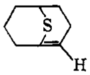
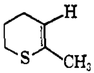
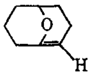
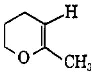
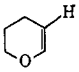
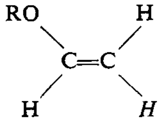
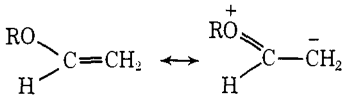
Table I. Nmr Chemical Shifts of Vinyl Hydrogens β to Oxygen and Sulfur

Compound	Chemical shift of vinyl hydrogens (δ)	Ref
 2	6.25	*a*
 11	5.34	*a*
Bicyclo[3.3.1]non-1-ene	5.62	*c*
Cyclohexene	5.63	
 1	5.74	*b*
 12	4.34	*b*
	4.55	*e*
	3.75–3.78	*d*

[a] This work. [b] Reference 5a. [c] Reference 3d. [d] J. Feeney, A. Ledwith, and L. H. Sutcliffe, *J. Chem. Soc.*, 2021 (1962). [e] R. M. Silverstein and G. C. Bassler, "Spectrophotometric Identification of Organic Compounds," Wiley, New York, N. Y., 1967, p 200.

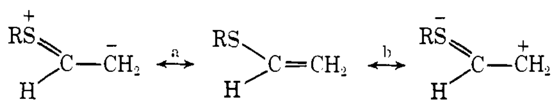
causes the β vinyl hydrogens to resonate at approximately 1.3 ppm higher field than alkene vinyl hydrogens. This interaction, which is equivalent to the resonance interaction depicted in **13**, is absent in bridged vinyl ether **1** owing to an unfavorable orientation of the orbitals.[5a]

In vinyl sulfides, the nmr resonance position of the β hydrogens is only 0.3 ppm higher than that of alkene vinyl hydrogens. Sulfur may donate electron density to the β position of a vinyl sulfide by mixing of a 3p orbital with the π and π^* orbitals (**14**, resonance arrow a) and at the same time may accept electron density into a 3d orbital from the π bond (resonance arrow b).[12] This combination of dative and acceptive resonance by sulfur explains the slightly upfield-shifted nmr resonance position of the β protons of normal vinyl sulfides. In bicyclic vinyl sulfide **2**, the dative resonance (a) is inhibited while the acceptive resonance (b) is allowed by the orientation of the pertinent orbitals. Thus, the vinyl hydrogen of **2** is strongly dishielded.



$$\mathrm{RO(H)C{=}CH_2} \longleftrightarrow \overset{+}{\mathrm{RO}}\mathrm{{=}C(H)}-\overset{-}{\mathrm{C}}\mathrm{H_2}$$

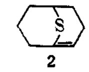
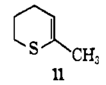
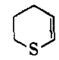
13



$$\overset{+}{\mathrm{RS}}\mathrm{{=}C(H)}-\overset{-}{\mathrm{C}}\mathrm{H_2} \overset{a}{\longleftrightarrow} \mathrm{RS(H)C{=}CH_2} \overset{b}{\longleftrightarrow} \overset{-}{\mathrm{RS}}\mathrm{{=}C(H)}-\overset{+}{\mathrm{C}}\mathrm{H_2}$$

14

Table II. Ultraviolet Spectra of Saturated and Unsaturated Sulfides

Compound	λ_{max} (ϵ)	Solvent	Ref
 2	196 (4700) 210 (4560)	Pentane	*a*
Dimethyl sulfide	210 (1020) 229 (138)	Ethanol	*b*
Diethyl sulfide	210 (1780) 229 (138)	Ethanol	*b*
Dibutyl sulfide	210 (1230) 229 (138)	Ethanol	*b*
	207 (1630) 235 (70)	Methanol	*c*
 11	228 (6000) 248 (2700)	Pentane	*a*
Butyl vinyl sulfide	229 (7000) 240 (5500)	Cyclohexane	*c*
Butyl 1-butenyl sulfide	232 (6300) 248 (4500)	Cyclohexene	*c*
	226 (5300) 251 (2600)	Cyclohexane	*c*

[a] This work. [b] E. A. Fehnel and M. Carmack, *J. Amer. Chem Soc.*, **81**, 84 (1949). [c] M. Prochazka and M. Palecek, *Collect. Czech. Chem. Commun.*, **32**, 3149 (1967).

