NMR ($CDCl_3$) a isomer shows signals at δ 5.85 (s, 2 H), 3.08 (s, 3 H), 1.31 (s, 3 H) and the other at 5.91 (s, 2 H), 3.2 (s, 3 H), 1.29 (s, 3 H).

Registry No. I, 106-42-3; V, 90554-25-9; VI, 90554-26-0; α-methoxy-*p*-xylene, 3395-88-8; α,α-dimethoxy-*p*-xylene, 3395-83-3; α,α'-dimethoxy-*p*-xylene, 6770-38-3.

Reduction of Esters and Other Carboxylates by Sodium Borohydride/Ethanedithiol: Improved Procedures and an Investigation into the Nature of the Reducing Species

Wayne C. Guida,* Edward E. Entreken, and Anne R. Guida

Department of Chemistry, Eckerd College, St. Petersburg, Florida 33733

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The reduction of carboxylate esters by sodium borohydride is normally a slow process, particularly in ether solvents.[1] Several years ago, it was reported that esters can be reduced at a synthetically useful rate (20 h) by sodium borohydride in refluxing THF if ethanedithiol is added to the reaction mixture.[2] Subsequently, this reducing system was effectively utilized for the reduction of nitro compounds (to the amine and partially reduced species) and carboxamides.[3] However, the nature of the actual reducing species in these reductions has not yet been determined.

The ethanedithiol/sodium borohydride system appears to be milder than reducing agents like lithium aluminum hydride since the reduction of ethyl *p*-cyanobenzoate was observed to occur without concommitant reduction of the cyano group.[2] Since this reducing system is more powerful than sodium borohydride itself, it appears to be an attractive one for the selective reduction of esters and other carboxylates. Nonetheless, the reported procedures suffer from several disadvantages. For example, a considerable excess of sodium borohydride (3 mol/mol of substrate) and ethanedithiol (4 mol/mol of substrate) was employed for these reductions.[2,3] In addition, no workup procedure was given and removal of ethanedithiol from the reaction mixture, once reduction was complete, was not addressed (yields were determined by GC).

We decided to study this reducing system with hopes of alleviating these difficulties and of learning something about the nature of the reducing species. We now report the results of our investigation.

Results and Discussion

Mixtures of sodium borohydride and ethanedithiol in THF were found to evolve gas (presumably hydrogen) slowly at room temperature and rather rapidly at reflux. Conceivably, the relatively acidic thiol groups react with boreohydride ion to liberate hydrogen. Thus, the reaction of 1 mol of borohydride with 1 mol of ethanedithiol should leave 2 equiv of hydride for complete reduction of 1 mol of an ester to the 1° alcohol. Accordingly, we sought to determine whether a 1:1:1 molar ratio of ester to borohydride to ethanedithiol was sufficient for complete reduction to occur in refluxing THF within a 24-h period. Indeed, this ratio is sufficient to cause substantial reduction of ethyl benzoate. However, further investigation revealed that a moderate excess (25–50%) of sodium borohydride and ethanedithiol was necessary to drive the reduction to completion.[4] We have found that a molar ratio of 1.5:1.5:1.0 of borohydride to ethanedithiol to substrate is sufficient to effect reduction of various carboxylates within a 24-h period, and this ratio was utilized for most subsequent work.

Table I. Reduction of Carboxylates with Ethanedithiol/Sodium Borohydride[a]

entry	% yield of alcohol or amine[b]
1. $PhCO_2Et$	80
2. $CH_3(CH_2)_{10}CO_2Et$	94
3. *p*-CH_3OPhCO_2Et	88
4. *c*-$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2Me$	83
5. $PhCO_2$-*i*-Pr	83,[c] (20)[c,d]
6. $PhCO_2$-*t*-Bu	5,[c] (95)[c,d]
7. PhCN	(99)[d]
8. $PhCH_2CN$	(99)[d]
9. $PhCONH_2$	79
10. $PhCO_2H$	53,[e] (44)[d]

[a] Unless otherwise noted, reductions were performed in refluxing THF for 24 h with a 1.5:1.5:1.0 mol ratio of $NaBH_4$:$HSCH_2CH_2SH$:substrate. [b] Unless otherwise noted, refers to isolated yield of analytically pure material (by GC); the products gave NMR and IR spectra consistent with the assigned structure. [c] Determined by GC. [d] Numbers in parentheses refer to unreacted starting material. [e] 3 mol of $NaBH_4$ and $HSCH_2CH_2SH$/mol of acid.

