trimethylsilyl anion and that this may be the species responsible for the debrominations. To the best of our knowledge, this is the first time that BSA has been reported to be a reducing agent when used in combination with fluoride ion and a crown ether.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 spectrophotometer, using Me_2SO-d_6 as solvent and sodium 4,4-dimethyl-4-silapentane-1-sulfonate as internal standard unless otherwise stated. Thin-layer chromatography was carried out on microscope slides coated with chromatography-grade silica gel (silicAR) obtained from Mallinckrodt. Column chromatography was carried out by using J. T. Baker chromatographic-grade silica gel powder in glass columns. Concentrations were carried out in vacuo at 30–40 °C. Solvent system E is the upper layer of a mixture of ethyl acetate–*n*-propyl alcohol–water (4:1:2, v/v/v).

Standard Conditions for Debromination of Deblocked Nucleosides. To a suspension of dried (110 °C, 0.5 torr, 1 h), powdered nucleoside (0.5 mmol) in dry acetonitrile (distilled from calcium hydride) was added *N*,*O*-bis(trimethylsilyl)acetamide (0.6 mL, 2.5 mmol), using a dry syringe. A clear solution was obtained after stirring for 1 h. To this solution was added a mixture of potassium fluoride (58 mg, 1.0 mmol) and dicyclohexyl-18-crown-6 (14 mg, 0.05 mmol) in dry acetonitrile which was previously stirred for 30 min. The reaction mixture was heated at reflux temperature until starting material was no longer detected in the thin-layer chromatogram. Methanol (30 mL) was added to the reaction mixture and the solution was then stirred for 20 h at room temperature. Silica gel (1 g) was added to the solution and the solvent was removed in vacuo. The residual solid was applied to the top of a column (2 × 25 cm) containing silica gel (22 g) and the column eluted with the appropriate solvent. Progress of the chromatography was followed by TLC and fractions containing product were combined and concentrated.

Debromination of 6-Bromotoyocamycin. Treatment of 6-bromotoyocamycin[10] (**1**) under standard conditions for 45 h gave a product that was chromatographed as described above, using chloroform–methanol (13:3, v/v) as eluant. Combination of appropriate fractions yielded toyocamycin (50 mg, 34.3%), which was shown to be identical with an authentic sample of toyocamycin[11] (UV, ^{1}H NMR, R_f, IR, and mixture melting point). When the above reaction was carried out under the same conditions, but without potassium fluoride, no change in starting material was noted.

Debromination of 6-Bromosangivamycin. 6-Bromosangivamycin[12] (**6**, 194 mg) was treated as above for 72 h. Chromatography was carried out as described above, using first a mixture of chloroform–ethanol (600 mL, 8:2, v/v) and then solvent system E (300 mL). A faster running component was isolated (30 mg, 25%), which was shown to be toyocamycin by the usual criteria. A slower moving component (45 mg, 30%) was also isolated which proved to be sangivamycin.

Debromination of 8-Bromoadenosine. 8-Bromoadenosine (**4**, 173 mg) was treated as described for 96 h. Chromatography, using solvent system E, yielded 20 mg of starting material as well as a slow-moving component (40 mg, 36%, based on recovered starting material), which was shown to be adenosine by a direct comparison with an authentic sample.

2′,3′,5′-Tri-*O*-acetyl-6-bromotoyocamycin (1b). Acetic anhydride (0.7 mL, 7.54 mmol) was added to a suspension of 6-bromotoyocamycin (**1a**, 370 mg, 1.03 mmol) in pyridine (15 mL). The mixture was stirred at room temperature for 4 h (clear solution occurred in 10 min). The solvent was removed in vacuo and the residual solid was coevaporated in succession with ethanol (2 × 15 mL), water (2 × 15 mL), and finally toluene (2 × 15 mL). The solid was crystallized from methanol to afford 2′,3′,5′-tri-*O*-acetyl-6-bromotoyocamycin (**1b**) in a quantitative yield: mp 200 °C; ^{1}H NMR ($CDCl_3$) δ 2.00, 2.06, and 2.11 (3 s, 9, 3 CH_3CO), 5.77 (br s, 2, NH_2), 6.16 (m, 2, H_1', H_2'), 8.26 (s, 1, H_2).

