Rapid and Selective Reduction of Functionalized Aromatic Disulfides with Lithium Tri-*tert*-butoxyaluminohydride. A Remarkable Steric and Electronic Control. Comparison of Various Hydride Reagents[1]

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Lithium tri-*tert*-butoxyaluminohydride (LTBA), an exceptionally mild reducing agent in organic synthesis, reduces functionalized aromatic disulfides to the corresponding thiols in quantitative yield. The reaction is rapid (for example, *o*-tolyl disulfide is reduced to completion in 60 min at 25 °C) and can tolerate a wide variety of functional groups, such as halogen, nitro, carboxylic acid, and their derivatives. The presence of electron-withdrawing substituents dramatically enhances the rate of reduction (*p*-chlorophenyl disulfide is quantitatively reduced in 30 s) and electron-releasing substituents diminishes the rate of cleavage. The reaction is sensitive to steric effects (2,4-di-*tert*-pentylphenyl disulfide underwent 25% reduction in 24 h). However, such hindered disulfides can be rapidly and quantitatively reduced in refluxing THF. The reaction of LTBA with alkyl disulfides is extremely sluggish. The reaction provides a useful and simple means for the facile and selective reduction of aromatic disulfides where this is required in synthetic operations.

The disulfide linkage plays an important role in organic synthesis and biological systems.[2] Conversion of thiols to disulfides often serves as a convenient protecting-group technique in organic synthesis. The tertiary structure of a number of proteins is strongly influenced by the disulfide linkages present in them. Consequently, selective reduction of the disulfide linkage to thiols has been the subject of considerable study from both chemical and biological viewpoints. A number of hydride reagents, such as lithium aluminum hydride,[3] lithium trimethoxyaluminohydride (LTMA),[4] aluminum hydride,[5] lithium triethylborohydride,[6] sodium borohydride,[7] sodium borohydride/aluminum chloride,[8] and potassium triisopropoxyborohydride,[9] are known to reduce the disulfide linkage. However, stronger reducing agents such as lithium aluminum hydride (LAH) suffer from the disadvantage of poor functional group tolerance. A milder reducing agent, sodium borohydride, possesses little solubility in convenient organic solvents (ethyl ether, tetrahydrofuran). Other highly selective reducing agents, such as borane, thexylborane, disiamylborane, and 9-borabicyclo[3.3.1]nonane, are essentially inert toward the disulfide linkage.[10] In addition, zinc/acetic acid[11] and triphenylphosphine[12] are also known to reduce disulfides to thiols. Such procedures suffer from the disadvantage of being heterogeneous systems. Recently, the selective reduction of organic disulfides with potassium triisopropoxyborohydride (KIPB-H) has been investigated.[9b]

Lithium tri-*tert*-butoxyaluminohydride (LTBA) is an exceptionally mild reducing agent, capable of reducing only aldehydes, ketones, and acid chlorides.[13] It is readily synthesized from lithium aluminum hydride, soluble in tetrahydrofuran (THF), and stable. An earlier detailed survey of the reducing characteristics of LTBA toward representative organic functional groups revealed that this reagent rapidly reduces phenyl disulfide.[13] No further exploration was carried out. Consequently, we undertook a detailed study of the reaction of organic disulfides with LTBA in THF to explore the synthetic applicability of this reaction. Further, the mildness of LTBA permits the exploration of the effect of various substituents on the reactivity. It was also of interest to compare the effectiveness of other mild and highly selective reducing agents toward organic disulfides. The results of these investigations are reported in this paper.

Results and Discussion

In all experiments, crystal-clear solutions of LTBA in THF were employed. Such solutions were readily prepared by the addition of 3.03 equiv of freshly distilled *tert*-butyl alcohol to a THF solution of LAH. A representative series of organic disulfides with different structural features was selected to evaluate the electronic and steric effects. Such a series also served as a focal point for establishing the chemoselectivity and synthetic applicability of the reaction.

Synthesis of Substituted Aromatic Disulfides. A majority of the functionalized aromatic sulfides were synthesized in virtually quantitative yield from the corresponding aryl thiols by oxidation with dimethyl sulfoxide.[14] A number of aryl thiols were synthesized from the corresponding phenols via the *N,N*-dimethylthiocarbamate esters, followed by pyrolysis to yield the rearranged product—*N,N*-dimethylcarbamate ester of the thiophenol—which on hydrolysis with the base or lithium aluminum hydride reduction provided the aryl thiol in good to excellent yield[15] (Scheme I).

