inclined at 24.6° to the fourfold axis so as to increase intramolecular *tert*-butyl···*tert*-butyl separations; the acetonitrile molecule lies along the fourfold axis with the methyl group oriented toward the inside of the cavity. The structure was solved by direct methods and refined by full-matrix least-squares calculations to a final *R* value of 0.0754 for 843 reflections having $I > 3\sigma(I)$. Aspects of calixarene receptor topology are discussed.

In recent years there has been growing interest in inclusion phenomena with natural and synthetic unimolecular receptors with much emphasis on the macrocyclic effect.[1] In the natural series, the cyclodextrins[2-7] have been a rich source of information and ideas on guest–host interactions in biomimetic chemistry whereas crown ethers, cryptands, and related cavitands have been the main focus of attention with synthetic receptors.[8-14] Both solution and solid-state studies with unimolecular receptors have been used extensively to probe the guest–host interactions responsible for binding and transport of ionic and neutral molecules.

The calixarenes[15] constitute an homology of synthetic metacyclophanes 1, produced by phenol–formaldehyde cyclocondensation, whose structures bear a cursory resemblance to the cyclodextrins in as much as each has a single recurring structural subunit with several hydroxyl groups peripherally arranged about a central cavity. Like



(1)

the cyclodextrins, the calixarenes have the ability to receive and retain neutral organic molecules, e.g., from solvent of crystallization, by imprisoning the guest inside the discrete central cavity, i.e., true clathrate behavior.[16-19] They also exhibit *multimolecular* inclusion behavior in which the guest species is accommodated in continuous channels or layers within the crystal lattic.[20]

(1) For a recent comprehensive account of many aspects of inclusion phenomena with natural and synthetic systems including macrocycles, see: *Inclusion Compounds*, Alwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic: London, 1984; Vol. 1, 2, 3.
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