Anal. Calcd for $C_{18}H_{18}N_5O_7Br$: C, 43,52; H, 3.65; N, 14.17. Found: C, 43.85, H, 3.48; N, 13.73.

Debromination of 2′,3′,5′-Tri-*O*-acetyl-6-bromotoyocamycin (1b). 2′,3′,5′-Tri-*O*-acetyl-6-bromotoyocamycin (**1b**, 496 mg, 1.0 mmol) was dissolved in dry acetonitrile (20 mL). BSA (1.0 mL, 4.0 mmol) was added to the solution while stirring at 25 °C. To this solution was added a mixture of potassium fluoride (106 mg, 2.0 mmol) and dicyclohexyl-18-crown-6 (28 mg, 0.1 mmol) in dry acetonitrile which had already been stirred vigorously for 30 min. The reaction mixture was then heated at reflux for 9 h. The resulting dark-brownish solution was evaporated in vacuo to dryness. The residual syrup was dissolved in chloroform (7 mL) and applied to the top of a column (3 × 30 cm) of silica gel (30 g). The column was eluted with chloroform–ethyl acetate (4:1, v/v). Fractions containing the product were combined and concentrated to yield 250 mg (60%) of 2′,3′,5′-tri-*O*-acetyltoyocamycin (**3b**), mp 158 °C. The UV spectrum of this product was identical with that of toyocamycin: ^{1}H NMR (Me_2SO-d_6) δ 2.03, 2.05, 2.13 (3 s, 9, 3 CH_3CO), 6.30 (d, 1, H_1'), 6.94 (br s, 2, NH_2), 8.23 (s, 1, H_5 or H_2), 8.42 (s, 1, H_2 or H_5). Further treatment of **3b** (150 mg, 0.36 mmol) with methanolic ammonia (15 mL, saturated at 0 °C) at 5 °C for 2 h afforded 80 mg (76.4%) of toyocamycin (**3a**) which was shown to be identical with an authentic sample by a comparison of the UV, ^{1}H NMR, TLC, and melting point.

When BSA was left out of the above reaction, no change in starting material was observed.

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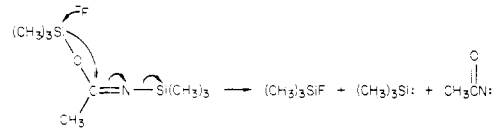
Registry No. **1a**, 20201-55-2; **1b**, 74112-93-9; **3a**, 606-58-6; **3b**, 74098-09-2; **4**, 2946-39-6; **5**, 5682-25-7; **6**, 20201-56-3; **7**, 18417-89-5.

(9) One could imagine fluoride ion attacking BSA to produce trimethylsilyl anion in the following manner:



This mechanism predicts the formation of acetyl nitrene which could rearrange to give methyl isocyanate or react with solvent. It is interesting to speculate that the reaction of BSA with other bases (e.g., alkoxides) might be a useful means of producing the trimethylsilyl anion.

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Orientation in Dehydrohalogenation of 2-Halobutanes Promoted by 2,6-Di-*tert*-butylpiperidide Base

Richard A. Bartsch* and Bong Rae Cho

Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

Jack C. Day

Department of Chemistry, Hunter College, City University of New York, New York, New York 10021

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Positional orientation in base-promoted 1,2-eliminations from 2-substituted alkanes is strongly influenced by base association.[1] For example, in *t*-BuOK-promoted eliminations from 2-bromobutane, the relative proportion of 1-butene increases from 30% in dimethyl sulfoxide (Me_2SO)