In addition, workup can be effected by stirring the reaction mixture with aqueous sodium hydroxide (10%) and hydrogen peroxide (3%). Hydrolysis of borate esters and mild oxidation of the ethanedithiol occurs to yield a mixture from which solid polymeric disulfides[5] can be removed by filtration. Extraction of the alcohol into dichloromethane followed by standard workup procedures affords the product (free of ethanedithiol by GC) in good yield.

Table I demonstrates our results. A number of esters (entries 1–5) can be reduced in good yield to the corresponding alcohol. Steric effects can have a profound influence on the reduction as is demonstrated by entries 5 and 6. Although isopropyl benzoate undergoes substantial reduction (entry 5) *tert*-butyl benzoate is only slightly reduced (entry 6) under the reaction conditions. Thus, it should be possible to reduce esters of 1° alcohols in the presence of esters of 3° alcohols with this reducing system. Plausibly, trivalent boron hydride species could exist in the reaction mixture, thus it is noteworthy that the reduction of methyl oleate (entry 4) proceeds smoothly without any apparent hydroboration of the double bond.

As anticipated from prior work,[2] the cyano group is inert to the reaction conditions. Both benzonitrile and phenylacetonitrile (entries 7 and 8) are unaffected by the reducing agent.

As is demonstrated by entry 9, benzylamine can be obtained in good yield from benzamide. This result demonstrates that the mole ratio employed should be sufficient

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[1] See, for example: (a) Brown, H. C. "Boranes in Organic Chemistry"; Cornell University Press: Ithaca, NY, 1972. (b) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972. For recent studies see: (c) Brown, H. C.; Narasimhan, S.; Choi, Y. M *J. Org. Chem.* **1982**, *47*, 4702.

[2] Maki, Y.; Kikuchi, K.; Sugiyama, H.; Seto, S. *Tetrahedron Lett.* **1975**, 3295.

[3] (a) Maki, Y.; Sugiyama, H.; Kikuchi, K.; Seto, S. *Chem. Lett.* **1975**, 1093. (b) Maki, Y.; Kikuchi, K.; Sugiyama, H.; Seto, S. *Chem. Ind. (London)* **1976**, 322.

[4] When ethanedithiol was omitted for the reaction mixture, an insignificant amount of reduction occurred.

[5] The action of mild oxidants on ethanedithiol is known to produce polymeric disulfides. See, for example: Kobayashi, N.; Osawa, A.; Fujisawa, T. *J. Polym. Sci., Polym. Lett. Ed.* **1973**, *11*, 225.

0022-3263/84/1949-3024$01.50/0

for the reduction of carboxamides to amines. Furthermore, since it has previously been demonstrated that *N*-alkyl and *N,N*-dialkyl carboxamides are not reduced in significant amounts by this reducing system,[3b] selective reductions involving amides should also be possible.

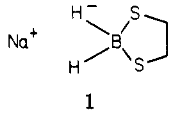
Interestingly, the carboxyl group of benzoic acid undergoes appreciable reduction by the ethanedithiol/sodium borohydride reducing system although in this case a substantial excess of sodium borohydride and ethanedithiol is necessary to cause only 53% reduction (see entry 10).

The reactivity of the ethanedithiol/sodium borohydride reagent appears to be most similar to that of lithium borohydride.[6] However, there are some noteworthy differences. In contrast to our observation on the reduction of methyl oleate by the ethanedithiol/sodium borohydride reagent, lithium borohydride is known to cause concomitant hydroboration to occur when olefinic esters are reduced.[7] Furthermore, observations on the reactivity of lithium borohydride toward carboxamides appear to significantly contrast the results obtained with ethanedithiol/sodium borohydride. Thus, benzamide is inert toward lithium borohydride in refluxing THF whereas *N,N*-dimethylbenzamide is partially reduced to the amine and alcohol under the same conditions.[8]

During the course of our synthetic studies, several observations were made which give some insight into the nature of the species present in the reductions desribed above. When ethanedithiol and sodium borohydride are allowed to react in refluxing THF (1:1 molar ratio) gas is evolved as was previously mentioned. The reagent that remains, when gas evolution ceases, reacts much more rapidly with water (even at high pH) than sodium borohydride itself. This reagent is fully capable of reducing esters to 1° alcohols. Thus, it is likely that in the reductions described above, reaction of sodium borohydride with ethanedithiol occurs to afford an activated species which is more reactive than sodium borohydride.

Hydrogen evolution measurements were conducted on the pre-formed reagent. When this species was quenched with dilute acid, 2 equiv of hydrogen were released. This result confirms the hypothesis that two reducing equivalents remain when sodium borohydride reacts with ethanedithiol in a 1:1 molar ratio.