Comparison of Selective Hydride Reducing Agents. Before any detailed study, it was desirable to compare the reactivity of representative selective reducing agents toward an organic disulfide. Accordingly, the reaction of phenyl disulfide was examined with representative selective reducing agents: lithium tri-*tert*-butoxyalumino-

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Table I. Selective Reduction of Organic Disulfides with Lithium Tri-*tert*-butoxyaluminohydride in Tetrahydrofuran[a]

disulfide	temp, °C	time[b] min	time[b] h	product	yield,[c,d] %
phenyl	25	30		benzenethiol	95
o-tolyl	25	60		*o*-thiocresol	100
2-ethylphenyl	25		6	2-ethylbenzenethiol	100
2,5-diisopropylphenyl	25		3	2,5-diisopropylbenzenethiol	92
2,4-di-*tert*-pentylphenyl	25		24	2,4-di-*tert*-pentylbenzenethiol	25
2,4-di-*tert*-pentylphenyl[e]	65		3	2,4-di-*tert*-pentylbenzenethiol	100
2-*tert*-butylphenyl	65		3	2-*tert*-butylbenzenethiol	90
p-tolyl	25		12	*p*-thiocresol	94 (91)
4-methoxyphenyl	25		4	4-methoxybenzenethiol	93 (100)
4-chlorophenyl	25	<1		4-chlorobenzenethiol	99 (93)
4-cyanophenyl	25	2		4-cyanobenzenethiol	100 (100)
n-octyl	25		24	1-octanethiol	31
n-octyl	65		8	1-octanethiol	70

[a] Except where indicated, reaction mixtures monitored by GLC were 0.25 M in disulfide and 0.56 M in LTBA; preparative reaction mixtures were 0.45 M in disulfide and 0.96 M in LTBA. [b] Represents for reactions monitored by GLC. [c] The yields reported were determined by GLC using a suitable internal standard and authentic synthetic mixtures. [d] Numbers in parentheses indicate the isolated yield. [e] Reaction mixture was 0.25 M in disulfide and 0.75 M in LTBA.

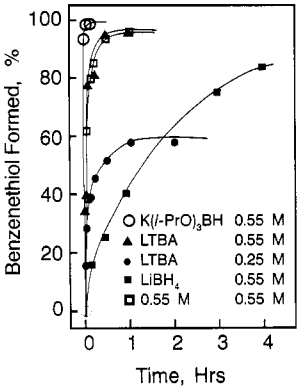

Figure 1. Rates of reduction of phenyl disulfide (0.25 M) with representative complex metal hydrides in tetrahydrofuran at 25 °C.

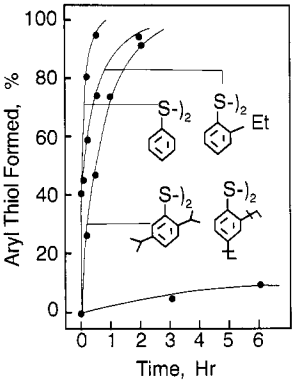

Figure 2. Reaction of representative *o*-alkylphenyl disulfides (0.25 M) with lithium tri-*tert*-butoxyaluminohydride in tetrahydrofuran at 25 °C.

hydride, lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride (LTEPA),[16] potassium triisopropoxyborohydride, and lithium borohydride under standard conditions (0.55 M in reagent, 0.25 M in disulfide, 25 °C, THF). Reaction with lithium borohydride is quite sluggish, requiring over 6 h for the completion of the reaction, whereas the corresponding reactions with LTBA, LTEPA, and KIPBH are exceedingly rapid, approaching completion in less than 30 min. Of the latter three reagents, KIPBH appears to exhibit a marginal advantage over both LTBA and LTEPA with respect to rate. The results are summarized graphically in Figure 1. The reductive cleavage of disulfides with KIPBH has been studied in detail and reported.[9b] Consequently, it was of interest to explore the scope and applicability of the reaction of organic disulfides with LTBA. Moreover, it was desirable to investigate the effect of the structure of the disulfide linkage on the rate of reaction.

