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Boron Hydride Derivatives for Neutron Capture Therapy. Antibody Approach

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A number of borane derivatives which have potential use in binding to proteins for neutron capture therapy have been synthesized from orthocarborane ($C_2B_{10}H_{12}$) and from decahydrodecaborate(2−). These modifying reagents contain either amine, imido ester, or aldehyde functions and are solubilized by ionic centers. Additional derivative chemistry of orthocarborane is reported. In particular, a six-membered ring amide carborane synthesized here is shown to resist hydrolysis under drastic acidic conditions.

The potential use of ^{10}B in neutron capture therapy of glioblastoma[1,2] is based on the ability of the ^{10}B nucleus to absorb thermal neutrons and undergo fission. The α particle produced by fission dissipates its ionizing energy within several cell diameters,[3,4] thereby localizing the destruction of cells.

Successful therapy depends on the selective incorporation of ^{10}B into tumor tissue after intravenous injection of the boron compound. The tumor/normal tissue and tumor/blood ratios of ^{10}B must be large to minimize injurious effects to healthy cells. Past efforts to localize boron compounds in the tumor have centered mainly on the use of boron hydrides containing functional groups capable of cellular interactions.[5-8]

The use of antibodies as specific tumor localizing agents has also been suggested.[1] A study involving the binding of diazotized 1-(4-aminophenyl)-1,2-dicarba-*closo*-dodecaborane(12) to a specific antibody and the subsequent neutron-initiated destruction of cells (*in vitro*) bound with this boron-labeled antibody has shown the feasibility of using antibodies as carriers of boron to tumor cells.[9] Preliminary binding results have also been reported by Mallinger and coworkers.[10] Work at Massachusetts General Hospital has indicated that only several molecules of diazotized 1-(4-aminophenyl)-1,2-dicarba-*closo*-dodecarborane(12) could be bound per molecule of antibody.† Assuming that 15 μg of ^{10}B per gram of tumor tissue is needed for successful therapy[11] and that the tumor has antigenic sites,[12] it can be estimated‡ that, for effective treatment, the number of polyhedral cages (containing ten ^{10}B) bound per protein must be one to two orders of magnitude greater than the binding results mentioned above.[9,10,†]

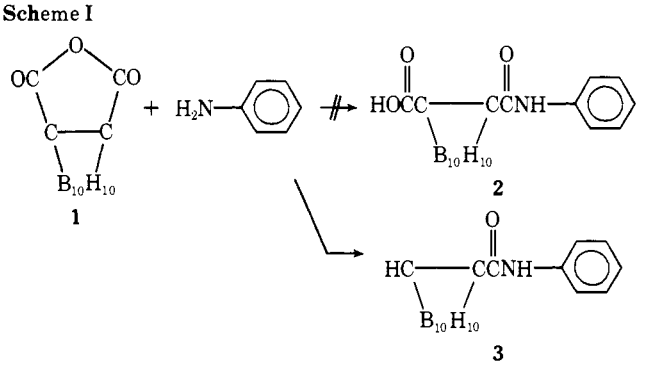
The low binding limit of diazotized 1-(4-aminophenyl)-1,2-dicarba-*closo*-dodecaborane(12) to antibody consisting primarily of IgG might be attributed either to the lowering of the already slight solubility of IgG[13] by the hydrophobic carborane or to the limited number of amino acid side chains modified by the diazonium reagent. Further study of the binding of modification reagents containing borane cages should lead to the synthesis of binding reagents which have better solubility properties and which bind more extensively.

We report here the syntheses of potential protein-modifying reagents containing borane cages. The solubilities of these reagents are enhanced by ionic centers. A variety of functional groups capable of reacting with various amino acid residues are attached to carboranes and borane anions (Table I). Inasmuch as expensive ^{10}B-enriched carborane may have to be used for neutron capture therapy, attention has been given to high-yield routes for chemical syntheses.

Chemistry. The literature contains numerous examples of chemical modifications of antibodies.[14-20] Perhaps the most promising, and certainly the most extensive, have been the modifications of ϵ-amino groups of lysine in IgG antibodies. These modifications produced only small effects on antigen binding and on protein solubility. Potentially, other amino acid residues are also susceptible to extensive modification (Table I). For example, diazonium ions have been found to modify tyrosine, histidine, amino, guanidino, and indole residues.[21,22]

Diazonium reagents can be prepared from the arylamine.[23] Carborane-1,2-dicarboxyanhydride (compound 1) was allowed to react with aniline (Scheme I). The purpose

Scheme I



† A. Soloway and J. Messer, private communication.

