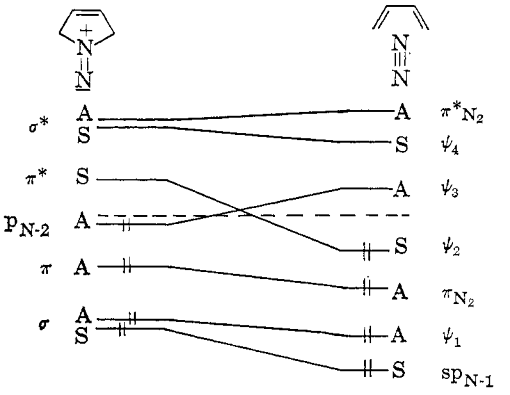


Figure 2. Axisymmetric fragmentation (orbital symmetries are given with respect to C_2).

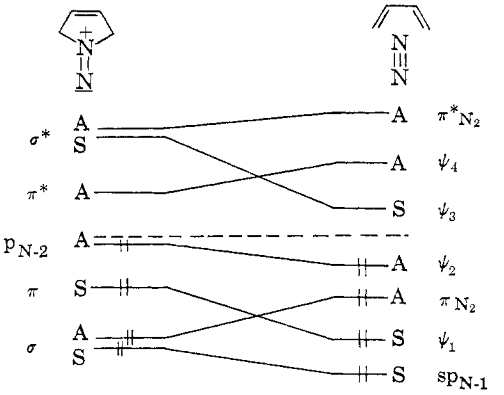
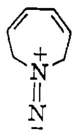


Figure 3. Sigmasymmetric fragmentation (orbital symmetries are given with respect to σ_v).

To be sure, the great majority of concerted cycloadditions and their *retro* counterparts should occur sigmasymmetrically because orbital overlap and steric problems make the axisymmetric transition state energetically inaccessible. The observed *cis* (sigmasymmetric) course of the Diels–Alder reaction, for example, is presumably attributable to these factors, for orbital symmetry considerations do not favor *cis* over *trans* addition. We wish to underline the possibility that *certain cycloadditions (or the corresponding fragmentations) may occur axisymmetrically, viz.*, those having (1) a bonding–antibonding correlation along the sigma-, and only the sigmasymmetric pathway, and (2) reasonable geometry for the axisymmetric transition state. A case in point is the decomposition of the yet unknown diazene 7, a vinylog of those discussed above.

The fragmentation stereochemistry of compounds which may elect the axially symmetric course is currently under investigation in our laboratory.



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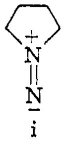
(11) Interestingly, decomposition of 3-cyclopentenones into carbon monoxide and dienes is predicted to occur in this fashion not only thermally, but in the photoexcited (n, π*) state as well.

(12) Concerted disintegration of i into ethylene and nitrogen (*via* a planar transition state) involves no bonding–antibonding correlation, and indeed the experimental evidence leaves little doubt that the three bond cleavages occur simultaneously (D. M. Lemal, T. W. Rave, and S. D. McGregor, *J. Am. Chem. Soc.*, **85**, 1944 (1963)).

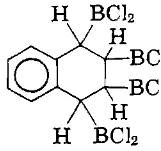


i

The Addition of B_2Cl_4 to 1,3-Cyclohexadiene and the Structural Similarity of the Adduct to That Formed between B_2Cl_4 and Naphthalene

Sir:

Until now, support for the structure proposed by Fox and Wartik[1] for the adduct between naphthalene and diboron tetrachloride ($C_{10}H_8 \cdot 2B_2Cl_4$) has been largely chemical in nature. The evidence was interpreted to favor a product involving four BCl_2 groups attached to a saturated ring, while the other ring retained its aromatic character. We have now prepared another organic polydichloroboryl compound using a synthetic route expected to lead to a molecule structurally similar to that postulated for the right-hand ring of I. The infrared and nuclear magnetic resonance spectra of the new molecule and of I lend strong support to the earlier structural views.