Stoichiometry of the Reaction. To understand the major characteristics of the reaction, we explored the possibility of utilizing solutions that were 0.25 M in both disulfide and LTBA. The reaction mixture was maintained at 25 °C, and the rate of reaction was monitored by GLC at appropriate time intervals for the formation of aryl thiol. Thus, the reaction of phenyl disulfide proceeds rapidly at 25 °C in the initial phases of the reaction up to 50% with concomitant evolution of hydrogen. However, further reduction is extremely sluggish (Figure 1). Obviously, the benzenethiol released during the reductive cleavage effectively competes for the residual LTBA (eq 1 and 2).

$$\mathrm{ArSSAr} + \mathrm{Li}(t\text{-BuO})_3\mathrm{AlH} \rightarrow \mathrm{ArSLi} + \mathrm{ArSH} + (t\text{-BuO})_3\mathrm{Al} \quad (1)$$

$$\mathrm{ArSH} + \mathrm{Li}(t\text{-BuO})_3\mathrm{AlH} \rightarrow \mathrm{ArSLi} + (t\text{-BuO})_3\mathrm{Al} + \mathrm{H}_2 \quad (2)$$

Indeed, it has been reported that LTBA reacts rapidly with benzenethiol, evolving hydrogen quantitatively.[13] Consequently, in order to avoid these complications, it was decided to increase the concentration of LTBA to 0.55–0.60 M.

Procedure for Rate Studies and Product Analysis. The general procedure adopted was to add 2 mmol of the organic disulfide to a mixture of 4.8 mmol of LTBA and a known amount of an internal standard (*n*-dodecane) in THF to give a final volume of 8 mL. This makes the reaction mixture 0.25 M in disulfide and 0.6 M in LTBA. The reaction mixture was maintained at 25 °C and analyzed periodically by GLC for the formation of the thiol and the residual disulfide.

The same reaction mixture was utilized for product analysis. The results are summarized in Table I.

Effect of the Structure of the Organic Disulfide on Reactivity. Reductions were carried out on substituted phenyl disulfides to evaluate the steric and electronic effects on the reactivity. Reduction of a series of *o*-alkyl-substituted phenyl disulfides with alkyl groups of increasing steric requirements was investigated. It is evident from the results summarized in Figure 2 that the steric effect of the ortho substituents plays a major role in con-

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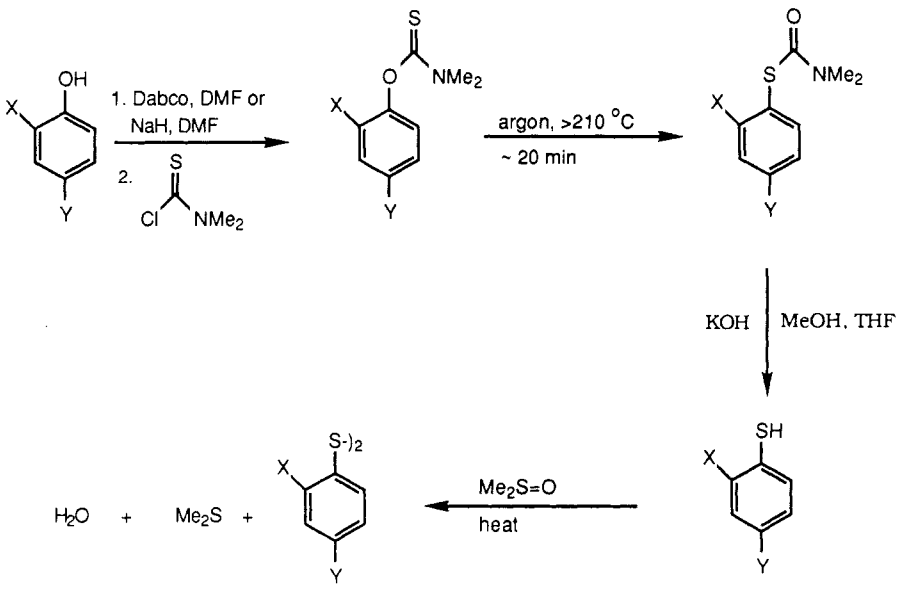
Scheme I



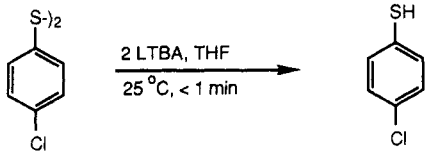
trolling the reactivity (H > Et > *i*-Pr > *t*-Am).

The reaction is exceptionally sensitive to the electronic effect of the substituents on the ring. The presence of electron-withdrawing substituents (*p*-Cl and *p*-CN) dramatically enhances the rate of reduction, and the electron-releasing substituents (*p*-Me and *p*-OMe) retard the rate of reductive cleavage (Figure 3).

