$$\tau_c = \frac{4\pi\eta a^3}{3kT} \tag{8}$$

A recent crystallographic study of chymotrypsin at 2-Å resolution shows that the over-all dimensions of the molecule are approximately 45 × 35 × 38 Å.[26] If the mean of these dimensions (39 Å) is taken as the effective radius of the enzyme in solution, the rotational correlation time for the enzyme as a whole is estimated to be 4 × 10^{-8} sec. The agreement between the calculated rotational correlation time of the enzyme molecule as a whole and the correlation time of tryptophan in the tryptophan–enzyme complex as determined by nmr is striking when the approximations involved are considered. This observation indicates that tryptophan interacts so strongly with the enzyme that the rotational motions of the amino acid are essentially identical with those of the enzyme and provides support for the proposition that chymotrypsin binds substrates tightly enough to seriously curtail molecular motion in the substrate.[27] It remains for further experimentation to more precisely define the details of this interaction.

Acknowledgments. We are indebted to Professors B. R. Baker and D. V. Santi for helpful discussions. This work was supported by Grant GM-14692 from the National Institutes of Health.

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[26] B. W. Matthews, P. B. Sigler, R. Henderson, and D. M. Blow, *Nature*, **214**, 652 (1967).

[27] M. L. Bender, F. J. Kézdy, and C. R. Gunter, *J. Am. Chem. Soc.*, **86**, 3714 (1964).

Communications to the Editor

The Borohydride-Catalyzed Reaction of Diborane with Epoxides. The Anti-Markovnikov Opening of Trisubstituted Epoxides

Sir:

Diborane is an interesting reducing agent with unusual characteristics.[1] However, in contrast to the simplicity of most other reactions, the reaction of diborane with epoxides is quite complex.[2] Thus, the reaction of 1,2-butylene oxide with diborane in tetrahydrofuran at 25° is a relatively slow reaction, requiring approximately 48 hr to proceed to the utilization of one "hydride" per mole of epoxide. However, analysis of the reaction mixture reveals the presence of only 48% of butanol (4% 1- and 96% 2-). The reaction is even more complex with trisubstituted epoxides, such as 1-methylcyclohexene oxide. In such cases the reaction proceeds with the utilization of 2 moles of hydride per mole of epoxide, with 1 mole of hydrogen being evolved. Only trace amounts of the simple alcohols are found in the reaction mixture. The major product is evidently an organoborane which is oxidized with alkaline hydrogen peroxide to the isomeric 2-hydroxymethylcyclohexanols.

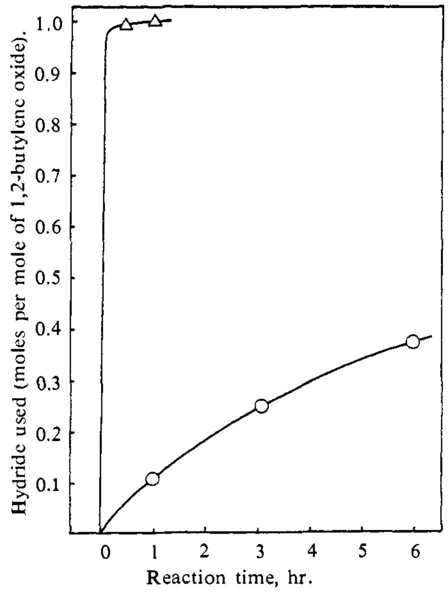
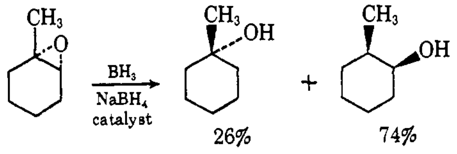


Figure 1. The reaction of borane (0.33 *M*) with 1,2-butylene oxide (0.25 *M*) in the presence (△) and absence (○) of sodium borohydride (0.036 *M*).

The presence of even minor amounts of sodium or lithium borohydride has a major effect on both the speed of the reaction and its course. In Figure 1 are shown the curves for the reaction of 1,2-butylene oxide with diborane in the presence and absence of a small quantity of sodium borohydride.[3] Not only is the rate affected, but the yield in 1 hr rises to 95% 2-butanol.

In the case of trisubstituted epoxides, such as 1-methylcyclohexene oxide, the rate of the reaction is also increased. Moreover, the course of the reaction is modified tremendously. One mole of hydride per mole of compound is utilized, hydrogen is not evolved, and there is observed a predominant anti-Markovnikov opening of the epoxide ring (1).



(1)

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[1] H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962.