Table II contains the ultraviolet spectra of various saturated and unsaturated sulfides.[13] It is evident that bridged sulfide **2** is not a typical vinyl sulfide. The spectrum appears to be a combination of the absorption bands due to an isolated carbon double bond and a saturated dialkyl sulfide. The twisting has completely disrupted the conjugation seen in normal α,β-unsaturated sulfides.

We shall report on the chemical reactions of **2** in our full paper.

Acknowledgment. This research was supported by a grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society.

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Received April 30, 1973

Geometrical Isomers of 9-Thiabicyclo[3.3.1]non-1-ene 9,9-Dioxides from β-Eliminations from Bridged Halo Sulfones[1,2]

Sir:

In 1969 Paquette and Houser[3] reported that treatment of *endo*-2-chloro sulfone (**1**) with potassium *tert*-butox-

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[12] C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962, Chapters 1 and 2.

[13] For compilations of ultraviolet spectra see (a) ref 12, appendix I; (b) R. C. Passerini in "Organic Sulfur Compounds," N. Kharasch, Ed., Vol. I, Pergammon Press, New York, N. Y., 1967, Chapter 7; (c) E. Block, *Quart. Rev. Sulfur Chem.*, 4, 237 (1969).

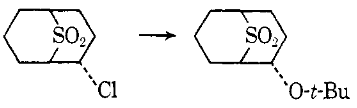
[14] National Institutes of Health Graduate Fellow, 1970–1973; NDEA Graduate Fellow, 1969–1970.

[1] Paper VIII in the Bredt's Rule series. For paper VII see C. B. Quinn and J. R. Wiseman, *J. Amer. Chem. Soc.*, **95**, 6120 (1973).

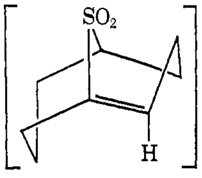
[2] Taken in part from the Ph.D. Dissertation of C. B. Quinn, University of Michigan, 1973.

[3] (a) L. A. Paquette and R. W. Houser, *J. Amer. Chem. Soc.*, **91**, 3870 (1969); (b) R. W. Houser, Ph.D. Dissertation, Ohio State University, 1970. These authors do not explicitly assign the stereochemistry of **3** but their discussion of the stereochemistry of the reaction of *tert*-butyl alcohol with **3** is consistent only with the zusammen configuraiton.

ide in *tert*-butyl alcohol produced the endo *tert*-butyl ether **2** in 82% yield. The stereochemistry of **2** is firmly based on chemical and spectral data. In particular the nmr spectrum of **2** shows the proton α to the ether oxygen as a doublet (J = 4 Hz) of triplets (J = 8 Hz) characteristic of compounds of that type.[4] Paquette and Houser invoked the bridgehead unsaturated sulfone **3**-(Z) as an intermediate in the reaction and explained the endo stereochemical course of the Michael addition of *tert*-butyl alcohol to **3**-(Z) on the basis of shielding of the exo face of **3**-(Z) by the sulfonyl oxygen atoms. We now present evidence that the stereochemical course of this addition is the result of formation of the highly strained entgegen isomer of **3** rather than the less strained zusammen isomer.[5]

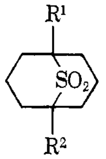


1 2

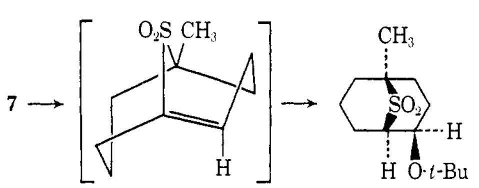


3-(Z)