The reduction of aromatic disulfide is much faster than that of aliphatic (Figure 4).

Synthetic Applicability and Scope. The rapid rate of reductive cleavage observed with a majority of the aromatic disulfides toward LTBA should provide a convenient synthetic procedure for the reduction of such disulfides under mild conditions where this is required in synthetic operations. In order to establish the synthetic utility, product studies for the reduction of representative organic disulfides were carried out. In the majority of the cases, even the standard conditions (0.55 M in LTBA and 0.25 M in disulfide at 25 °C in THF) were sufficient to bring about the reductive cleavage.

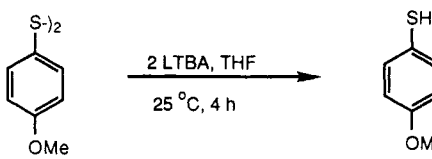
4-Chlorophenyl disulfide is converted to 4-chlorobenzenethiol in quantitative yield in less than 1 min under standard conditions (eq 3). Similarly, 4-cyanophenyl



100% (3)

disulfide is quantitatively reduced to 4-cyanobenzenethiol in 2 min.

The electron-rich 4-methoxyphenyl disulfide is smoothly reduced to the corresponding thiol in 4 h (eq 4).



93% (4)

The presence of ortho substituents of moderate steric requirements (methyl, ethyl, isopropyl) permits the reaction to go to completion under standard conditions. However, 2,4-di-*tert*-pentylphenyl disulfide with an ortho *tert*-alkyl substituent is reduced at an extremely sluggish rate. However, it is possible to rapidly reduce even such sterically hindered disulfides with excess LTBA in refluxing THF in quantitative yield (eq 5 and 6).

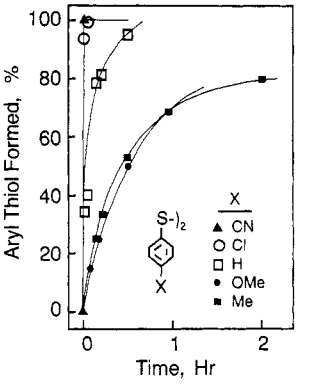


Figure 3. Rates of reduction of representative para-substituted phenyl disulfides (0.25 M) with lithium tri-*tert*-butoxyaluminohydride (0.56 M) in tetrahydrofuran at 25 °C.

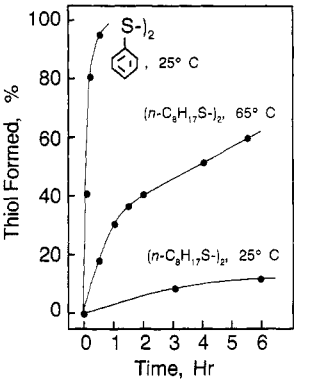
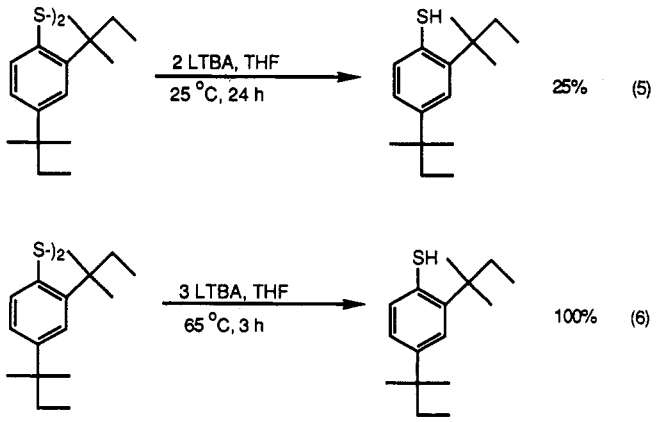


Figure 4. Reaction of phenyl disulfide (0.25 M) and *n*-octyl disulfide (0.25 M) with lithium tri-*tert*-butoxyaluminohydride (0.56 M) in tetrahydrofuran.

Reduction of *n*-octyl disulfide is extremely sluggish under standard conditions, being incomplete after 24 h. In refluxing THF, the reaction reached an asymptotic value of 70% conversion in 8 h, and further reduction was very slow.

