(157 g) in 1 l. of liquid ammonia. A mixture of 3-bromo-1-chloropropane (125 g) and sodium iodide (110 g) was refluxed and stirred for 24 hr in 1 l. of dried acetone. The excess of solvent was then distilled and the cooled residue treated with water. The upper layer was washed, dried, and rectified to yield 140 g (74%) of 5-iodo-1-phenyl-1-pentyne, bp 95–100° (0.05 mm). The iodide (43 g) was added while stirring to silver acetate (27 g) in 150 ml of benzene. After refluxing for 6 hr the cooled mixture was filtered and the benzene was evaporated. Distillation gave 25 g (72%) of 5-acetoxy-1-phenyl-1-pentyne, bp 100–105° (0.05 mm). The ester (25 g) was heated at reflux for 2 hr in a solution of potassium hydroxide (12 g) in water (20-ml)–ethanol (50 ml). Ethanol was removed by distillation and the residue was extracted with ether. The ether extract was washed with dilute acid, water, and dried. Distillation gave 11 g (53%), of 1-phenyl-1-pentyn-5-ol: bp 100–104° (0.04 mm), n^{20}D 1.5765 [lit.[16] bp 122° (2 mm), n^{20}D 1.5769]; ir (neat) 3500, 3200, 3080, 3020, 2220, 1600, 1500, 1060, 750, 690 cm^{-1}; nmr (CCl_4) 1.75 (q, J = 6.5 Hz, 2 H) 2.4 (t, J = 6.5 Hz, 2 H), 3.65 (t, J = 6.5 Hz, 2 H), 4.05 (s, 1 H), 7.1 (m, 5 H).

Preparation of 4-Alkynyl Nitrites.—They were prepared, like alkenyl nitrites,[6c] by alkynol esterification with nitrous acid at 0°.[17] Alkynol (0.2 mol) and sodium nitrite (21 g) were dissolved in water (75 ml). Concentrated sulfuric acid (15 g) in water (10 ml) slowly added with vigorous stirring to the solution maintained at 0° with external cooling and swept by a nitrogen stream. The upper layer was dried and 4-alkynyl nitrites RC≡C(CH$_2$)$_3$-ONO (1) distilled at temperature below 50°. **1a**: (R = H) (70%); bp 35° (25 mm); n^{20}D 1.4168; ir (neat) 3300, 2110, 1640, 1600, 780 cm^{-1}. **1b** (R = CH_3) (66%): bp 42° (15 mm); n^{25}D 1.4309; ir (neat) 2210, 1640, 1600, 700 cm^{-1}. **1c** (R = C_6H_5) (85%, crude because it decomposed by distillation): ir (neat) 2220, 1640, 1600, 790. [All these compounds have characteristic uv absorption spectra of nitrites[18] between 320 and 380 nm (hexane).]

Photolysis of 4-Alkynyl Nitrites.—The nitrite (0.1–0.05 mol) dissolved in 100 ml of benzene was added during 2 hr to 900 ml of benzene irradiated by an inside Hanau TQ 81 lamp provided with a Pyrex filter. A slow stream of nitrogen was maintained before and during the irradiation. The solution was maintained between 10 and 15° by external cooling. The photolysis was followed by uv spectra and carried to 80% completion. Benzene was removed under reduced pressure at temperature below 50°. The residue was distilled and fractions analyzed by vpc (Carbowax 20M). Compounds were isolated by preparative vpc and identified by comparative spectral analysis with authentic samples. Yields were calculated from the weight of nitrite ester used.

Photolyses were also run in the cavity of an epr (Varian E$_3$) apparatus irradiated with an SP 500 Philips lamp. Spectra of nitroxides were observed but these spectra were complex and important modification were observed during and after irradiation, not permitting yet, direct verification of the mechanism proposed as in the photolysis of 4-alkenyl nitrites.[6d]

Photolysis of 4-Hexynyl Nitrite.—As described above 9 g (0.07 mol) of the nitrite was irradiated in 1 l. of benzene for 20 hr. Distillation gave 3.7 g, bp 75–90° (13 mm), and undistillable residue, 1.84 g (21%). Only two compounds could be detected by vpc of the distilled fraction; they were identified after vpc preparative and comparison with authentic samples of 4-hexynol (47%) and γ-butyrolactone (6%).