‡ C. Dohen, Massachusetts General Hospital, Boston, private communication.

Table I. Several Protein Modification Reagents and Their Reactions[a]

No.	Name	Residues modified
1	Diazonium ion	Lysine, histidine, tyrosine, guanidino, indole
2	Amine and carbodiimide	Aspartate, glutamate
3	Imido ester	Lysine

No.	Reaction[b,c]
1	$ArNN^+ + NH_2—P \longrightarrow ArNNH—P$
2	$RNH_2 + HOC—P + EDC \longrightarrow RNH—C—P + EDC$
3	$RC(=NH_2^+)—OR' + NH_2—P \longrightarrow RN(NH_2)=N—P$

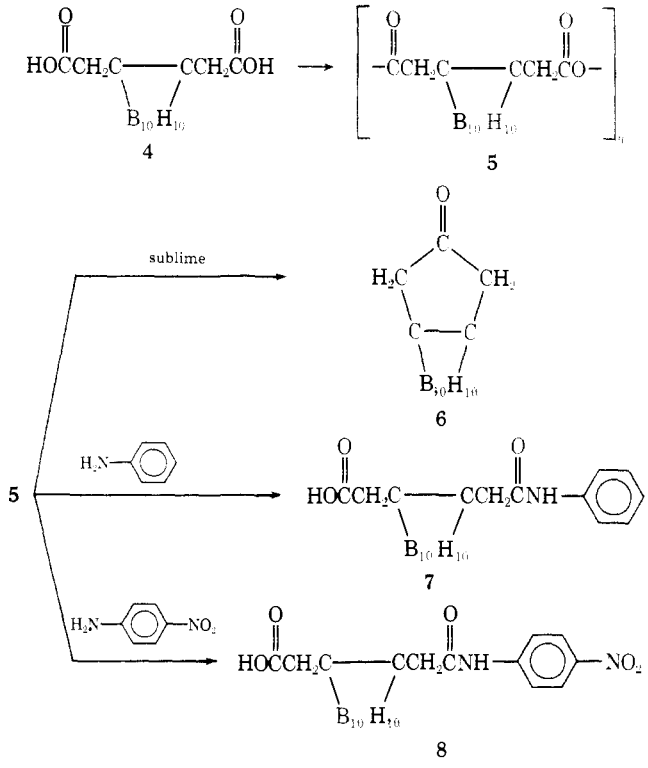
[a] G. E. Means and R. E. Feeney, "Chemical Modification of Proteins," Holden-Day, Cambridge, Mass., 1971. [b] Only one exemplary reaction was given when several are possible. [c] P represents a protein.

was to obtain compound **2** for conversion[24] to an arylamine acid carborane. However, this reaction did not yield **2** as might have been expected, but instead gave a decarboxylated product **3**, which had been prepared by other methods.[23] Similar decarboxylation under basic conditions has been observed with 1-phenylcarborane-2-carboxylate.[25] Carborane-1,2-dicarboxyanhydride (compound **1**) is "self blocked" carborane-1,2-dicarboxylic acid.[26] Reaction Scheme I is an example where "self blocking" of two identical functions on symmetry-related carbons of orthocarborane can subsequently differentiate the original two identical functions.

In order to ameliorate the electron-withdrawing effects of the α-carborane on the carboxyl group,[27] the synthesis of the orthocarborane analog (compound **5**) of adipic anhydride was investigated. Here, there is a methylene group between the carboxyl function and the orthocarborane cage. The chemically analogous polymeric and monomeric adipic anhydrides have been made by the reaction of adipic acid and acetic anhydride.[28,29] Similarly, 1,2-bis(carboxymethyl)carborane (compound **4**) was allowed to react with acetic anhydride to yield a mixed polymeric anhydride (compound **5**) shown in Scheme II. A slight weight increase in the flask of **5** over **4** indicated that the anhydride was not pure polymeric bis(carboxymethyl)carborane anhydride. When **5** was sublimed, 1,2-(2-oxopropylene)carborane (compound **6**) was formed, not the monoanhydride, similar to the use of acetic anhydride to make cyclopentanone derivatives.[28,29] Actually, five-membered exopolyhedral rings often form with orthocarborane.[26] On the other hand, the possible anhydride monomer of 1,2-bis(carboxymethyl)orthocarborane has indeed been reported as a by-product in another synthesis of 1,2-(2-oxopropylene)carborane (compound **6**).[30] Returning now to Scheme II, we find that when **5** is allowed to react with aniline and *p*-nitroaniline, the respective monoamides **7** and **8** are formed in low yield. Variation of conditions did not increase the overall poor yield of **8** from orthocarborane. Hence, we did not investigate the hydrogenation of this nitro derivative to the amino derivative but instead turned our efforts toward a more direct, high-yield route to a solubilized aminophenylcarborane.