[2] D. J. Pasto, C. C. Cumbo, and J. Hickman, *J. Am. Chem. Soc.*, 88, 2201 (1966).

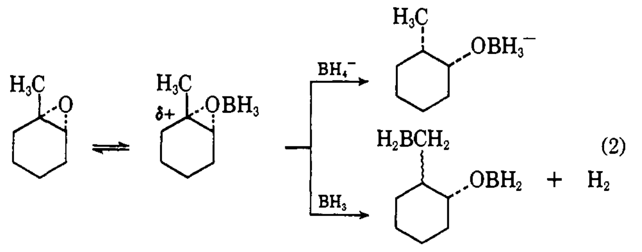
[3] The solubility of sodium borohydride in 0.33 *M* THF–BH_3 was determined to be 0.036 *M* at 25°.

Table I. The Borohydride-Catalyzed Reduction of Representative Epoxides

Epoxide[a]	Reagent	Temp, °C	Time,[f] hr	Yield, %	Products[g] (%)
1,2-Butylene oxide	BH_3[b]	25	48	48	1-Butanol (4) 2-Butanol (96)
	$BH_3(NaBH_4)$[c]	25	1.0	95	2-Butanol (100)
	$AlH_3 \cdot 2AlCl_3$[d]	0	1.0	71	2-Butanol (100)
2-Methyl-2-butene oxide	BH_3[b]	0	24	4	3-Methyl-2-butanol (100)
	$BH_3(NaBH_4)$[c]	0	48	59	3-Methyl-2-butanol (78) 2-Methyl-2-butanol (22)
	$BH_3(LiBH_4)$[e]	0	24	98	3-Methyl-2-butanol (75) 2-Methyl-2-butanol (25)
1-Methylcyclopentene oxide	BH_3[b]	25	48	2[h]	2-Methylcyclopentanols
	$BH_3(LiBH_4)$[e]	0	24	88	*cis*-2-Methylcyclopentanol (72) 1-Methylcyclopentanol (28)
1-Methylcyclohexene oxide	BH_3[b]	25	24	Tr[h]	
	$BH_3(NaBH_4)$[c]	0	24	100	*cis*-2-Methylcyclohexanol (74) 1-Methylcyclohexanol (26)
	$BH_3(LiBH_4)$[e]	0	3.0	100	*cis*-2-Methylcyclohexanol (74) 1-Methylcyclohexanol (26)
	$AlH_3 \cdot 2AlCl_3$[d]	0	1.0	40[i]	*cis*-2-Methylcyclohexanol (47) *trans*-2-Methylcyclohexanol (29) 1-Methylcyclohexanol (24)
1-Methylcycloheptene oxide	BH_3[b]	25	6.0	Tr[h]	
	$BH_3(LiBH_4)$[e]	0	24	41	*cis*-2-Methylcycloheptanol (83) 1-Methylcycloheptanol (17)
α-3,4-Epoxycarene	$BH_3(LiBH_4)$[e]	0	96	70	Neocaranol (66) Caranol (1) 3-Caranol (33)

[a] 0.25 *M* in THF. [b] 10 mmoles of BH_3 for 10 mmoles of epoxide. [c] 13.3 mmoles of BH_3 and 0.1 g of $NaBH_4$ for 10 mmoles of epoxide. [d] 10 mmoles of AlH_3 and 20 mmoles of $AlCl_3$ for 10 mmoles of epoxide. [e] 10 mmoles of BH_3 and 10 mmoles of $LiBH_4$ for 10 mmoles of epoxide. [f] Reactions were followed and halted after the hydride uptake became essentially constant. [g] Only the simple reduction products are indicated. Analysis by glpc. [h] Hydrogen evolved during reaction. After oxidation with alkaline hydrogen peroxide, 70–80% yields of diols (2-hydroxymethylcycloalkanols) could be isolated. [i] The remaining 60% was 1-methylcyclopentylcarbinol (see eq 4).

A somewhat faster reaction, with similar products, could be realized by the use of higher concentrations of the more soluble lithium borohydride.