It is clearly evident from this study that LTBA offers potential for the selective reduction of aromatic disulfide linkages that differ markedly in steric and electronic re-



quirements and for the chemoselective reduction of aromatic disulfides in the presence of aliphatic disulfides. Such a wide difference in reactivity between aromatic and aliphatic disulfides has also been observed with KIPBH. Indeed, Brown and co-workers have demonstrated the feasibility of the selective reduction of aromatic disulfides in the presence of aliphatic disulfides.[9b] Finally, it should be pointed out that the current methodology offers no difficulties in the isolation of thiol product in excellent yields of good purity, revealing the synthetic applicability of the reaction.

Conclusions

The reduction of organic disulfides to the corresponding thiols was explored with highly selective reducing agents. Of the reagents examined, both LTBA and KIPBH cleave aryl disulfides rapidly and quantitatively. Reaction of representative organic disulfides with LTBA was explored in detail with respect to structure–reactivity relationships as well as synthetic applicability. Aromatic disulfides are reduced far faster than the aliphatic disulfides. The reaction is exceptionally sensitive to electronic and steric effects. The mildness of LTBA permits the presence of a variety of other functional groups in the molecule. Even sterically hindered aryl disulfides are smoothly reduced to their corresponding aryl thiols. The product, aryl thiol, is clean and formed in essentially quantitative yield.

Experimental Section

General Comments. All glassware was oven dried, assembled hot, and cooled under a stream of argon. Reactions were carried out under a blanket of argon. Solvents and reagent solutions were transferred with hypodermic syringes or double-ended needles.[17] ^{1}H NMR spectra were recorded on either a Varian EM-390 (90 MHz) or a QE-300 FT NMR (300 MHz) spectrometer with tetramethylsilane as the internal standard. Thin-layer chromatography (TLC) was performed on glass plates precoated with silica gel 60 F-254 (0.25-mm layers); the eluent was 80:20:5:2 mixture of CH_3CCl_3/EtOAc/MeCN/HOAc and the detection was by UV. Gas chromatographic (GLC) analyses were carried out on a Hewlett-Packard 5890A instrument equipped with an FID detector and HP 3393A integrator, using a 15 m × 0.32 mm DB5-15W column; the injector temperature was 225 °C, detector temperature was 250 °C, initial column temperature was 75 °C, and programmed at 20 °C/min to achieve a final temperature of 225 °C.

Materials. Tetrahydrofuran was dried over calcium hydride and distilled over lithium aluminum hydride, bp 65 °C. *tert*-Butyl alcohol was distilled over calcium hydride. Standard solutions of lithium tri-*tert*-butoxyaluminohydride in THF were synthesized from lithium aluminum hydride solutions in THF by the addition of 3.03 equiv of *tert*-butyl alcohol. Lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride was conveniently synthesized in quantitative yield by the addition of 3.05–3.2 molar equiv of 3-ethyl-3-pentanol to a tetrahydrofuran (THF) solution of lithium aluminum hydride at 25 °C, followed by gentle reflux of the resulting mixture for 1 h. Standard solutions of lithium borohydride in THF and potassium triisopropoxyborohydride in THF were the commercial products. The hydride reagents were standardized by hydrolyzing a known aliquot with a mixture of water, glycerine, and THF (1:1:1) and measuring the volume of hydrogen evolved.[17] The majority of the disulfides were prepared from the corresponding thiols by oxidation or from the corresponding phenols employing literature procedures. Phenyl disulfide and *p*-tolyl disulfide were the commercial samples, further purified by recrystallization from ethanol.

General Procedure for the Synthesis of Aryl Disulfides. The following procedure for the synthesis of 4-cyanophenyl disulfide from 4-cyanophenol is representative.

a. *O*-4-Cyanophenyl *N,N*-Dimethylthiocarbamate. A 1-L flask equipped with a magnetic stirring bar was charged with 62 g (520 mmol) of *p*-hydroxybenzonitrile, 146 g (1.3 mol) of 1,4-diazabicyclo[2.2.2]octane (dabco), and 600 mL of DMF. To this well-stirred mixture, 80 g (650 mmol) of *N,N*-dimethylthiocarbamoyl chloride was added. The resulting mixture was heated (60–70 °C) and monitored by TLC. The reaction was complete in 1.5 h. The mixture was poured into crushed ice and acidified to pH 3 with 6.0 N hydrochloric acid. The precipitate formed was collected and dried to yield 105 g (98%) of essentially pure (TLC) *O*-4-cyanophenyl *N,N*-dimethylthiocarbamate; recrystallization from ethanol provided 88.7 g (83%): mp 112 °C [lit.[18] mp 116–117 °C]; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 3.35 (s, 3 H, Me-N-*Me*), 3.45 (s, 3 H, *Me*-N-Me), 7.19 (d, 2 H, aromatic), 7.7 (d, 2 H, aromatic).