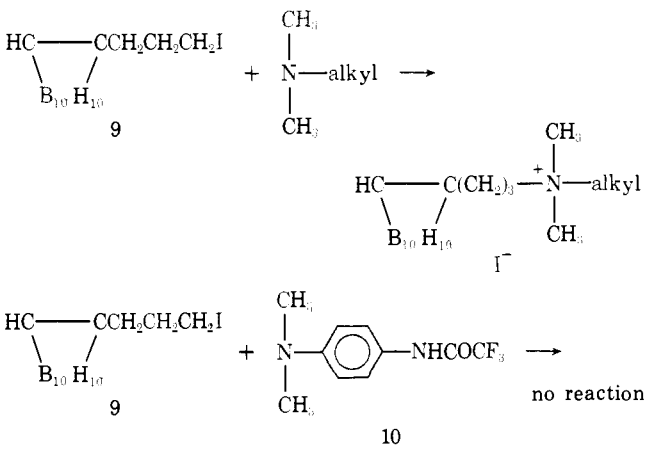
Scheme III shows a general method that we developed for the overall high-yield synthesis of several compounds that can bind to proteins. A dimethylaminoalkyl was re-

Scheme II



fluxed in benzene with γ-iodopropylorthocarborane (compound **9**).[31] After several days, the pure product precipitated. The reaction did not work with less nucleophilic arylamines. For example, no product was formed when *p*-(*N,N*-dimethylamino)-2,2,2-trifluoroacetanilide (**10**) was refluxed in benzene with **9** for 2 days. Also, the reaction of dimethylaminoalkyls with γ-iodoethylorthocarborane did not proceed. Probably, displacement of the iodide in γ-iodoethylorthocarborane was retarded by inductive and steric effects of the carborane cage. Primary or secondary alkylamines could not be used because they degraded the cage.

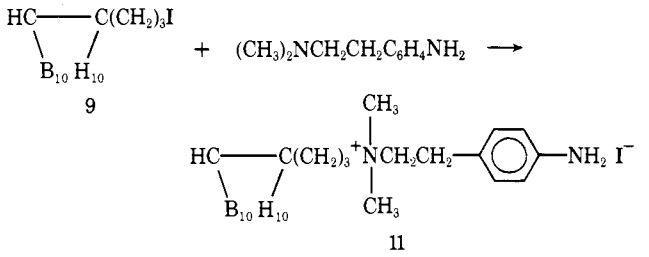
Scheme III



In Scheme IV, an arylamine capable of forming a diazonium ion was produced in 95% yield from the reaction of **9** with p-$NH_2C_6H_4CH_2CH_2N(CH_3)_2$.[32] This reaction takes advantage of the difference in reactivities of the aryl- and alkylamines. The chloride salt is slightly soluble in H_2O.

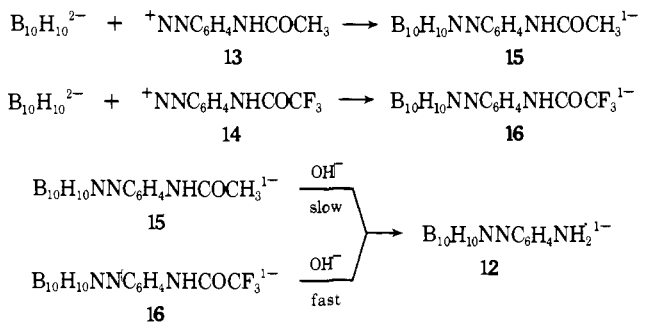
An azoarylamine derivative (compound **12**) of $B_{10}H_{10}^{2-}$

Scheme IV



was prepared, as shown in Scheme V, for possible conversion to a diazonium ion or for possible use in additions to carbodiimide-activated protein (Table I). The inherent solubility of $B_{10}H_{10}^{2-}$ suggested that its derivatives might be good reagents for protein modification. The diazonium salts **13** and **14** were prepared from their respective arylamines[33,34] and allowed to react with $B_{10}H_{10}^{2-}$ according to a known method.[35] One arylamine, *p*-amino-2,2,2-trifluoroacetanilide (compound **14**), was prepared by reacting nitroaniline with trifluoroacetic anhydride and then hydrogenating the trifluoroacetylated *p*-nitroanilide formed over platinum on charcoal. The acetanilide derivative **15** is slowly hydrolyzed, over several days, in hot aqueous KOH to the amine, while the trifluoroacetanilide derivative **16** is completely hydrolyzed within about 5 min to the amine under similar conditions.