Spectral analysis of the pre-formed reagent proved to be difficult. Limited solubility in a number of solvents and moisture sensitivity of the isolated reagent[9] precluded obtaining satisfactory IR spectra. An ^{11}B NMR spectrum of the pre-formed reagent was obtained in dry diglyme (the reagent was insufficiently soluble in THF) and consisted of a sharp five-line multiplet at 60 ppm (upfield from trimethylborate) and a broader triplet at 32 ppm (upfield from trimethylborate). The quintet is attributable to unreacted sodium borohydride (which is quite soluble in diglyme). Both the chemical shift[10] and multiplicity of the other resonance are consistent with the structure 1 although polymeric species or larger membered rings cannot be excluded. We favor structure 1 by analogy with the known cyclic species 1,3-dithiaborolane (2) that is formed by reaction of ethanedithiol with diborane.[11,12]



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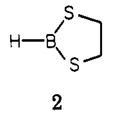

2

In summary, the reagent prepared via the reaction of ethanedithiol with sodium borohydride possesses enhanced reactivity over sodium borohydride. Nevertheless, this reagent possesses selectivity properties which should render it quite useful in organic synthesis. The failure of the ethanedithiol/sodium borohydride reagent to cause significant reduction of *tert*-butyl benzoate, *N*-alkyl carboxamides or *N,N*-dialkyl carboxamides demonstrates that it is sensitive to the steric environment of the carbonyl group thereby enhancing its utility for selective reductions. The procedures described in this paper allow reductions with this reagent to be performed without the necessity of employing a large excess of the reagent. Furthermore, a simple workup procedure allows for the removal of ethanedithiol once the reaction is complete.

Experimental Section

General Methods. Infrared spectra were recorded on a Perkin-Elmer Model 457 grating spectrophotometer. ^1H NMR spectra were obtained on a Varian EM-360A spectrometer. ^{11}B NMR spectra were obtained on a JEOL FX-90Q spectrometer operating in the FT mode at 28.74 MHz and chemical shifts are reported in parts per million relative to trimethylborate which was used as an external standard. Solutions of the ethanedithiol/sodium borohydride reagent were transferred under Ar to a 5-mm NMR tube via a gas-tight syringe; the tube was then flame-sealed. GC analyses were performed on a Varian Model 3700 gas chromatograph equipped with flame ionization detectors and a 6 ft × 0.25 in column packed with 3% OV-17 on Chromasorb W.

Materials. The substrates used in the reductions were reagent grade and were used as received. Sodium borohydride was obtained from Ventron and was used as received for synthetic work. It was recrystallized from diglyme for hydrogen evolution measurements and for ^{11}B NMR studies. Ethanedithiol was obtained from Eastman, distilled, and then stored over molecular sieves (Linde 4 Å). THF was distilled from sodium benzophenone.

General Synthetic Procedure. To a suspension of 0.48 g (10 mmol) of sodium borohydride in 10 mL of dry THF was added 0.94 g (10 mmol) of ethanedithiol and 6.7 mmol of substrate. The resulting mixture was heated at reflux under a nitrogen atmosphere for 24 h. The mixture was allowed to cool to room temperature and then diluted with 25 mL of CH_2Cl_2. To the resulting suspension was added 15 mL of 10% NaOH and 15 mL of 3% H_2O_2. The mixture was stirred at room temperature for 4 h and then suction filtered through a pad of Celite. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined CH_2Cl_2 layers were dried over Na_2SO_4 and then evaporated under reduced pressure. Kugelrohr distillation afforded the products listed in Table I.

Acknowledgment. We thank Morton-Thiokol, Inc., Ventron Division for partial support of this work. We thank Professor Douglas J. Raber of the University of South Florida for many helpful discussions. We are indebted to Dr. Christopher Janks formerly of USF for his assistance in obtaining the ^{11}B NMR spectra on the FX-90 Q spectrometer at USF. W.C.G. expresses his deepest gratitude to Professor James A. Marshall and the Department of Chemistry, University of South Carolina, for

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(6) Nystrom, R. F.; Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 3245. For a recent indepth study of the reactivity of lithium borohydride toward esters, see ref 1c.

(7) Brown, H. C.; Narasimhan, S. *Organometallics* **1982**, *1*, 762.

(8) Davis, M. *J. Chem. Soc.* **1956**, 3981.

(9) Because of this moisture sensitivity we have preferred to generate the reagent in situ rather than prepare batch quantities of the pre-formed reagent.

(10) Eaton, G. R.; Lipscomb, W. N. "NMR Studies of Boron Hydrides and Related Compounds"; W. A. Benjamin: New York, 1969.