Treatment of sulfone **4**[4] in benzene successively with methyllithium and iodomethane gave a 2:1 mixture of sulfones **5** and **6**. Treatment of the mixture successively with methyllithium and bromine gave bromo sulfone **7** (mp 145.5–146.5°; ir (CCl_4) ν_{max} 1315, 1125 cm^{-1}; nmr, 3 H singlet δ 1.37) in 15% yield based on **4**. Treatment of bromo sulfone **7** with potassium *tert*-butoxide in *tert*-butyl alcohol gave 2-*exo*-*tert*-butoxy sulfone **8** (mp 99–100°; ir (CCl_4) ν_{max} 1305, 1195, 1120, 1055 cm^{-1}; nmr ($CDCl_3$) δ 4.08 (1 H, d, t, J = 2, 5 Hz), 2.96 (1 H, br), 2.52–1.63 (10 H, complex), 1.28 (3 H, s), 1.20 (9 H, s)). The coupling constants for the proton at δ 4.08 require the proton to be equatorial. Thus the *tert*-butoxy group must be axial and exo. This result requires that the bridgehead-unsaturated sulfone **9** formed by elimination of hydrogen bromide from **7** must be stereochemically different from the unsaturated sulfone **3** derived from endo chloro sulfone **1**. The following experiments prove the stereochemistry of **3** and **9**.

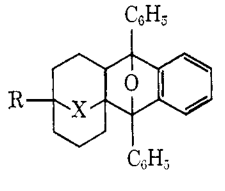


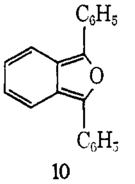
4, $R^1 = R^2 = H$
5, $R^1 = CH_3$; $R^2 = H$
6, $R^1 = R^2 = CH_3$
7, $R^1 = CH_3$; $R^2 = Br$



9 8

Reaction of chloro sulfone **1** with potassium *tert*-butoxide in the presence of 1,3-diphenylisobenzofuran (**10**) gave two Diels–Alder adducts: A (40% yield, mp 265–270°) and B (40% yield, mp 262.5–263°).[6] Analytical and spectral data for both adducts are consistent with general formula **11a** ($C_{28}H_{26}SO_3$). Dehydrobromination of methyl sulfone **7** with potassium *tert*-butoxide in the presence of 1,3-diphenylisobenzofuran (**10**) produced a Diels–Alder adduct **11c** (47% yield) which had molecular formula $C_{29}H_{28}SO_3$, *m/e* 454, mp 245–247°, and consistent ir and nmr spectra.

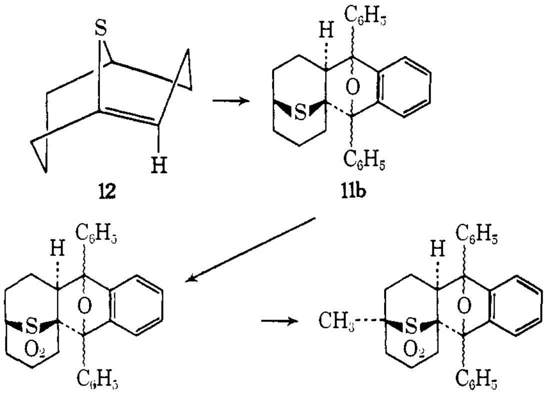




10

11a, R = H; X = SO_2
b, R = H; X = S
c, R = CH_3; X = SO_2

Adduct **11c** was synthesized by an alternative route which permitted partial assignment of its stereochemistry. Diels–Alder adduct **11b** (mp 225–228°, *m/e* 410) was prepared from 9-thiabicyclo[3.3.1]non-1-ene (**12**).[1]



adduct C (general formula **11a**) **11c**

Because sulfide **12** is isolable it is assigned zusammen stereochemistry, and **11b** is assigned the partial stereochemistry shown based on exo approach of **10** in the Diels–Alder reaction. The orientation of the ether oxygen relative to the sulfur bridge is presently unknown.