b. *S*-4-Cyanophenyl *N,N*-Dimethylthiocarbamate. A 500-mL flask equipped with a magnetic stirring bar and a reflux condenser connected to a mineral oil bubbler was charged with 40.0 g (194 mmol) of *O*-4-cyanophenyl *N,N*-dimethylthiocarbamate. The contents of the flask were maintained under a blanket of argon. The flask was immersed in a preheated oil bath maintained at 210 °C, and the mixture was stirred well. The reaction was monitored by withdrawing a small sample by a pipet under a stream of argon, diluting with ether, and analyzing by TLC. The reaction was complete in 2 h, yielding a single, clean, rearranged product, *S*-4-cyanophenyl *N,N*-dimethylthiocarbamate. Upon cooling of the reaction mixture, the product crystallized in quantitative yield: mp 100 °C (lit.[18] mp 102–103 °C); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 3.08 (d, 6 H, NMe_2), 7.62 (m, 4 H, aromatic).

c. 4-Cyanobenzenethiol. To the reaction mixture obtained in the previous reaction was added 250 mL of THF and 24 g (436 mmol) of potassium hydroxide dissolved in 100 mL of methanol. The mixture was stirred at room temperature for 3 h to completion of hydrolysis. The mixture was poured into crushed ice, acidified with hydrochloric acid to attain a value of pH 2, and stirred well until the oil solidified. The precipitate formed was collected, washed with cold water, and dried to yield 21.3 g (81%) of 4-cyanobenzenethiol as a cream-colored solid.

d. 4-Cyanophenyl Disulfide. A 100-mL flask equipped with a magnetic stirring bar and a reflux condenser was charged with 5.0 g (37 mmol) of 4-cyanobenzenethiol and 50 mL of DMSO. The well-stirred mixture was heated (ca. 65 °C), and the oxidation was monitored by TLC to completion. The mixture was allowed to cool to room temperature and then poured into vigorously stirred crushed ice; the solid was filtered and washed twice with water; drying the solid over vacuum yielded the desired 4-cyanophenyl disulfide, 4.3 g (87%) as a white solid, essentially pure by TLC. Recrystallization from ethanol gave 3.8 g (78%): mp 171–173 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.57 (m, 4 H, aromatic). Anal. Calcd for $C_{14}H_8N_2S_2$: C, 62.7; H, 3.00; N, 10.44; S, 23.90. Found: C, 62.51; H, 2.97; N, 10.24; S, 23.68.

Procedure for Study of the Rate and Stoichiometry. An oven-dried 50-mL flask equipped with a side arm fitted with a Teflon stopcock, silicone rubber stopple, and a magnetic stirring

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bar and connected to a mineral oil bubbler was cooled to room temperature under argon. The flask was immersed in a water bath at 25 °C. Then 3.35 mL of THF, 1.6 mL (2 mmol) of a 1.25 M solution in THF of lithium tri-*tert*-butoxyaluminohydride, and 1.0 mL (2 mmol) of a 2.0 M solution of *n*-dodecane in THF (to serve as the internal standard) were introduced in the order indicated. Finally, 2 mL (2 mmol) of a 1.0 M solution of phenyl disulfide in THF was added to this well-stirred mixture. The reaction mixture was now 0.25 M in both LTBA and disulfide. Vigorous hydrogen evolution was observed during the initial phases of the reaction. After 2 min, 0.1 mL of the reaction mixture was withdrawn by a syringe, quenched with dilute HCl, extracted with ether, and dried ($MgSO_4$). The dry ether extract was analyzed by capillary GLC. The analysis revealed the presence of 16% benzenethiol. Similarly, the reaction was monitored at 5, 10, 15, 30, 60, and 120 min. At 30 min, 53% of the reaction was complete. At the end of 120 min, reaction had proceeded only to the extent of 58%.