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Table I. Olefinic Products from Reactions of 2-Halobutanes[a] with Anionic Bases in Different Solvents at 50 °C

system	X of 2-BuX	base[b]	solvent	added crown ether[c]	% 1-butene[d]	*trans*-2-butene/ *cis*-2-butene
1	I	*t*-BuOK	diglyme	none	17.7	3.43
2	I	*t*-BuOK	diglyme	18-crown-6	18.6	3.58
3	I	*t*-BuOK	Me_2SO	none	18.5	3.39
4	I	1	diglyme	none	26.1	3.92
5	I	1	diglyme	15-crown-5	20.6	4.13
6	I	1	diglyme	12-crown-4	17.2	3.98
7[e]	I	*t*-BuOK	*t*-BuOH	none	34	2.17
8	Br	1	diglyme	none	40.3	3.81
9[f]	Br	*t*-BuOK	*t*-BuOH	none	50.0	1.51

[a] [2-BuX] = 0.10 M. [b] [Base] = 0.15 M. [c] [Crown ether] = 0.15 M. [d] Relative alkene proportions were reproducible to ±0.5%. [e] Reference 5. [f] Reference 6.

to 51% in *t*-BuOH. Bartsch and co-workers[1,2] have proposed that for eliminations from 2-substituted alkanes unfavorable steric interactions of the *t*-BuOK ion pairs and aggregates of ion pairs in *t*-BuOH occur in transition states leading to the 2-alkenes which produce the exhalted proportion of the thermodynamically less stable 1-alkene.

The synthetic utility of positional orientation control by associated bases is lessened by a low reactivity when compared with that of dissociated bases. Base species which combine the orientation control of an associated base with the higher reactivity of a dissociated one would offer considerable synthetic advantage.

Orientation was determined in eliminations from 2-iodobutane induced by highly ramified tertiary alkoxides, such as potassium tri-2-norbornylmethoxide, in Me_2SO,[3] in order to determine if such bases exist. Although a steric influence upon positional orientation was found, the percentage of terminal olefin was always lower than that observed with the commonly employed associated base in *t*-BuOK–*t*-BuOH. The concept of sterically hindered dissociated bases which combine the orientation control of associated bases with high reactivity was therefore judged to be unworkable.[3]

However, the possibility remains that even more ramified dissociated bases might produce the desired orientation control.[4] Although oxyanion bases more hindered than tri-2-norbornylmethoxide are difficult to imagine, Day[4] has recently reported the synthesis of *cis*-2,6-di-*tert*-butylpiperidine. CPK space-filling models indicate that the anionic center of the corresponding piperidide base would be extremely sterically hindered. We now report the results of dehydrohalogenations from 2-halobutanes promoted by lithium *cis*-2,6-di-*tert*-butylpiperidide (1).

Diglyme was found to be an appropriate solvent for studying the reactions of 1 with 2-halobutanes using a nitrogen gas sweep technique which removes butenes from the reaction vessel as they are formed. Base-promoted isomerization of olefinic products and butene formation by solvolysis were demonstrated to be absent under the reaction conditions. Since orientation in eliminations promoted by ordinary bases in diglyme is unknown, reactions of *t*-BuOK with 2-iodobutane in diglyme were also conducted. Results are recorded in Table I.

For reaction of 2-iodobutane with *t*-BuOK in diglyme (system 1), positional and geometrical orientation are identical with those in Me_2SO (system 3). This result indicates that orientation data previously obtained for base-promoted eliminations in Me_2SO may be extrapolated to diglyme solvent. The absence of ion pairing of the *t*-BuOK base in diglyme was demonstrated by a negligible influence of 18-crown-6 upon the relative olefinic proportions (compare systems 1 and 2).

Positional orientation in the reaction of *cis*-2,6-di-*tert*-butylpiperidide (1) with 2-iodobutane in diglyme (system 4) is similar to that previously observed in reactions of this substrate with ramified tertiary alkoxides in Me_2SO.[3] However, the importance of base ion pairing is shown by the decreased percentages of 1-butene noted in the presence of lithium ion complexing crown ethers (systems 5 and 6). Thus, free *cis*-2,6-di-*tert*-butylpiperidide base provides even poorer positional orientation control than the previously examined dissociated but highly ramified tertiary alkoxides. That this unexpected result is not due to some fundamental difference between dissociated nitrogen and carbon bases is strongly suggested by the recent investigations of orientation in eliminations from 2-iodobutane involving more ordinary nitrogen and oxygen bases.[7]