I

The new compound, 1,2,3,4-tetrakis(dichloroboryl)cyclohexane, was produced by allowing a mixture of B_2Cl_4 (26.6 mmoles) and 1,3-cyclohexadiene (8.45 mmoles) to warm slowly from −80° to room temperature over a period of about 10 days in approximately 20° intervals. At the first appearance of the characteristic red color which signaled the decomposition of the excess B_2Cl_4, the reaction was terminated. Repeated molecular distillation of the crude product, an orange oil, yielded approximately 250 mg of a wet, orange, crystalline material which underwent rapid thermal decomposition above about 100° and which was extremely sensitive to air and moisture. The 2:1 reaction stoichiometry was supported both by the mole ratio of reactants consumed ($2.12B_2Cl_4$ to $1.00C_6H_8$) and, more reliably, by elemental analysis after treatment with fuming nitric acid at 350° in a sealed tube. *Anal.* Calcd for $C_6H_8 \cdot 2B_2Cl_4$: B, 10.6; C, 17.7; Cl, 69.7. Found: B, 10.9; C, 17.9; Cl, 70.0.

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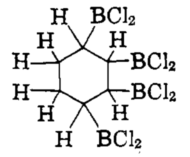
[1] W. B. Fox and T. Wartik, *J. Am. Chem. Soc.*, **83**, 498 (1961).

The infrared spectrum (KBr smear) of the new polydichloroboryl compound exhibits features expected of a molecule with the structure



II

and, in addition, is similar in many ways to the spectrum of I. Both spectra are shown in Figure 1. It will be noted that the chief differences are those attributable to the aromatic ring present in I but absent in II (the aromatic C—H stretch at 3010 cm^{-1}, C=C vibrations in the region 1610–1430 cm^{-1}, and possibly C—H out-of-plane bending below 800 cm^{-1}).[2] Spectra for both I and II revealed aliphatic C—H absorptions below 3000 cm^{-1} as well as the characteristic BCl_2 stretching vibrations between 850 and 1000 cm^{-1}.[3]

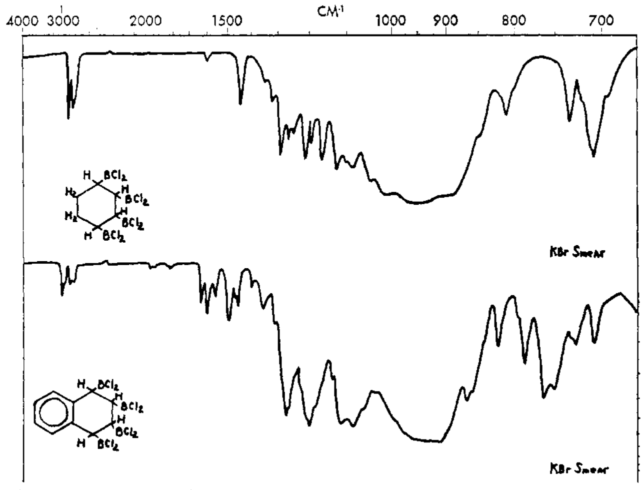


Figure 1. Comparison of the infrared spectra of I (bottom) and II (top).

The proton nmr spectra of compounds I (neat, supercooled liquid) and II (in dry Spectrograde carbon tetrachloride) are shown in Figures 2 and 3. Tetramethylsilane is used as an external reference. The spectrum of I (Figure 2), consisting of three lines with chemical shifts and relative peak intensities as indicated in Table I, is in agreement with the proposed structure, in which the dichloroboryl groups occupy either a–e–e–a or e–a–a–e positions. This structure gives rise to two pairs of nonequivalent aliphatic protons (δ_{H_a} = 3.18; δ_{H_b} = 3.79). Proton H_b would be expected to appear downfield from H_a owing to deshielding by the vacant p orbitals on the adjacent boron as well as on the two near-neighbor boron atoms. Proton H_a, on the other hand, is in a deshielding environment of one adjacent boron, one near-neighbor boron, and the aromatic ring. The magnitude of the latter effect depends on the position of H_a relative to the center of the benzene ring.[4]

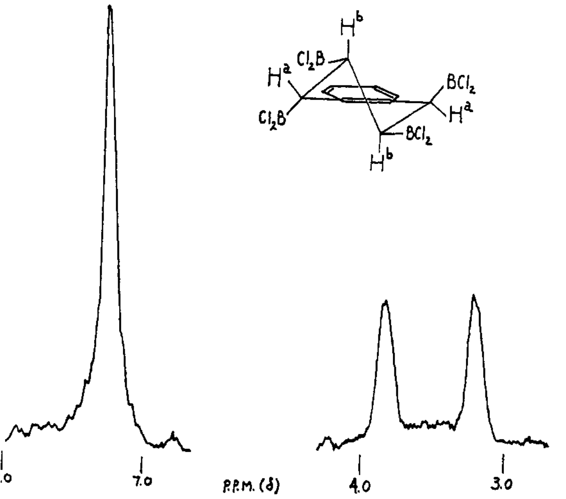


Figure 2. Proton nmr spectrum of adduct I (supercooled liquid) relative to TMS.