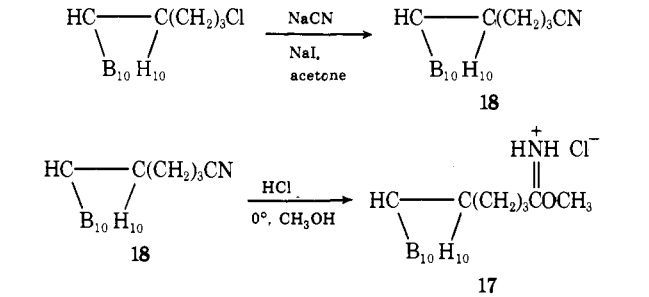
Scheme V



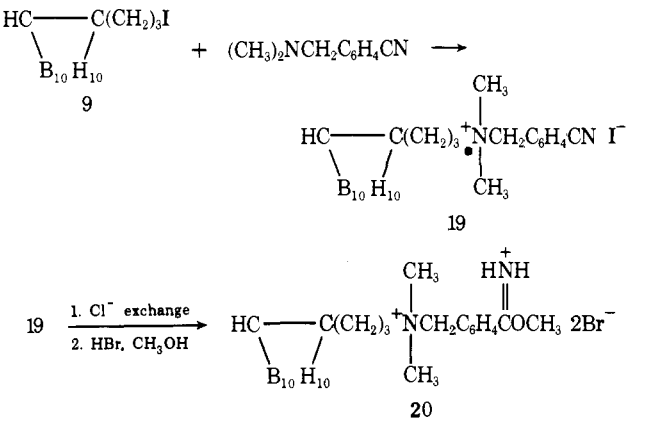
In general, diazonium reagents react unselectively with the side chains of several amino acids, including lysine. A more specific reagent for the ϵ-amino group of lysine and also for α-amino groups is an imido ester. In order to obtain such a selective borane reagent, the methyl imido ester **17** of the γ-cyanopropylorthocarborane (compound **18**) was prepared as shown in Scheme VI. The monopositively charged imido ester salt **17** was formed from the nitrile **18** by the standard procedure[36,37] in methanol which was saturated with hydrogen chloride.

In Scheme VII, **9** was allowed to react with 4-(dimethylaminomethyl)benzonitrile.[38] The product (**19**) was converted to the chloride form by passage through an ion-exchange column, and the salt was then allowed to react with methanol saturated with hydrogen bromide to form the dipositively charged imido ester salt **20**.[39]

Scheme VI

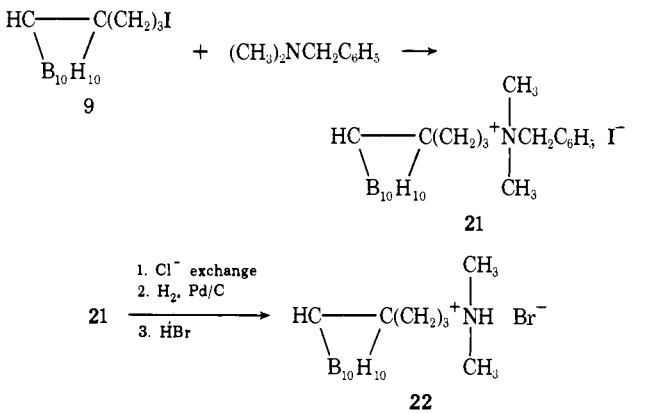


Scheme VII



Imido esters hydrolyze slowly under conditions of protein modification to give the corresponding ester or nitrile.[40] Since expensive ^{10}B-enriched carborane may be used in neutron therapy, it would be advantageous to be able to reuse the hydrolyzed imido ester. A method of recovering hydrolyzed **20** involves replacing the benzyl group in the hydrolyzed imido ester with a hydrogen atom.[41] In order to demonstrate this method, the chloride salt of the product (**22**) of **9** with benzyldimethylamine (Scheme VIII) was hydrogenated over palladium on carbon to give the tertiary amine salt **22**. This tertiary amine can be reacted with α-bromo-*p*-tolunitrile to give **19** (Scheme VII) and then the imido ester **20**.