Although bimolecular elimination reactions of 1 with 2-bromobutane in diglyme produced sufficient butenes for analysis (system 8), 2-butyl chloride, 2-butyl tosylate, and 4-methyl-2-pentyl iodide failed to yield measurable quantities of olefinic products under the standard reaction conditions. The inability of 1 to induce eliminations from 4-methyl-2-pentyl iodide under conditions where elimination from 2-butyl iodide is appreciable is probably caused by the steric bulk of 1.

Comparison of positional orientation for reactions of 2-iodo- and 2-bromobutane with 1 in diglyme (systems 6 and 8) with that for *t*-BuOK–*t*-BuOH as the base–solvent combination (systems 7 and 9) reveals a higher percentage of 1-butene from the latter.

Failure of even highly ramified dissociated bases to provide the orientation control observed with *t*-BuOK–*t*-BuOH could be attributed to two factors. First, stretching of the C_β–H bond in the transition states for dissociated base-induced eliminations may increase with ramified bases which would effectively reduce the base steric effect. Second, the proposed model of unfavorable steric interactions[1,2] caused by bulky bases in transition states for associated base-promoted elimination reactions may be incorrect.

The first factor is rendered unlikely by the kinetic investigations of Alunni, Baciocchi, Perucci, and Ruzziconi[8] which demonstrate that the transition-state structure for E2 reactions is only slightly changed by variation of an

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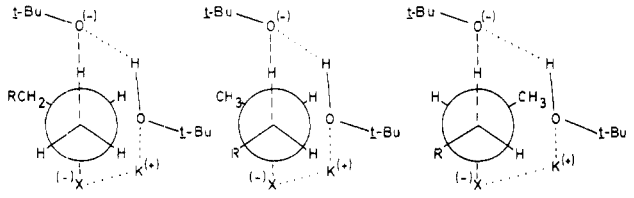
attacking dissociated base from phenoxide to bulky 2,6-di-*tert*-butylphenoxide.

Recent kinetic studies by Závada and Pánková[9,10] have demonstrated that the steric properties of associated and dissociated *t*-BuOK are very similar for eliminations conducted in *t*-BuOH. The Czech workers propose[10] that the positional orientation control produced by associated *t*-BuOK base in eliminations from $RCH_2CH(X)CH_3$ may be rationalized by considering transition-state structures **2**–**4**.



2 **3** **4**

In these transition states, the base species is the homo-hydrogen-bonded *t*-BuOK ion pair which provides electrostatic interactions of the base counterion with the leaving group. These attractive interactions are stronger in transition states forming 1-alkene, **2**, and *cis*-2-alkene, **3**, than in that leading to *trans*-2-alkene, **4**, because of the disruptive α-methyl group in **4**. In going from dissociated to associated base, the repression of *trans*-2-alkene formation results in proportional increases in the production of 1-alkene and cis-2-alkene. This leads to the observed enhancement of 1-alkene proportion and a decrease in the *trans*-2-alkene–*cis*-2-alkene ratio (Table I).

The observed inability of even highly ramified dissociated bases to produce the positional orientation control exhibited by *t*-BuOK–*t*-BuOH lends support to the Závada and Pánková model.

Experimental Section

Reagents. The 2-halobutanes were distilled commercial products. 2-Butyl tosylate,[11] 4-methyl-2-pentyl iodide,[11] and *cis*-2,6-di-*tert*-butylpiperidine[4] were available from previous investigations. The *t*-BuOK (Aldrich) was used as received. Reagent-grade Me_2SO was kept over molecular sieves. Diglyme was distilled from lithium aluminum hydride.

Base–solvent solutions of *t*-BuOK in Me_2SO were prepared by dissolving the base powder in the solvent. Solutions of **1** in diglyme were prepared by treating solutions of *cis*-2,6-di-*tert*-butylpiperidine in diglyme with stoichiometric amounts of *n*-BuLi in hexane (Aldrich) under nitrogen followed by removal of the hexane by sweeping with nitrogen gas at 50 °C.