Photolysis of 5-Phenyl-4-pentynyl Nitrite.—An amount of 9.9 g (0.048 mol) was irradiated in 1 l. of benzene for 60 hr. Distillation gave a first fraction, 0.1 g, bp 36–40° (0.05 mm), a second fraction, 1.9 g, bp 110–115° (0.2 mm), and an undistillable residue, 2 g (20%). Only two compounds were detected in the first fraction, identified as γ-butyrolactone (1%) and benzonitrile (1%). 1-phenyl-1-pentyn-5-ol was the major product of the second fraction (57%).

Photolysis of 4-Pentynyl Nitrite.—As above 6.7 g (0.059 mol) of the nitrite was irradiated for 18 hr. Distillation gave fraction 1, 1.8 g, bp 50–65° (13 mm), fraction 2, 0.7 g, bp 60–65° (0.2 mm), and an undistillable residue, 1.6 g (24%). Fraction 1 was composed of 4-pentynol (32%) and traces of 4-pentynal and unreacted nitrite ester. Fraction 2 was composed of six compounds. Two of them were identified as 4-pentynol (6%) and γ-butyrolactone (2%). The photolysis of 4.13 g (0.047 mol) of 4-pentynyl nitrite in 250 ml of benzene as above but with a plunging lamp, Hanau TQ 150 (150 W), gave still two fractions: fraction 1, 0.7 g, bp 32–50° (0.05 mm), fraction 2, 0.7 g, bp 50–80° (0.05 mm), undistillable residue, 1 g (24%), 4-pentynal (4%), 4-pentynol (16%), and traces of nitrite ester composed the first fraction. Six compounds were present in the second fraction, two of them were identified as 4-pentynol (7%) and γ-butyrolactone (traces).

Photolysis of 7.83 g of nitrite ester in 1 l. of benzene with a TQ 81 lamp as above but with a quicker stream of nitrogen gave 4-pentynal (8%) and 4-pentynol (23%) in fraction 1. In fraction 2, the proportion of two unidentified compounds increased but γ-butyrolactone could only be detected. When the stream of nitrogen was replaced by nitric oxide we observed the formation of γ-butyrolactone (2.2%), 4-pentynal (traces), 4-pentynol (10%), four unidentified compounds, and polymeric material (40%).

Registry No.—**1a** (R = H), 30428-24-1; **1b** (R = CH_3), 34886-47-0; **1c** (R = Ph), 34886-48-1; 5-chloro-1-phenyl-1-pentyne, 24463-87-4; 5-iodo-1-phenyl-1-pentyne, 34886-50-5; 5-acetoxy-1-phenyl-1-pentyne, 29313-49-3; 1-phenyl-1-pentyn-5-ol, 24595-58-2.

(16) A. S. Atavin and N. V. Egorov, *Khim. Atsetilena, Dokl. Vses. Nauch. Konf., 1965*, 17 (1968) [*Chem. Abstr.*, **71**, 70,019c (1969)].

(17) C. S. Coe and T. F. Doumani, *J. Amer. Chem. Soc.*, **70**, 1516 (1948).

(18) C. H. Purkis and H. W. Thompson, *Trans. Faraday Soc.*, **32**, 1466 (1936).

A Terminology for the Chiral Attributes of Steric Elements[1]

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In a recent analysis of stereoisomerism we concluded[2] that the conventional types of stereoisomerism (the center, axis, plane, "conformational helix," and cis–trans isomerism at double bonds)[3,4] could be reduced to two elements, the center and the line of torsion, and that these elements of stereoisomerism may possess or lack one or both of two distinct chiral characteristics. The first of these determines whether the configuration of the element by itself has to be specified with a chiral descriptor and the second whether the element can contribute to the chirality of a compound. Either of these tests may be thought to be suitable for determining the chiral character of the element. We suggested, at least as a temporary expedient, to call an element chiral if it meets both of these tests, as this would preserve existing practices. The problem of selecting the most useful criterion for a chiral element, however, remained unsolved. We now find that the need for making this difficult choice would be avoided

(1) Supported in part by Grants AM 9105 and K6-AM-14367 from the National Institutes of Health (H. H.), and GB 29021-X from the National Science Foundation (K. R. H.).

(2) H. Hirschmann and K. R. Hanson, *J. Org. Chem.*, **36**, 3293 (1971). This paper should be consulted for the definition of all terms and symbols not explained in this note.

(3) R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385, 511 (1966).