(11) Egan, B. Z.; Shore, S. G.; Bonnell, J. E. *Inorg. Chem.* **1964**, *3*, 1024.

(12) If 1 is indeed the species responsible for reductions performed with the ethanedithiol/sodium borohydride reagent, it is tempting to speculate on its enhanced reactivity over sodium borohydride. It was suggested by a referee that electron donation by sulfur should enhance delivery of hydride by 1. We too, have invoked this argument when interpreting our results. However, it is unclear whether such electron donation actually occurs. See ref 11 and references cited therein.

their hospitality during his sabbatical leave when this manuscript was prepared.

Registry No. 1, 90605-30-4; $PhCO_2Et$, 93-89-0; $CH_3(CH_2)_{10}CO_2Et$, 106-33-2; *p*-$MeOC_6H_4CO_2Et$, 94-30-4; *cis*-$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2Me$, 112-62-9; $PhCO_2$-*i*-Pr, 939-48-0; $PhCO_2$-*t*-Bu, 774-65-2; PhCN, 100-47-0; $PhCH_2CN$, 140-29-4; $PhCONH_2$, 55-21-0; $PhCO_2H$, 65-85-0; $PhCH_2OH$, 100-51-6; $CH_3(CH_2)_{11}OH$, 112-53-8; *p*-$MeOC_6H_4CH_2OH$, 105-13-5; *cis*-$CH_3(CH_2)_7CH{=}CH(CH_2)_8OH$, 143-28-2; $PhCH_2NH_2$, 100-46-9.

Conformational Analysis of S–C–P Anomeric Interactions. 2.[1] X-ray Crystallographic Evidence against the Importance of $n_S \rightarrow \sigma^*_{C-P}$ Conjugation in Axial 2-[1,3]Dithianyldiphenylphosphine Oxide

Eusebio Juaristi,* Bertha A. Valenzuela, and Lucía Valle

Departamento de Química, Centro de Investigación y de
Estudios Avanzados del Instituto Politécnico Nacional,
Apartado Postal 14-740, 07000-México, D.F., México

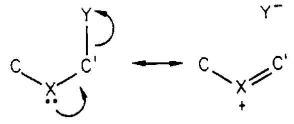
Andrew T. McPhail*

Paul M. Gross Chemical Laboratory, Duke University,
Durham, North Carolina 27706

Received December 13, 1983

The discovery of a predominant axial conformation in 2-[1,3]dithianyldiphenylphosphine oxide (1) was reported recently.[1] This finding was remarkable from several points of view: (1) it constituted the first account of the existence of an anomeric interaction between second-row elements sulfur and phosphorus,[2] (2) unlike other reported examples of the anomeric effect,[3] it involved a fully bonded substituent (i.e., there are no lone pairs of electrons on the axially oriented phosphorus atom),[4] and (3) the overall steric demands of an axial diphenylphosphinoyl group may be quite substantial (Scheme I).[5]

Although dipole–dipole interactions were initially invoked to account for the anomeric effect,[6] X-ray crystallographic data led Romers, Altona, et al.[7] to suggest that delocalization of nonbonding electrons into the antiperiplanar adjacent polar bond contributes to the stability of the axial conformer. According to this proposal, in gauche (axial) C–X–C′–Y systems the C′–X distances are significantly shorter than normal while the C′–Y bond lengths are longer than normal. This description of the anomeric effect has received support from the results of a considerable number of experimental[8] and theoretical[9] investigations.



Scheme I

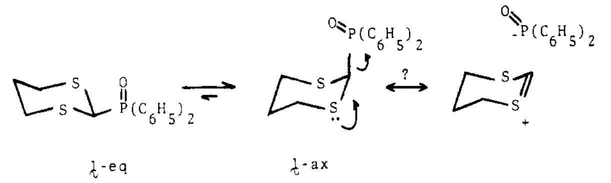
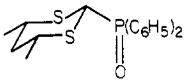


Table I. Selected Interatomic Distances and Angles in 1-Axial, 2, and 3, with Standard Deviations in Parentheses