Oxidation of **11b** with *m*-chloroperbenzoic acid gave 89% of a third isomer of formula **11a** which will be called adduct C (mp 296.5–297.5°, *m/e* 442, ir and nmr similar to adducts A and B). Methylation of adduct C by successive treatment with methyllithium and iodomethane in ether produced **11c**. Therefore, **11b**, **11c**, and adduct C have the same stereochemistry.

Since variation of the orientation of 1,3-diphenyliso-

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(4) (a) E. J. Corey and E. Block, *J. Org. Chem.*, 31, 1663 (1966); (b) E. D. Weil, K. J. Smith, and R. J. Gruber, *ibid.*, 31, 1669 (1966).

(5) In the entgegen isomer the double bond is trans in the six-membered ring and cis in the eight-membered ring. The zusammen isomer has the double bond trans in the eight-membered ring and cis in the six-membered ring. See IUPAC Tentative Rules for the Nomenclature of Organic Chemistry, Section E-2, *J. Org. Chem.*, 35, 2849 (1970).

(6) Earlier attempts to trap 3 were unsuccessful.[3]

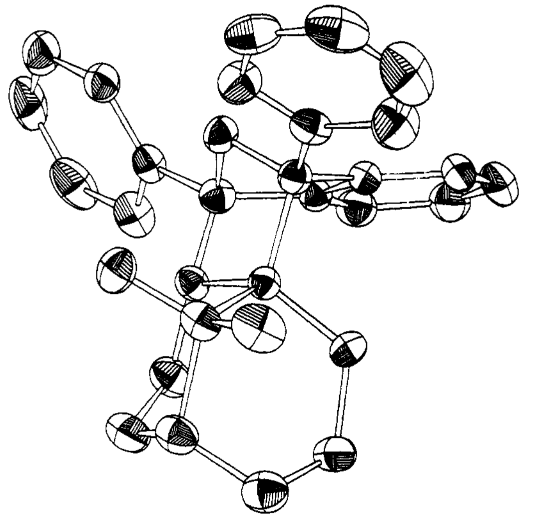


Figure 1. Crystallographically determined molecular configuration of Diels–Alder adduct A.

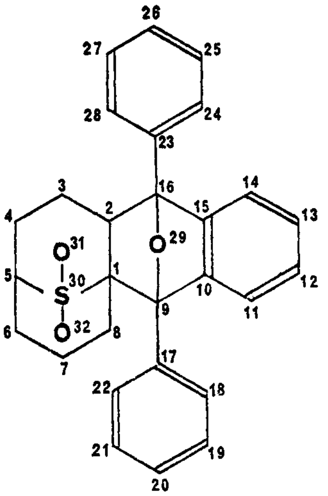


Figure 2. Numbering scheme for adduct A.