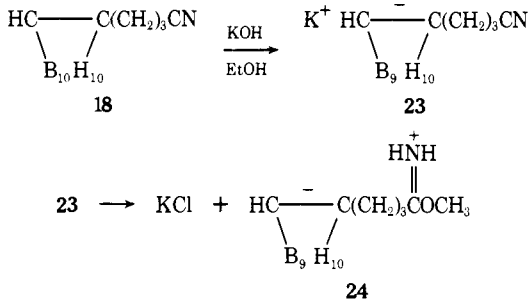
Scheme VIII



Another water-soluble imido ester (**24**), here of the carbollide ion ($C_2B_9H_{12}^-$), was also synthesized (Scheme IX). The carborane cage (compound **18**) was degraded by KOH in ethanol.[42] In this reaction the nitrile group of **18** was found to be relatively stable toward ethoxide compared with the carborane cage and was unaltered at the completion of controlled KOH degradation. The imido ester **24** was subsequently synthesized (Scheme IX). The compound (**24**) is an inner salt and is soluble in polar organic solvents and alkaline aqueous solutions. A primary amine amidine derivative (**25**, not shown in Scheme IX) can be made by reaction with propylamine.

While imido esters show specificity to ϵ-amino groups, reagents containing amines can react specifically with carboxyl groups through carbodiimide-activated additions

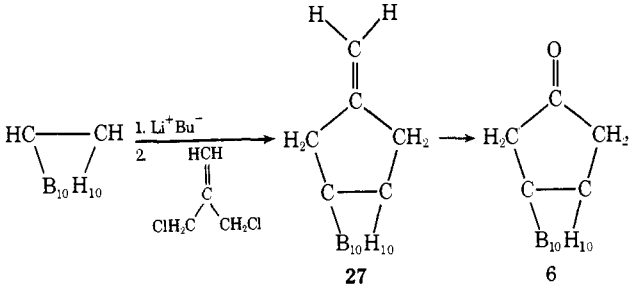
Scheme IX



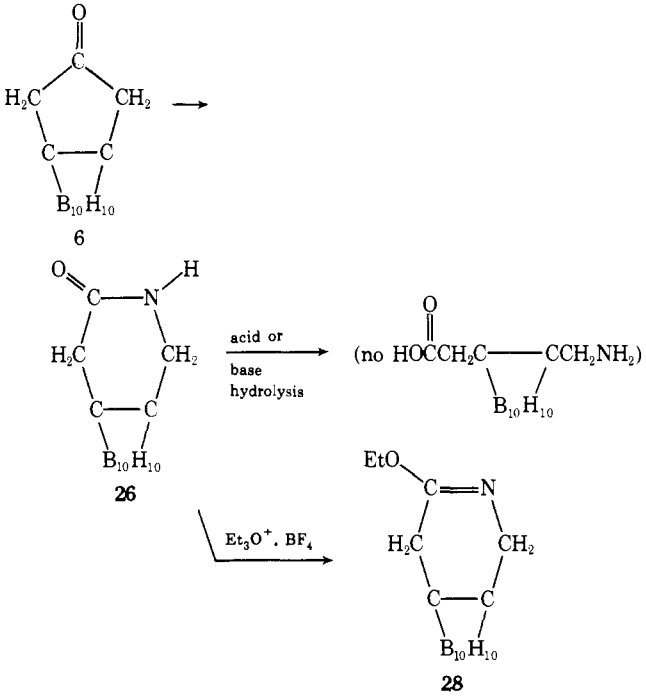
(Table I). The syntheses of several solubilized amines were therefore investigated.

After obtaining 1,2-(2-oxopropylene)carborane (compound 6) in Scheme II, we thought that it might be opportune to use the Schmidt reaction[43] to create the cyclic amide 26 shown in Scheme X. This could hopefully be hydrolyzed to the amino acid.