Procedure. The nitrogen gas sweep procedure and gas chromatographic analysis of olefinic products were the same as previously described.[11] A 10-min reaction period was employed.

Control Experiments. The absence of concomitant solvolysis was demonstrated as before.[11] That no isomerization of butene products occurred under the highly basic reaction conditions was demonstrated by injecting solutions of 1-butene, *trans*-2-butene, and *cis*-2-butene mixtures into the base–solvent combinations of *t*-BuOK–diglyme, 1–diglyme, and 1–diglyme in the presence of 12-crown-4. In all cases, the trapped butenes had the same isomeric distribution as the original solution.

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Registry No. 2-Iodobutane, 513-48-4; 2-bromobutane, 78-76-2; lithium *cis*-2,6-di-*tert*-butylpiperidide, 74465-46-6; *t*-BuOK, 865-47-4; 1-butene, 106-98-9; *trans*-2-butene, 624-64-6; *cis*-2-butene, 590-18-1.

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Synthesis of Some Aromatic Diisocyanides with Trichloromethyl Chloroformate

Avi Efraty,* Irene Feinstein, Lorenz Wackerle, and Alexander Goldman

Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

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Dehydration of *N*-alkyl- or *N*-arylformamides represents the method of choice for the preparation of isocyanides.[1] Among the dehydrating agents, application of phosgene in the presence of tertiary amines was found to be particularly effective. Though effective chemically, phosgene is a volatile toxic material whose handling, especially in large quantities, requires special precautions. Moreover, availability of phosgene outside production plants appears to be limited owing to strict transport safety regulations. A new synthetic route to isocyanides which utilizes trichloromethyl chloroformate (diphosgene) as the dehydrating agent has recently been reported[2] by Skorna and Ugi to afford certain monoisocyanides in excellent yields. Diphosgene is easily prepared[3] in significant quantities, and its handling is considerably simpler compared to phosgene. The advantages presented by the new diphosgene method, coupled with our interest in the coordination properties of certain polyisocyanides, prompted the investigation described below.

Application of diphosgene in the synthesis of the aromatic diisocyanides 1,3-diisocyanobenzene (Ia), 1,4-diisocyanobenzene (Ib), 4,4'-diisocyanobiphenyl (Ic), and 4,4'-diisocyanodiphenylmethane (Id) was investigated during the course of the current study. These diisocyanides were prepared by treating a boiling suspension of the corresponding diformylamino derivative II, in a dichloromethane–triethylamine mixture, with diphosgene dissolved in dichloromethane. Relevant information

$$\underset{\text{II}}{Ar(NHCHO)_2} + ClCOOCCl_3 + 4NEt_3 \rightarrow \underset{\text{I}}{Ar(NC)_2} + 2CO_2 + 4NEt_3{\cdot}HCl$$

concerning the characterization of the diisocyanides Ia–d is furnished in Tables I and II. A comparison between the phosgene and diphosgene methods reveals consistently higher yields with the former approach. In the instance of Ia, the 35% yield obtained with diphosgene compares rather unfavorably with those of 55, 74, and 83% which have previously been reported for the phosgene method.[4,5] Incidentally, attempts to improve the yield of Ia by performing the diphosgene reaction at lower temperatures (e.g., −20 °C) have so far been unsuccessful. The preparations of the other diisocyanides with diphosgene afford yields (≥70%), which are either within the range or slightly lower than those previously reported by the phosgene method[4,5] for Ib (47, 75, and 90%), Ic (79 and 94%), and Id (72 and 83%). In spite of the somewhat lower yields,

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(3) Diphosgene is best prepared by the photochlorination of methyl chloroformate rather than methyl formate as was originally reported by H. C. Ramsperger and G. Waddington, *J. Am. Chem. Soc.*, **55**, 214 (1933). A laboratory-scale prepartion of diphosgene starting with methyl chloroformate is described in the experimental section.
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