(4) IUPAC Tentative Rules for the Nomenclature of Organic Chemistry. Section E. Fundamental Stereochemistry: *J. Org. Chem.*, **35**, 2849 (1970).

and the discussion of both relevant properties would be facilitated if we had two separate and concise terms to characterize all elements of stereoisomerism that meet one or the other of these tests. Accordingly we propose to call an element *graphochiral*[5] if its configuration, viewed apart from that of any other element of the same molecule, can be specified only by a chiral descriptor, and *pherochiral*[5] if the element would contribute to the chirality of a chiral molecule. Operational definitions of these and of related terms follow. They utilize the same criteria that were presented before[2] and are stated here in a manner applicable to all elements, on the understanding that the atom at a center of stereoisomerism or of prostereoisomerism represents the core of these elements.

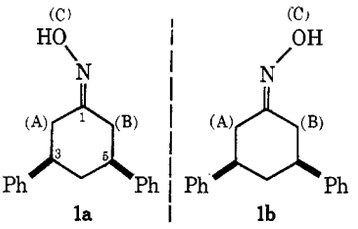
An element of stereoisomerism is graphochiral or agraphochiral, respectively, if its assembly of differentiated atoms ([3], [14])[2] cannot or can be superposed on its mirror image. An element of prostereoisomerism ([8], [16])[2] or an agraphochiral element of stereoisomerism is prographochiral if there are linked to the core two superposable *cf*-ligands ([2], [13])[2] so located that the element would be graphochiral if one of these ligands were considered to be different from all others.

An element of stereoisomerism is pherochiral or apherochiral, respectively, if its assembly cannot or can be superposed on the assembly of corresponding atoms ([5], [15])[2] derived from the reflected model. An element of prostereoisomerism is propherochiral if it should become pherochiral on assuming that one of a pair of equivalent proximal atoms is different from all others in the assembly.

To make the concept fully effective, a correlation is needed between the pherochirality of the individual elements and the chirality of the whole structure. This relationship can be expressed as follows. A compound is chiral if it contains a pherochiral element of stereoisomerism that cannot be paired within the same molecule with another element whose *cf*-ligands can be superposed after a reflection upon the *cf*-ligands of the first.

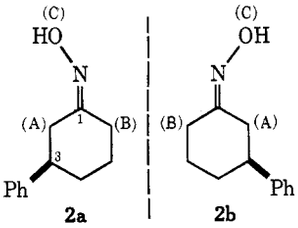
As before,[2] only those elements of stereoisomerism that are both graphochiral and pherochiral are designated as chiral, all others as achiral. The retention of these simpler terms is desirable because in the vast majority of cases an element that meets one test for chirality also meets the other. The exceptions to this rule always involve elements with at least one pair of enantiomeric ligands. Similarly elements of prostereoisomerism are called prochiral, if they are both prographochiral and propherochiral. They are called proachiral if they are "not prographochiral" and/or "not propherochiral." Consequently, there is no conflict between this supplement and any of the statements of the earlier paper.[2]

Application of these new terms will be illustrated by compounds **1**–**4**. In analyzing **1a**[6] one first identifies its elements of stereoisomerism (factorization). These



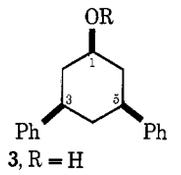
1a

1b

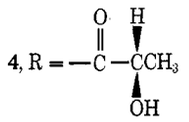


2a

2b



3, R = H



4, R = —C—CCH$_3$

are the most compact parts of the structure for which one has to define the spatial distribution of the bonds to the individual ligands in order to differentiate the compound from its stereoisomers. The elements of **1a** are two centers C-3 and C-5 which are chiral, and the C=N double bond. To examine this last element one replaces its three *cf*-ligands by three points which are all distinct (A, B, C) as the ligands represented by the points are not superposable. The assembly consisting of C=N and of the three points which we have called the differentiated proximal atoms[2] has a plane of symmetry, as all atoms of the assembly lie in this plane. The element represented by this assembly is, therefore, agraphochiral. As the assembly cannot be superposed on the assembly derived from the enantiomer **1b** with all corresponding atoms coinciding, the double bond is pherochiral. The description of the double bond as agraphochiral and pherochiral brings out the unusual relationship between **1a** and **1b**. They are enantiomers which can be distinguished by a pair of achiral descriptors (*Z* and *E*)[4] because they are also cis–trans isomers. If we merely designate the double bond of **1a** as achiral we would obscure an important difference from **2a**, which derives its chirality only from the chiral center C-3 as its other element of stereoisomerism, the double bond, is both agraphochiral and apherochiral. Factorization of the stereoisomerism of **3** shows three elements which are all centers. Those at C-3 and C-5 are chiral as in **1**, whereas that at C-1 is graphochiral and apherochiral. Therefore, as for the double bond in **1a**, the chirality of C-1 of **3** is incomplete but the combination of properties is the reverse of that found for the double bond. This combination of graphochirality and apherochirality fully characterizes all elements traditionally designated as pseudoasymmetric. As expected for a graphochiral center, it requires a chiral descriptor (*e.g.*, *s*) to specify its configuration without relating it to the configurations of the two other centers. The further conclusion that C-1 is apherochiral is consistent with the achirality of **3**, as any compound with an odd number of pherochiral elements is necessarily chiral. However, it is not essential for a compound to be achiral in order to have such an apherochiral element. The character of C-1 remains un-