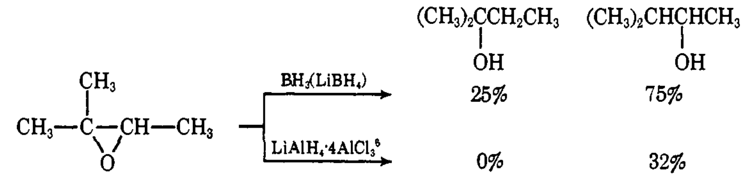


(2)

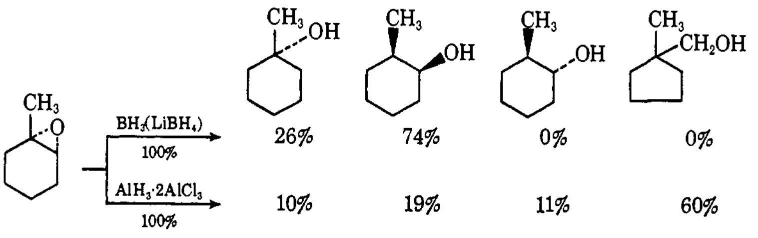
The reaction presumably involves preferentially the attack by borohydride at the polarized tertiary position, with inversion, to form the *cis*-2-methylcycloalkanol,[5] whereas electrophilic attack by diborane occurs at the methyl group (2).

Mixed hydride ($LiAlH_4$:$AlCl_3$ 1:4) has also been reported to give the less substituted carbinol as a major product.[6] However, the low yields suggest that the tertiary alcohol is probably formed preferentially but is selectively destroyed (3).

In the case of 1-methylcyclohexene oxide, mixed hydride gave a complex mixture of products (4).



(3)



(4)

The generality of this anti-Markovnikov opening of trisubstituted epoxides is indicated by the results with 2-methyl-2-butylene oxide, 1-methylcyclopentene oxide, 1-methylcycloheptene oxide, and α-3,4-epoxycarene (Table I). It is noteworthy that this procedure provides a simple entry into the neocaranol series, otherwise very difficult to achieve.[4]

Consequently, the present procedure appears to offer

(4) H. C. Brown and A. Suzuki, *J. Am. Chem. Soc.*, **89**, 1933 (1967).

(5) An alkoxy borohydride would be the first product, but it is known that such derivatives are rapidly converted to borohydride by diborane, accounting for the need of only minor amounts of borohydride: H. I. Schlesinger, H. C. Brown, H. R. Hockstra, and L. R. Rapp, *ibid.*, **75**, 199 (1953).

(6) E. L. Eliel, *Record Chem. Progr.*, **22**, 129 (1961).

major advantages for the anti-Markovnikov opening of such trisubstituted epoxides.

The following procedure is representative. A dry 100-ml flask, fitted with a rubber syringe cap and a magnetic stirring bar, was placed in an ice bath and flushed with dry nitrogen and then maintained under a static atmosphere of the gas. There was then introduced into the flask 10 mmoles of borane (4.4 ml of a 2.28 *M* solution in THF), 10 mmoles of lithium borohydride (5.6 ml of a 1.79 *M* solution in THF), and 20 ml of THF. The reaction was initiated by the injection of 10 mmoles of 1-methylcyclopentene oxide (0.981 g) in 10 ml of THF at 0°. After 24 hr at 0°, the reaction mixture was hydrolyzed with 10 ml of a 1:1 mixture of 1.0 *M* sulfuric acid and THF; 10 mmoles of cyclohexanol (10 ml of a 1.00 *M* solution in THF) was added as an internal standard. Potassium carbonate was added to saturate the aqueous phase, and the THF phase was separated, dried over anhydrous magnesium sulfate, and analyzed by glpc. The analysis revealed an 88.3% yield of alcohols (27.6% 1-methylcyclopentanol and 72.4% *cis*-2-methylcyclopentanol). No trace of the *trans* isomer was detected.

The hydroboration–oxidation of 1-substituted cycloalkenes provides a highly satisfactory route to the pure *trans*-2-substituted cycloalkanols.[1] The present development now provides a convenient route to the isomeric *cis* derivatives.

(7) Graduate assistant on Research Grant DA 31-124 ARO(D) 453, supported by the U. S. Army Research Office, Durham.

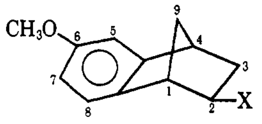
Herbert C. Brown, Nung Min Yoon[7]
Richard B. Wetherill Laboratory
Purdue University, Lafayette, Indiana 47907
Received March 1, 1968

Solvolyses of 6- and 7-Methoxybenzonorbornen-2-yl Derivatives. Directing Effects of a Methoxy Substituent for Participation

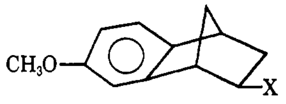
Sir:

Studies of substituent effects such as carried out by us in the solvolysis of benzonorbornenyl brosylates[1] have been evaluated as a decisive test for π-participation effects.[2] We now report the directing effects of a methoxy substituent in the solvolyses of 6- and 7-methoxybenzonorbornen-2-yl derivatives I and II, evidencing the presence of large participation in solvolysis of these compounds.