Procedure for Rate Studies and Product Analysis. The following procedure for the reduction of *p*-tolyl disulfide is representative. The experimental setup was the same as in previous experiments. THF (1.3 mL) was injected into the reaction flask followed by 3.8 mL (4.8 mmol) of a 1.28 M solution of LTBA in THF and 0.9 mL of *n*-dodecane (internal standard). To this well-stirred solution maintained at 25 °C, 2 mL (2 mmol) of a 1.0 M solution of *p*-tolyl disulfide in THF was injected. Hydrogen evolution was observed. At appropriate intervals of time, 0.1 mL of the reaction mixture was withdrawn and monitored by capillary GLC as in the previous experiment.

General Preparative Procedure for the Selective Reduction of Organic Disulfides with Lithium Tri-*tert*-butoxyaluminohydride. The following procedure for the selective reduction of 4-cyanophenyl disulfide is representative. An oven-dried 250-mL flask equipped with a side-arm, a magnetic stirring bar, and a pressure-equalizing graduated addition funnel connected to a mineral oil bubbler was cooled to room temperature under a stream of argon. The flask was charged with 9 g (33.5 mmol) of 4-cyanophenyl disulfide and 17 mL of freshly distilled THF. To this well-stirred slurry, maintained at ca. 25 °C (water bath) was added 56.3 mL (70 mmol) of a 1.25 M solution of lithium tri-*tert*-butoxyaluminohydride in THF (previously transferred to the addition funnel through a double-ended stainless steel needle) over a 15-min period. Vigorous hydrogen evolution was observed in the initial phases of the addition, which then subsided toward the end of addition. The resulting clear mixture was stirred for an additional period of 1 h. Water (3 mL) was added dropwise to destroy the excess hydride. The mixture was acidified by the addition of 6.0 N hydrochloric acid to attain a pH of <3. The organic phase was separated, and the aqueous phase was extracted with 3 × 50-mL portions of ether. The combined extracts were washed with 2 × 150-mL portions of saturated brine and dried ($MgSO_4$). Removal of volatile solvents on a rotary evaporator (ca. 35 °C) followed by vacuum drying yielded 9.1 g (100%) of 4-cyanobenzenethiol: mp 47–49 °C (lit.[18] mp 50–51 °C), >97.5% pure by HPLC; ^1H NMR ($CDCl_3$, 300 MHz, ppm) 3.70 (s, 1 H, SH), 7.34 (d, 2 H, aromatic), 7.52 (d, 2 H, aromatic).

Quantitative Determination of the Ring–Chain Hydrolysis Equilibrium Constant for Anabaseine and Related Tobacco Alkaloids

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Anabaseine (1) (3,4,5,6-tetrahydro-2,3′-bipyridine), a neurotoxin, rapidly hydrolyzes in aqueous solution to its open-chain amino ketone. The constituents over the acidity range pD 2–10 include 1, its conjugate iminium ion acid 2, open-chain keto alkylammonium ion 3, and its conjugate acid 4, a pyridinium–ammonium dication. Three equilibrium constants are required to describe quantitatively the titration curve over this acidity range: the two dissociation constants for acids 2 and 4 as well as the hydrolysis constant K_H for [3]/[2]. Values were established by using proton NMR (D_2O) at 22 °C and 0.6 M ionic strength. They are based on computer fitting of chemical shifts and areas. The major forms under physiological conditions and the interval pD 4.5–7.5 are 2 and 3, the latter slightly predominating (K_H 1.2). Similar equilibrium constants were derived from literature data on the alkaloid myosmine (6) (3-(1-pyrrolin-2-yl)pyridine) and its *N*-methyl analogue 7 as well as for 2-phenyl-1-pyrroline 12 and its *N*-methyl analogue 13. Comparison of the pK_a values for the 5- and 6-membered iminium ions shows that the smaller ring is more acidic by at least 1.5 (ΔpK_a), a most surprising conclusion considering that the saturated ammonium ion counterparts have very similar pK_a values.

Anabaseine (1) is a naturally occurring neurotoxin.[1-4] Hoplonemertines, a class of ubiquitous predatory marine worms, produce it to paralyze their prey and to repel potential predators. The toxin is more active than nicotine on cholinergic receptors.[5]

Two rings are present in 1, an aromatic 3-pyridine and a tetrahydropyridine (a 1-piperideine) attached to the former by its 2-position in such a way that the aromatic ring and the imine are in conjunction. The imino group in the tetrahydropyridine ring is water labile,[6] as in many other imines,[7,8] easily hydrolyzing to its acyclic amino ketone 3 via the conjugate acid of 2 of 1, Scheme I.

Interesting questions arise concerning the biological roles of the ring-opened versus the closed forms of 1 and its

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