(5) The prefix grapho is derived from the Greek verb graphein, to write, which was used by Greek mathematicians in the sense "to describe a figure." The prefix phero is derived from the Greek pherein, to bear, to cause. It seems appropriate as "phore," which is derived from the same root, is used in the same sense in chromophore.

(6) Compound **1** is a close analog of one prepared and resolved by R. E. Lyle and G. G. Lyle, *J. Org. Chem.*, **24**, 1679 (1959), to serve as a first example of what they called "geometrical enantiomorphic isomerism." The term shows how blurred the traditional distinction between geometrical and optical isomerism has become and that a classification of the elements of stereoisomerism requires terms that are mutually exclusive in all situations.

changed, but the plane of symmetry is lost if the hydroxyl group of **3** is esterified (as in **4**) with (*S*)-lactic acid.

In our full paper[2] we summarized the classification of steric centers by a chart which separated centers of stereoisomerism into chiral and achiral and then subdivided the achiral centers into those having and not having chiral configurations. Centers of prostereoisomerism were treated in an analogous manner. This classification brought out pherochiral properties only if the element was also graphochiral (and propherochiral properties only if it was also prographochiral). The present terminology[7] is therefore better balanced and it allows one to focus on the relevant property, as we have illustrated in discussing examples **1–4**.

(7) Of the examples listed in Chart 1,[2] Cghij, $Cg^{+}g^{-}hi$, **8a–c,f,g** are graphochiral; tetragonal Xghij, octahedral Xgghgig, **8d, e, h** are agraphochiral. (Of this last group **8d, e, h** can be further classed as prographochiral whereas the two others are not prographochiral.) Cgghi and $Cggh^{+}h^{-}$ are prographochiral; tetragonal Xgggh and octahedral Xgggggh are not prographochiral. In the alternative classification Cghij, **8a–e** are pherochiral; $Cg^{+}g^{-}hi$, tetragonal Xghij, **8f–h** and octahedral Xgghgig are apherochiral; Cgghi is propherochiral; $Cggh^{+}h^{-}$, tetragonal Xgggh, and octahedral Xgggggh are not propherochiral.

Potential Inhibitors of L-Asparagine Biosynthesis. I. β-Elimination Reactions with β-Hydroxyaspartic Acid Derivatives[1a,b]

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In the course of a study aimed at preparing irreversible inhibitors of the enzyme L-asparagine synthetase we observed a β-elimination reaction with derivatives of β-hydroxyaspartic acids, the results of which form the text of this paper.

In view of the usefulness of the diazoacetate group in the design of irreversible enzyme inhibitors, we attempted to synthesize the *O*-diazoacetyl derivative of both *threo*- (**1a**) and *erythro*-β-hydroxyaspartic acid (**1b**). Initially we began with **1a** since it was readily obtainable,[2] whereas **1b** was more difficult to obtain. Because of contradictory reports[2,3] concerning the stereospecific synthesis of **1a** and **1b**, we used two methods to ascertain their stereointegrity, namely a chemical vanadate test[4] and analysis *via* an automatic amino acid analyzer;[5] both confirmed the stereopurity of **1a** and **1b**.

(1) (a) This work was supported by Grant M-28 from the Health Research and Services Foundation, Pittsburgh, Pa., and Grant CA-11714 from the National Cancer Institute, NIH, Bethesda, Md. (b) Presented in part at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, Medi 26. (c) Taken in part from the M.S. Dissertation of B. S. P., University of Pittsburgh, July 1971.