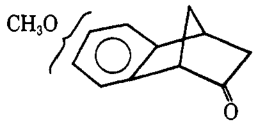
The hydrochlorination of benzonorbornadiene was reported to give solely *exo*-2-chlorobenzonorbornadiene.[3] The reaction with 6-methoxybenzonorbornadiene[4] gave a 7:3 mixture of *homo-para* and *homo-meta* chlorides I-Cl and II-Cl, respectively. On hydrolysis of the mixture in 70% aqueous acetone in the presence of 1 equiv of $NaHCO_3$ for 3 hr at 75°, I-Cl was converted into the *homo-para exo*-alcohol I-OH, mp 51–52°,[5] whereas II-Cl remained unreacted; I-OH and II-Cl were separated by chromatography. When the reaction with the separated II-Cl was carried out once again for 6 hr, II-Cl was isolated in a pure state, $n^{22}\mathrm{D}$ 1.5670. Treatment of I-OH with thionyl chloride led to I-Cl, bp 115° (1 mm), $n^{25}\mathrm{D}$ 1.5672. Solvolysis of II-Cl in boiling 70% aqueous acetic acid for 1 day followed by treatment of thus-formed acetate–alcohol mixture with $LiAlH_4$ afforded the *homo-meta exo*-alcohol II-OH, bp 120° (1 mm), $n^{23}\mathrm{D}$ 1.5684. Oxidation of I-OH and II-OH gave the *homo-para* ketone III, bp 110° (bath temperature, 1 mm), $n^{20}\mathrm{D}$ 1.5689, and the *homo-meta* IV, $n^{23}\mathrm{D}$ 1.5664, respectively. By comparison of the characteristic ^1L_a bands in the ultraviolet spectra of III (λ_{max} 238 mμ (ϵ 8660)) and IV (shoulder at 228 mμ (ϵ ~5620)), the *homo-para* and *homo-meta* assignments were confirmed.[6,7] Lithium aluminum hydride re-



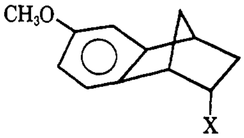
I-Cl, X = Cl
I-OH, X = OH



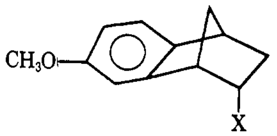
II-Cl, X = Cl
II-OH, X = OH



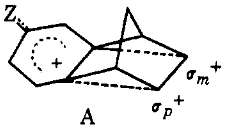
III, 6-CH₃O
IV, 7-CH₃O



V-OH, X = OH
V-OBs, X = OBs



VI-OH, X = OH
VI-OBs, X = OBs



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(1) (a) H. Tanida, *J. Am. Chem. Soc.*, **85**, 1703 (1963); (b) H. Tanida, T. Tsuji, and H. Ishitobi, *ibid.*, **86**, 4904 (1964); (c) H. Tanida and H. Ishitobi, *ibid.*, **88**, 3663 (1966); (d) H. Tanida, Y. Hata, S. Ikegami, and H. Ishitobi, *ibid.*, **89**, 2928 (1967).

(2) (a) P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965; (b) N. Brookhart, A. Diaz, and S. Winstein, *J. Am. Chem. Soc.*, **88**, 3135 (1966), ref 12; (c) H. C. Brown and K. Takeuchi, *ibid.*, **88**, 5336 (1966).

(3) S. J. Cristol and R. Caple, *J. Org. Chem.*, 31, 2741 (1966).

(4) H. Tanida, R. Muneyuki, and T. Tsuji, *Bull. Chem. Soc. Japan*, 37, 40 (1964).

(5) All new compounds gave spectral and microanalytical data consistent with the proposed structure.

(6) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p 260.

(7) The Diels–Alder reaction of β-naphthol with maleic anhydride is a good method for synthesis of benzobicyclo[2.2.2]octen-2-one derivatives: K. Takeda, S. Nagakura, and K. Kitahonoki, *Pharm. Bull. Japan*, **1**, 135 (1953). According to a private communication from Dr. Takeda, the reactions with 2,6- and 2,7-dihydroxynaphthalenes lead to 6- and 7-hydroxybenzobicyclo[2.2.2]octen-2-one-9,10-dicarboxylic acid anhydrides, respectively. The ^1L_a bands in 6- and 7-methoxybenzobicyclo[2.2.2]octen-2-ones, prepared from the anhydrides, correspond to those in III and IV, respectively. We thank Dr. Takeda for his informing us of the results *prior* to publication.