	1-axial[a]	2[b,c]	3[d]
	Bond Lengths (Å)		
S(1)–C(2)	1.809 (3)[e]	1.810 (4), 1.808 (4)	1.792 (5)[e]
S(1)–C(6)	1.810 (3)[e]	1.818 (5), 1.835 (5)	1.823 (4)[e]
C(2)–P	1.825 (3)	1.840 (4)	
C(5)–C(6)	1.517 (5)[e]	1.520 (7), 1.506 (7)	1.518 (5)[e]
P–O	1.486 (2)	1.481 (3)	
	Bond Angles (deg)		
C(2)–S(1)–C(6)	101.3 (1)[e]	97.9 (2), 97.3 (2)	99.2 (2)[e]
S(1)–C(2)–S(3)	114.5 (1)	113.1 (2)	114.5 (3)
S(1)–C(2)–P	110.4 (1)[e]	106.4 (2), 112.5 (2)	
S(1)–C(6)–C(5)	113.9 (2)[e]	112.7 (4), 113.3 (4)	112.8 (3)[e]
C(4)–C(5)–C(6)	113.3 (3)	115.6 (4)	116.7 (3)

[a] Reference 1. [b] Present work. [c] Since this molecule deviates significantly from C_s symmetry the bond lengths and angles of each half are listed separately. [d] Reference 10. [e] Mean values, averaged assuming C_s ring symmetry.

We here report the results of an X-ray analysis of *r*-2-(diphenylphosphinoyl)-*c*-4,*c*-6-dimethyl-1,3-dithiane (2).



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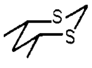

3

Comparisons with structural data for 1-axial[1] as well as *cis*-4,6-dimethyl-1,3-dithiane (3)[10] were made in order to examine the possible importance of $n_S \rightarrow \sigma^*_{C-P}$ interactions which, if significant, would be manifested in shortened C–S and elongated C–P distances in the axial vs. equatorial form.

Results and Discussion

The crystal structure of 2 was solved by direct methods.[11] Refinement of atomic parameters[12] converged to

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[1] For part 1, see: Juaristi, E.; Valle, L.; Mora-Uzeta, C.; Valenzuela, B. A.; Joseph-Nathan, P.; Fredrich, M. F. *J. Org. Chem.* **1982**, *47*, 5038–5039.

[2] The evaluation of the S–C–S anomeric interaction has been effected: Hartmann, A. A. Ph.D. Dissertation, 1971, University of Notre Dame, Notre Dame, IN. Zefirov, N. S.; Blagoveshchenskii, V. S.; Kazimirchik, I. V.; Yakovleva, O. P. *J. Org. Chem. USSR* (*Engl. Transl.*) **1971**, *7*, 599–602. Juaristi, E.; Tapia, J.; Keys, B.; Eliel, E. L., unpublished results.

[3] Lemieux, R. U.; Koto, S. *Tetrahedron* **1974**, *30*, 1933–1944. Bailey, W. F.; Eliel, E. L. *J. Am. Chem. Soc.* **1974**, *96*, 1798–1806. Szarek, W. A.; Horton, D., Eds. "Anomeric Effect, Origin and Consequences"; American Chemical Society: Washington, D.C., 1979; ACS Symp. Ser. No. 87. Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen", Springer-Verlag: Berlin, 1983.

[4] It is then clear that the anomeric effect does not require a lone pair of electrons on the acceptor atom.

[5] In spite of the long C–P and C–S bonds, the steric repulsion present in axial-1 may be worth ca. 1.25 kcal/mol (see footnote 16 in ref 1). The experimental measurement of the steric demand of an axial diphenylphosphinoyl group on model compounds has been initiated (Juaristi, E.; López-Núñez, N. A.; Hutchins, R. O., work in progress).

[6] Edward, J. T. *Chem. Ind.* (*London*) **1955**, 1102–1104.

[7] Romers, C.; Altona, C.; Buys, H. R.; Havinga, E. *Top. Stereochem.* **1969**, *4*, 73–77. See also: Altona, C.; Knobler, C.; Romers, C. *Acta Crystallogr.* **1963**, *16*, 1217–1225. Altona, C.; Romers, C. *Ibid.* **1963**, *16*, 1225–1232.

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[9] Jeffrey, G. A.; Pople, J. A.; Radom, L. *Carbohydr. Res.* **1972**, *25*, 117–131. Gorenstein, D. G.; Findlay, J. B.; Luxon, B. A.; Kar, D. *J. Am. Chem. Soc.* **1977**, *99*, 3473–3479. Jeffrey, G. A.; Pople, J. A.; Binkley, J. S.; Vishveshwara, S. *Ibid.* **1978**, *100*, 373–379. Davis, S. "Anomeric Effect, Origin and Consequences", American Chemical Society: Washington, D.C., 1979; ACS Symp. Ser. No. 87, pp 1–16. Wolfe, S.; Whangbo, M.-H.; Mitchell, D. J. *Carbohydr. Res.* **1979**, *69*, 1–26.

[10] McPhail, A. T.; Onan, K. D.; Koskimies, J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1004–1008.

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