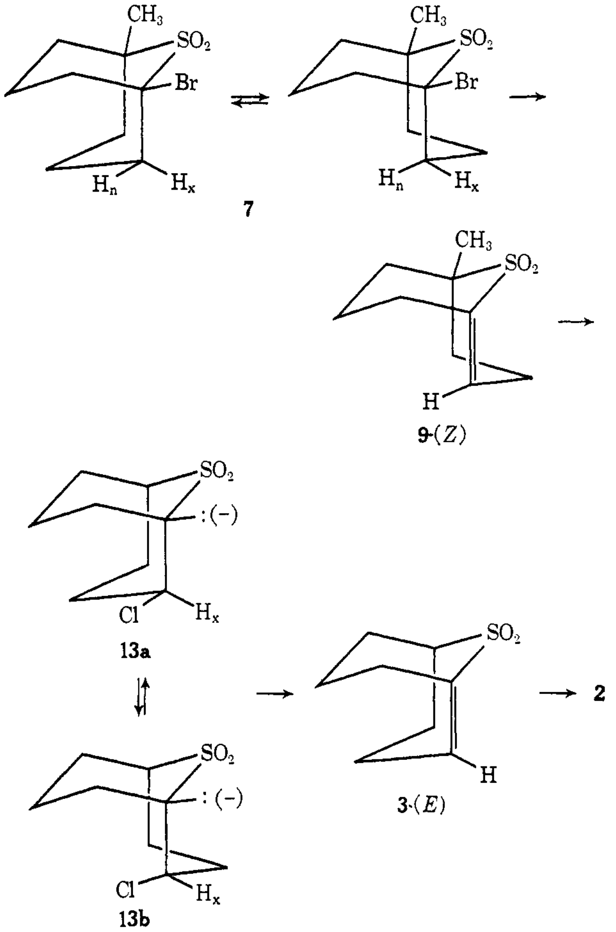
benzofuran (**10**) in the Diels–Alder reactions with the bridgehead unsaturated sulfone **3** (or **9**) can account for only two isomers of formula **11a** (or **11c**), adducts A and/or B must differ from C in the orientation of the hydrogen at C-2. In either A or B or both this hydrogen must be exo. This necessitates assignment of entgegen (*E*) stereochemistry to the unsaturated sulfone **3**.

The stereochemical assignment inferred for adducts A and B was confirmed for A from a direct-method determination[7] of its structure by single-crystal X-ray diffraction.[8,9] Figure 1 shows the 9-thiabicyclo[3.3.1]-nonane 9,9-dioxide part of the molecular adduct A to possess a chair–chair conformation with equatorial bonds at C(1) and C(2) to the 1,3-diphenylisobenzofuran moiety. The ether oxygen (29) is syn to the sulfone bridge. The numbering scheme of adduct A is shown in Figure 2. Bond distances and angles are within expected tolerances with the exception of the somewhat long C(1)–C(9) single bond distance of 1.624 (5) Å which can be attributed to the steric limitations imposed by the interaction of the two moieties. An X-ray study of adduct B is in progress.

In the reaction of *tert*-butoxide with bromo sulfone **7** either the exo or the endo hydrogen may be selected by the base. Probably the exo hydrogen is eliminated in a syn transition state from the chair–boat conformation leading to the zusammen isomer **9**-(*Z*).

Evidently, **3**-(*E*) is formed in a kinetically controlled elimination of hydrogen chloride from chloro sulfone **1**. This elimination probably proceeds by an E1cb mechanism involving the conjugate base **13**. Models indicate that the orientation of the bridgehead lone-pair orbital with respect to the carbon–chlorine bond is more favorable in **13a** than in **13b**. However, the controlling factor may be the ground-state conformational population of **13**, which should be largely **13a**. Addition of *tert*-butyl alcohol to **3**-(*E*) occurs from the exo face but leads to endo *tert*-butyl ether **2** (Scheme I).

Scheme I



Cycloaddition reactions of 1,3-diphenylisobenzofuran (**10**) with **3**-(*E*) and **9**-(*Z*) proceed supra-supra leading to trans and cis ring junctures, respectively. The formation of two adducts from **3**-(*E*) and only one adduct from **9**-(*Z*) is consistent with the expected differences in strain energy. The more strained compound, **3**-(*E*), shows no selectivity in its reactions with **10** and gives a

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(7) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, 27, 368 (1971); J. Karle, *Acta Crystallogr.*, 9, 635 (1968).