Scheme X

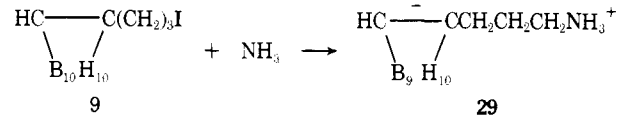


Scheme XI



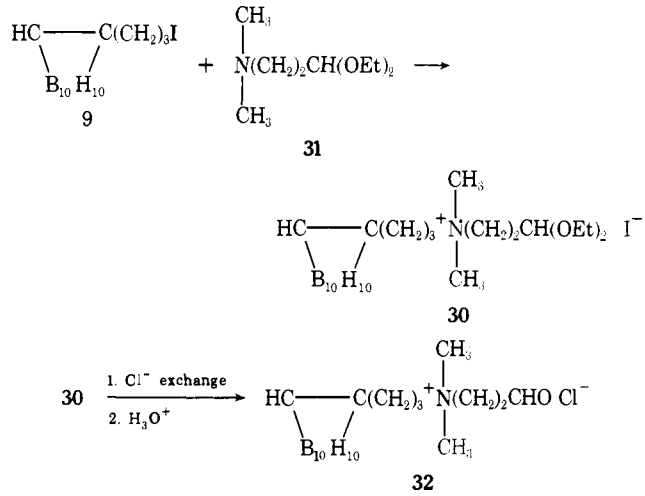
In an attempt to increase the overall yield of the ketone 6 from carborane, 1,2-(2-methylenepropylene)orthocarborane (compound 27) was prepared and converted to the ketone 6 (Scheme XI). The alkene 27 was prepared in excellent yield by reaction of the dilithioorthocarborane with 3-chloro-2-chloromethyl-1-propene.[44] The alkene 27 was oxidized with OsO_4-$NaIO_4$[45,46] to yield the ketone 6. Since OsO_4 degraded orthocarborane to boric acid on prolonged contact, the oxidation must be monitored by tlc (silica gel sheets§ with hexane solvent) and terminated before all the alkene has reacted. The unreacted alkene can be recovered using chromatographic separation as indicated in the Experimental Section. The ketone 6 was converted to the amide 26 by reaction with sodium azide in a mixture of trichloroacetic and sulfuric acids.[43] Many attempts were made to hydrolyze the amide under various acidic[47,48] and basic conditions. These conditions, however, either degraded the cage to the carbollide as indicated by the B-H shift in the ir spectrum and by reduction of silver nitrate solution or did not affect the amide 26. Some evidence for slight amino acid formation after acidic hydrolysis was obtained from mass spectral analysis of a mixture of minor products. For example, one by-product had a maximum isotope band centered on the mass of the hydrolyzed amide. In order to provide additional evidence for the amide structure, the imino ether 28 was synthesized by reacting the amide 26 with triethyloxonium fluoroborate,[49,50] as shown in Scheme X. Although the 2,3-(1,2-orthocarboranyl)butyrolactone[51] is easily hydrolyzed to the alcohol acid, the analogous lactam (26) resists hydrolysis. Differences in either bond free energies and/or steric factors could explain these results.[52]

Scheme XII



In Scheme XII, the γ-aminopropyl-1,2-dicarbaundecarborate (compound 29) inner salt was prepared from 9 in a manner similar to that used for other inner salts.[53] This zwitterion amino derivative was not very soluble at pH 7 in water, probably due to internal ion pairing. Possibly, the charged amine is near the negatively charged open face of the degraded cage.

Scheme XIII

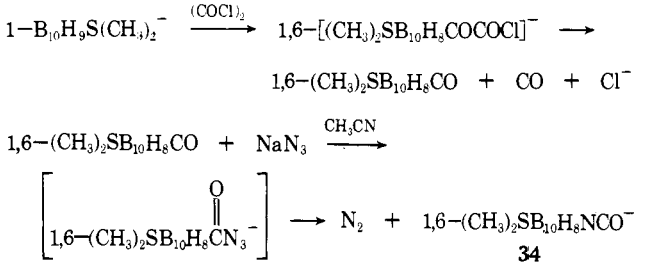


A very selective method for the alkylation of lysyl-ϵ-amino groups is reductive alkylation.[54] A solubilized aldehyde carborane derivative for amino alkylation was synthesized from the acetalcarborane. The quaternary amine acetal 30 was prepared from diethylpropylacetal-*N*,*N*'-dimethylamine (31) as in Scheme XIII. Treatment of the chloride form of the acetal 30 with concentrated HCl gave

§ Kodak 6060 precoated silica gel tlc plates.

the crude aldehyde **32**. This aldehyde (**32**) polymerizes too readily for isolation in pure form, but spectral data support its preparation (^{1}H nmr at 9.70 ppm and ir peak at 1725 cm^{-1}). A 2,4-dinitrophenylhydrazone derivative **33** was also prepared.

Scheme XIV



Isocyanates have been known to react selectively with ϵ-amino groups at alkaline pH's.[55-58] The isocyanate **34** was synthesized following literature methods[59-62] according to Scheme XIV. The 1-dimethylsulfonium decarborate(10) was prepared by the method of Muetterties.[61,63] The sodium salt of **34** is very soluble in water and can react with a model primary amine, propylamine, to give a ureido derivative **35** (not shown in scheme).

The derivatives herein described were subsequently bound under appropriate conditions to proteins. Some of these results appear in the following paper.

Experimental Section

Chemicals and solvents used were reagent quality and further purified only when indicated. Microanalyses were performed by Schwartzkopf Microanalytical Laboratory, Woodsides, N. Y. Ir spectra were recorded on a Perkin-Elmer 137 or 337 spectrophotometer. Mass spectra of all volatile compounds were obtained from an AEI MS-9 mass spectrometer. Nmr spectra were taken with a Varian T-60 spectrometer. Melting points were corrected.