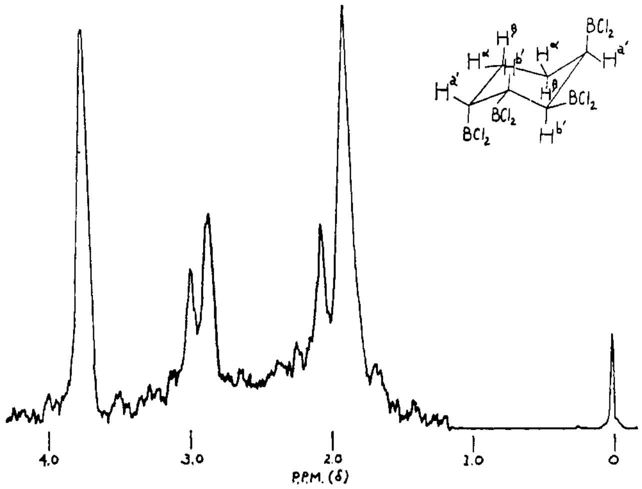


Figure 3. Proton nmr spectrum of adduct II (in dry CCl_4) relative to TMS.

The above assignments are consistent with the proton magnetic resonance spectrum of II (Figure 3) where the environment about $H_{b'}$ would be expected to remain essentially unchanged (δ_{H_b} = 3.79; $\delta_{H_{b'}}$ = 3.78). Proton $H_{a'}$ no longer experiences a ring anisotropic effect and is, therefore, shifted upfield. The areas under these two proton bands are not exactly equivalent; however, the sum of the relative intensities of the two high-field peaks is identical, within experimental

Table I. ^1H Nmr Assignments and Relative Peak Intensities for Compounds I and II

	δ, ppm	Rel peak intensity
	Compound I	
H_a	3.18	1.05
H_b	3.79	1.00
$H_{aromatic}$	7.20	2.00
	Compound II	
$H_{a'}$	1.92	
$H_{b'}$	3.78	1.00 } 1.96
H_α	2.92[a]	1.00 }
H_β	2.02	
$J_{\alpha\beta}$	7 cps	

[a] Determined from center of gravity corrections. The assignment of H_α, rather than H_β, to the larger of two shifts is arbitrary.

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(2) L. J. Bellamy, "The Infrared Spectra of Complex Organic Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958.

(3) L. P. Lindeman and M. K. Wilson, *J. Chem. Phys.*, **24**, 242 (1956).

(4) L. M. Jackman, "Applications of N.M.R. Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1962, pp 89–90.

error, with the sum of the three peaks lying downfield, indicating that the doublet at 2.92 ppm is half of a symmetrical AB system ($J_{H\alpha\beta}/\Delta\nu = 0.13$) associated with protons H_α and H_β, one variety *cis* and the other *trans* to a BCl_2 group. The postulated overlap in the assigned $H_{a'}$ peak is verified by the intensity ratio of the resolved doublet at 2.92 ppm (calcd, 1.27; found 1.28).[4]

In the above discussion it has been assumed that both adducts are single, crystalline isomers, resulting from *cis* addition of B_2Cl_4 to the carbon–carbon π bonds of a conjugated system. That such an interpretation is correct is implied by the simplicity of the proton resonance spectra of these adducts. Further, in the case of adduct I, the relatively narrow melting range (46.5–47.5°) supports this view. (This latter criterion could not be applied to adduct II which, as mentioned above, decomposes before its melting point.)

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Received January 8, 1966

Racemization Control in the Synthesis of Peptides by the Mixed Carbonic–Carboxylic Anhydride Method

Sir:

Of presently known methods for forming the peptide bond, only the azide procedure is considered to be safe to use to avoid racemization in sensitive cases.[1] Consequently, the synthesis of peptides by the stepwise addition of amino acids to the amino end of the growing peptide chain has become the most common procedure, because racemization is unlikely when commonly used amino-protecting groups and methods for forming the peptide bond are used. Since the azide procedure has limitations,[2] reliable methods of coupling suitably protected peptides are badly needed to avoid the inherent disadvantages of the stepwise approach, particularly when long-chain peptides are desired. Our reinvestigation of the mixed carbonic–carboxylic anhydride procedure,[3] briefly reported here, indicates that it might fill the need when reaction conditions are suitably controlled.