(8) Adduct A: monoclinic colorless plates; $P2_1/c$; $a = 11.640$ (3), $b = 10.891$ (2), $c = 17.255$ (3) Å; $\beta = 103.72$ (2)°; volume = 2125.0 (7) Å^3; $\rho_{\text{obsd}} = \rho_{\text{calcd}} = 1.383$ g cm^{-3} for $Z = 4$. Least-squares refinement of 1549 independent reflections ($I > 2\sigma(I)$), collected on $P\bar{1}$ Syntex diffractometer with graphite-monochromated Cu Kα radiation converged at $R_1 = 0.042$ with anisotropic thermal coefficients for all 32 nonhydrogen atoms and idealized nonvaried coordinates for all 26 hydrogen atoms which were revealed from a difference Fourier map.

(9) See paragraph at end of paper regarding supplementary material.

1:1 mixture of adducts A and B. The less strained compound **9-(*Z*)** shows greater selectivity and gives a single adduct with **10**.

It is remarkable that **3-(*E*)** does not rapidly isomerize to its geometric isomer **3-(*Z*)**. Thus, **3-(*E*)** must lie in an energy well of sufficient depth to prevent isomerization at a rate competitive with its reactions with **10** and *tert*-butyl alcohol. Other examples of intermediates with trans double bonds in six-membered rings are bicyclo[2.2.1]hept-1-ene,[10] adamantene,[11] and the *trans*-cyclohexenones[12] formed in photochemical reactions.

Acknowledgment. This research was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society. The authors also thank Professor Charles Casey for his help and encouragement.

Supplementary Material Available. A listing of atomic parameters and calculated structure factor amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for \$4.00 for photocopy or \$2.00 for microfiche, referring to code number JACS-73-6121.

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[10] (a) R. Keese and E. P. Krebs, *Angew. Chem., Int. Ed. Engl.*, **10** 262 (1971); (b) R. Keese and E. P. Krebs, *ibid.*, **11**, 518 (1972).

[11] (a) D. Lenoir, *Tetrahedron Lett.*, 4049 (1972); (b) D. Grant, M. A. McKervey, J. J. Rooney, N. G. Samman, and G. Step, *J. Chem. Soc., Chem. Commun.*, 1186 (1972); (c) J. E. Gano and L. Eisenberg, *J. Amer. Chem. Soc.*, **95**, 972 (1973).

[12] J. A. Marshall, *Accounts Chem. Res.*, 2, 33 (1969).

[13] NDEA Graduate Fellow, 1969–1970; National Institutes of Health Graduate Fellow, 1970–1973.

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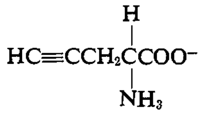
Acetylenic Enzyme Inactivators. Inactivation of γ-Cystathionase, *in Vitro* and *in Vivo*, by Propargylglycine

Sir:

It has previously been shown that the enzyme β-hydroxydecanoylthiolester dehydrase is inactivated by a 3-decynoylthiolester;[1] the basis for inactivation derives from enzymatic abstraction of a C_2 hydrogen as a proton, followed by rearrangement to a conjugated allene which is attacked by a nucleophilic active site histidine.[2]

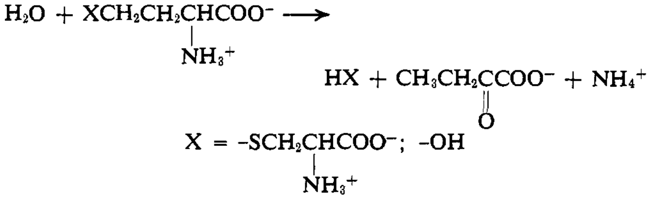
It occurred to us that acetylenic substrate analogs may be generally useful in the inactivation of enzymes which abstract carbon-bound hydrogens as protons at a position adjacent to the acetylenic linkage. Such inactivations are particularly attractive since their specificity is not based merely on structural similarity to substrates but also upon the mechanism of the catalytic process; the acetylenic linkage is made chemically reactive as a result of specific enzymatic action on the inhibitor molecule. These inactivators are therefore not only useful as active site directed reagents for purified enzymes but also as agents for *in vivo* inactivation of the target enzymes.