α-Carboranylformanilide (3). To 0.610 g (2.63 mmol) of carborane-1,2-dicarboxyanhydride in 4 ml of benzene was added 1.04 ml of aniline. The solution was heated on a steam bath for 10 min. The solution was then extracted three times with 5 ml of dilute hydrochloric acid and dried over magnesium sulfate. After filtration, the volatiles were removed, and the 0.246 g (33%, 0.94 mmol) of product melted at 130° after recrystallization from heptane. *Anal.* ($B_{10}C_9H_{17}NO$) C, H, N.

1,2-(2-Oxopropylene)orthocarborane (6). Method I. 1,2-Bis(carboxymethyl)orthocarborane (1.21 g, 5.00 mmol) was added to 4 ml of acetic anhydride, and the solution was heated to 120° for 4 hr. After cooling, the excess acetic anhydride was removed under vacuum (0.2 mm). The residue was sublimed (0.1 mm) during heating from 80 to 140°. The sublimate was dissolved in 7 ml of ether and extracted twice with aqueous potassium carbonate. The ether layer was dried over magnesium sulfate, and then the ether was removed. The product was resublimed to 0.628 g (67%, 3.16 mmol) melting at 172°. *Anal.* ($B_{10}C_5H_{14}O$) C, H, B.

Method II. 1,2-(2-Methylenepropylene)orthocarborane (8.54 g, 44 mmol) was added to a solution of 45 ml of water and 180 ml of dioxane freshly distilled from lithium aluminum hydride. Osmium tetroxide (140 mg) was then added. After stirring for 2 min, sodium periodate (20.5 g, 96 mmol) was added in small portions over a 45-min period. Stirring was continued for an additional 2 hr. After adding 200 ml of water, the solution was extracted three times with 200 ml of ether. The ether layer was saturated with hydrogen sulfide, dried over magnesium sulfate, and filtered. The ether was removed from the filtrate, and the residue was chromatographed on alumina (Woelm neutral). Unreacted alkene was first eluted with petroleum ether, and then the ketone was eluted with ether–methanol (4:1). After removing the solvent by rotary evaporation, there was obtained 3.02 g (35%, 15.3 mmol) of product.

2-(2-Carboxymethylorthocarboranyl)acetanilide (7). For 0.5 hr, 0.60 g (2.5 mmol) of 1,2-bis(carboxymethyl)orthocarborane (compound 4) and 2.0 ml of acetic anhydride were heated under vacuum (0.2 mm); 1.5 ml of benzene and then 0.7 ml of aniline were added and stirred for 0.5 hr. After adding 8 ml of ether, the solution was twice extracted with dilute hydrochloric acid and then six times with 1 *N* lithium hydroxide. The lithium hydroxide solution was continuously extracted[64] with ether for 4 hr. The ether layer was reduced to a small volume, extracted with dilute hydrochloric acid, and then dried over anhydrous magnesium sulfate. After removing the ether, the product was recrystallized from bromobenzene–heptane to yield 177 mg (21%, 0.53 mmol) of product melting at 190–191°. *Anal.* ($B_{10}C_{12}H_{21}NO_3$) B, C, H, N.

2-(2-Carboxymethylorthocarboranyl)-*p*-nitroacetanilide (8). The nitroacetanilide **8** was prepared similarly to 2-(2-carboxymethylorthocarbonyl)acetanilide (**7**). *p*-Nitroaniline was used instead of aniline for the preparation of **8**. The yield was 7% of product melting at 150° after recrystallization from bromobenzene: mass calculated for $^{12}C_{12}{}^{1}H_{20}{}^{16}O_5{}^{14}N_2{}^{11}B_{10}$, 382.2309; found, 382.2321.

***p*-(*N*,*N*-Dimethylamino)-2,2,2-trifluoroacetanilide (10).** To 15.0 g (110 mmol) of *p*-dimethylaminoaniline in 50 ml of ethyl acetate was added 15.6 ml (111 mmol) of trifluoroacetic anhydride. After stirring for 3 hr, the mixture was heated with steam for 15 min, and then the volatiles were removed by rotary evaporation. The residue was washed with a solution containing 8.6 g of potassium carbonate dissolved in 200 ml of water. The product was recrystallized from ethanol–water to give a quantitative yield of product melting at 176°. *Anal.* ($C_{10}H_{11}F_3N_2O$) C, H, F, N.