We have recently reported[4] that racemization is proportional to the time allowed for mixed anhydride formation (activation time), using our test system of forming the mixed anhydride between Z-Gly-L-Phe-OH and ethyl carbonate by the reaction of ethyl chloroformate with the dipeptide derivative in the presence of triethylamine, adding H-Gly-OEt, isolating Z-Gly-Phe-Gly-OEt, and separating the racemate by fractional crystallization from ethanol. Since yields are a little better if isobutyl chloroformate is the reagent,[5] we have subsequently used this compound routinely. Although several other solvents have given good results, tetrahydrofuran was used in the experiments reported here.

The most important factor has been found to be the nature of the tertiary amine used. Most of our studies have been done at a reaction temperature of −15°. Yieldwise, optimum activation times vary with the tertiary amine used; with 1 equiv of amine, a 4-min activation time is more than adequate for any useful amine. We have routinely allowed 12 min before adding the ethyl glycinate in order to exaggerate racemization when it occurs. Workup of reaction mixtures was the customary removal of solvent under vacuum, solution of the product in ethyl acetate, and washing of this with water, bicarbonate solution, water, 1 *N* hydrochloric acid, and water. After drying over sodium sulfate, the ethyl acetate solution was concentrated under vacuum and the crystalline product was fractionally crystallized from a 2% solution in ethanol.

Under the above conditions, racemization could not be avoided completely when triethylamine was used. With trimethylamine, using exactly 1 equiv or a 5% excess of isobutyl chloroformate to ensure no excess of the amine, a 90% yield of pure Z-Gly-L-Phe-Gly-OEt was obtained and no racemate; in contrast, with 2 equiv, only a trace of L isomer was obtained, but 68% of DL isomer was isolated.

Another test was the synthesis of For-Phe-Gly-OEt (L) in 82% yield with no racemization by the use of 1 equiv of $(CH_3)_3N$ with 10% excess of isobutyl chloroformate, and a 1.5-min activation time at −6°; Sheehan and Yang[6] reported a 50% yield of racemate by a conventional mixed anhydride procedure, and they were unable to avoid racemization by changing reaction conditions. Likewise, Z-Val-Tyr-Ileu-OMe was obtained by us in 84% yield without racemization, whereas Schwarz and Bumpus[7] reported considerable racemization.

Of numerous aliphatic tertiary amines, those containing at least one methyl group were generally useful in giving good yields and no racemate when not used in excess, and those not containing a methyl group were not, indicating the importance of steric factors. It was now of interest to test inductive effects. One amine tested, N-methylmorpholine, was found to give 94% yields of pure L peptide and no DL when either 1 or 2 equiv was used. Several other promising amines are being investigated.

Williams and Young[8] have found that benzoyl-L-leucine is more readily racemized than Z-Gly-L-Phe-OH and have developed as a test system the activation of this compound and subsequent reaction with H-Gly-OEt. The amount of racemate present in the resulting Bz-Leu-Gly-OEt is estimated by comparing the optical rotation with that of the pure material and by saponifying and fractionally crystallizing the resulting Bz-Leu-Gly-OH. We have found that when small amounts of racemate are present in the ester, these may be detected by ether extraction and fractionally crystallizing the

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(1) E. Schröder and K. Lübke, "The Peptides," Vol. 1, Academic Press Inc., New York, N. Y., 1965, p 326. Abbreviations used here are standard, and are described in this book.

(2) Reference 1, p 82.

(3) T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951); R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); J. R. Vaughan, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **73**, 3547 (1951).

(4) G. W. Anderson, F. M. Callahan, and J. E. Zimmerman, *Acta Chim. Hung.*, **44**, 51 (1965).

(5) J. R. Vaughan, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **74**, 676 (1952).

(6) J. C. Sheehan and D-D. H. Yang, *ibid.*, **80**, 1154 (1958).

(7) H. Schwarz and F. M. Bumpus, *ibid.*, **81**, 890 (1959).

(8) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963).