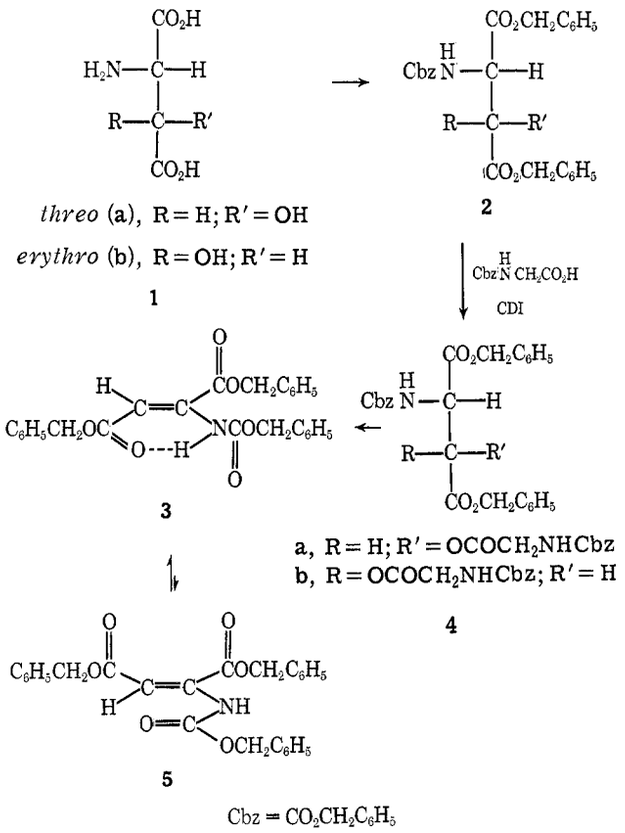
(2) C. W. Jones, III, D. E. Leyden, and C. H. Stammer, *Can. J. Chem.*, **47**, 4363 (1969).

(3) H. Okai, N. Imamura, and N. Izumiya, *Bull. Chem. Soc. Jap.*, **40**, 2154 (1967).

(4) Y. Liwschitz, Y. Robinson, and A. Haber, *J. Chem. Soc.*, 3589 (1962).

(5) Recorded on a Beckman Model 116 A.A.A. The authors thank Mr. J. P. Vergnes, Department of Biochemistry, University of Pittsburgh, for these determinations.

The amino function of **1a** was readily protected by carbobenzoxylation followed by esterification of the carboxyl groups to give **2a**.[6] Esterification of **2a** with carbobenzoxyglycine in the presence of the condensing agent *N*,*N*′-carbonyldiimidazole (CDI)[7] afforded an oil which, according to tlc, was composed of three components. Separation by preparative tlc afforded starting material, the supposed **4a**, and compound **3**, a product of β elimination. Compound **4a** could not be



Cbz = $CO_2CH_2C_6H_5$

crystallized and attempts to prepare an analytical sample failed because of a tendency for it to decompose to **3**. The tentative assignment of the structure for **4a** was based on nmr data [δ 3.88 (d, CH_2 of glycyl, singlet after shaking with D_2O), 5.65 (m, β-H)] and the fact that stirring **4a** in THF with imidazole (this base is a side product of reactions with CDI) readily affords some of compound **3**.

By a scheme similar to that used in the threo series, **2b** was obtained in a 72% overall yield from **1b**. In an attempt to synthesize the coupled product **4b**, similar results were obtained using CDI and carbobenzoxyglycine, namely, small amounts of starting material and unsaturated **3** were obtained and the major product presumably was **4b**. The latter was noncrystalline and attempts to prepare an analytical sample caused some decomposition to **3**. The tentative assignment of the structure for **4b** was based on nmr data [δ 3.92 (d, CH_2 of glycyl) and 5.66 (m, β-H)]. Furthermore, stirring the supposed **4b** in THF with imidazole very slowly (in contrast to the facile **4a**) formed some of **3**. As a control experiment both **2a** and **2b** were separately stirred with imidazole but only

(6) Y. Liwschitz and A. Singerman, *J. Chem. Soc.*, 1696 (1967); H. Okai and N. Izumiya, *Bull. Chem. Soc. Jap.*, **42**, 3550 (1969).

(7) H. A. Staab, *Angew. Chem., Int. Ed. Engl.*, **1**, 351 (1962).