We have synthesized and tested a number of acetylenic enzyme substrates[3,4] and now report the irreversible inactivation of the pyridoxal phosphate dependent rat liver enzyme, γ-cystathionase, both *in vitro* and *in vivo* by D,L-2-amino-4-pentynoic acid (propargylglycine) (I).[5] γ-Cystathionase catalyzes the elimination of a number or substituents from the γ carbon of susceptible amino acid substrates.[6]



$$HC\equiv CCH_2\overset{H}{\underset{NH_3}{C}}COO^-$$

I



$$H_2O + XCH_2CH_2\underset{NH_3^+}{C}HCOO^- \longrightarrow HX + CH_3CH_2\underset{O}{\underset{\|}{C}}COO^- + NH_4^+$$

$$X = \text{-}SCH_2\underset{NH_3^+}{C}HCOO^-;\ \text{-}OH$$

Incubation of highly purified γ-cystathionase[7] with D,L-propargylglycine produces a time-dependent pseudo-first-order irreversible loss of catalytic activity. At 6.6×10^{-5} M inactivator,[8] the loss of enzymatic activity has a $t_{1/2}$ of 2 min at 25°. Enzymatic activity could not be recovered by dialysis for 12 hr or by gel filtration of the enzyme through Sephadex or by addition of pyridoxal phosphate, suggesting a covalent modification of the enzyme. In support of this idea, incubation of [2-^{14}C]propargylglycine with the enzyme followed by gel filtration on a Sephadex G-25 column resulted in incorporation of radioactivity into the protein peak. One mole of ^{14}C inactivator is incorporated per 80,000 g of protein.[9] (A control experiment in which the bound pyridoxal coenzyme had been reduced by borohydride treatment prior to addition of [^{14}C]-propargylglycine resulted in no radioactivity associated with the protein after gel filtration.) Radioactivity was not removed from the ^{14}C-labeled protein by subsequent dialysis against 6 M urea or 10^{-3} M HCl. These experiments suggest that propargylglycine inactivates γ-cystathionase by covalent modification of

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[1] G. M. Helmkamp, R. R. Rando, D. J. H. Brock, and K. Bloch, *J. Biol. Chem.*, **243**, 3229 (1968).

[2] K. Bloch, *Accounts Chem. Res.*, 2, 193 (1969); K. Bloch, *Enzymes, 3rd Ed.*, **5**, 441 (1971).

[3] C. T. Walsh, A. Schonburnn, O. Lockridge, V. Massey, and R. H. Abeles, *J. Biol. Chem.*, **247**, 6004 (1972).

[4] R. Hevey and R. H. Abeles, unpublished experiments; W. Washtien and R. H. Abeles, unpublished experiments.

[5] DL-Propargylglycine was synthesized by the method of A. C. A. Jansen, R. J. M. Weustink, K. E. T. Kerling, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **88**, 819 (1969) and gave a satisfactory melting point (185–187°), nmr spectra, and chromatographic mobility compared with a sample of authentic L-propargylglycine kindly provided by Dr. H. R. Kaback, The Roche Institute for Molecular Biology, Nutley, N. J.

[6] L. Davis and D. E. Metzler, *Enzymes, 3rd Ed.*, 7, 33 (1972).

[7] γ-Cystathionase, purified and assayed according to D. Greenberg, *Methods Enzymol.*, **5**, 936 (1962).

[8] Inactivation experiments utilized 3–10 units of γ-cystathionase, 4×10^{-5} M 2-mercaptoethanol, 6×10^{-3} M EDTA, and 8×10^{-7} M potassium phosphate (pH 7.5). To this was added varying amounts of propargylglycine or other inhibitors at 25°. At intervals, aliquots were withdrawn and used to assay the remaining enzymatic activity.

[9] A minimum molecular weight of 85,227 has been reported: J. Loiselet and F. Chatanger, *Biochem. Biophys. Acta*, **230**, 434 (1971).