***N*-[4,5-(1,2-Orthocarboranyl)pentyl]-*N*-(2-*p*-aminophenylethyl)-*N*,*N*-dimethylammonium Iodide (11).** In 50 ml of dry benzene was added 1.00 g (3.21 mmol) of γ-iodopropylorthocarborane (**9**) and 0.58 g of $NH_2C_6H_4CH_2CH_2N(CH_3)_2$. The solution was refluxed for 6 days. After cooling, the solution was filtered. the 1.49 g (97%, 3.13 mmol) of precipitate was recrystallized from ethanol–water to give needles melting at 213°. *Anal.* ($B_{10}C_{15}H_{33}N_2I$) B, C, H, N, I.

***p*-Diazoacetanilide Hexafluorophosphate (13).** The salt was prepared from *p*-aminoacetanilide by the method in the literature.[34]

***p*-Azodecaborate(10)-Acetanilide (15).** To 1.5 g of $K_2B_{10}H_{10}$ in 150 ml of acetonitrile at −35° was slowly added 2.38 g of *p*-diazoacetanilide hexafluorophosphate (**13**). After 0.5 hr, the product was allowed to warm to room temperature and worked up to give 1.396 g (51%, 3.95 mmol) of the tetramethylammonium salt of the protonated dye.[35] *Anal.* ($B_{10}C_{12}H_{30}N_4O$) B, N.

***p*-Nitro-2,2,2-trifluoroacetanilide (14a).** To 25.0 g (181 mmol) of nitroaniline in 75 ml of pyridine was slowly added 25.8 ml (18.3 mmol) of trifluoroacetic anhydride at 0°. After ten more hours at room temperature, 75 ml of concentrated hydrochloric acid was added. After adding 1200 ml of ice–water, the solution was filtered. The precipitate (90%, 162 mmol) was recrystallized from ethanol–water to give needles melting at 140°. *Anal.* ($C_8H_5F_3N_2O_3$) C, H, F.

***p*-Amino-2,2,2-trifluoroacetanilide (14b).** A solution containing 18 g (68 mmol) of *p*-nitro-2,2,2-trifluoroacetanilide (**14a**) and 0.80 g of 10% platinum on charcoal in 150 ml of ethyl acetate was hydrogenated (1 atm) until the reaction ceased. The solution was filtered, and the filtrate was rotary evaporated. The residue was recrystallized from ethanol–water to yield 13 g (94%, 64 mmol) melting at 118°. *Anal.* ($C_8H_7F_3N_2O$) C, H, F, N.

***p*-Diazo-2,2,2-trifluoroacetanilide Tetrafluoroborane (14).** The salt was prepared from *p*-amino-2,2,2-trifluoroacetanilide (**14b**) by the method in the literature.[33]

Tetramethylammonium *p*-Azodecaborate(10)-2,2,2-Trifluoroacetanilide (16). To 2.50 g (12.7 mmol) of $K_2B_{10}H_{10}$ in 250 ml of acetonitrile at −35° was slowly added 3.84 g (12.6 mmol) of *p*-diazo-2,2,2-trifluoroacetanilide tetrafluoroborate (compound **14**) in 15 ml of acetonitrile. The product (50%, 6.4 mmol) was worked up[35] and precipitated with tetramethylammonium bromide. Recrystallization was from ethanol–water. *Anal.* ($B_{10}C_{12}H_{27}F_3N_4O$) B; F was 0.1 high and N was 1.6 low.

Tetraethylammonium *p*-Azodecaborate(10)-Aniline (12). A solution of 0.80 g (1.96 mmol) of **16** and 0.56 g of potassium hydroxide in 5 ml of water was heated at 95° for 15 min. An aqueous solution of tetraethylammonium bromide was added to precipitate the salt (85%, 166 mmol). The salt was recrystallized from ethanol–water. *Anal.* ($B_{10}C_{14}H_{36}N_4$) B, C, H, N.

γ-Cyanopropylorthocarborane (18). In 50 ml of dry acetone (by distillation from phosphorus pentoxide), 2.5 g (11.3 mmol) of γ-chloropropylorthocarborane,[65] 0.5 g (3.33 mmol) of sodium iodide, and 4 g (81.6 mmol) of sodium cyanide were refluxed for 2 days. After removal of solvent, the residue was extracted with ether and the extracts were washed with water, dried with mag-

nesium sulfate, and evaporated to a white solid. Recrystallization from hot *n*-heptane gave 2.0 g (9.4 mmol, 83%) of clear needles of the nitrile **18**, mp 81–82°. *Anal.* ($C_6H_{17}B_{10}N$) C, H, B.

Methyl Imido Ester (17) of γ-Cyanopropylorthocarborane (18). An amount of 500 mg (2.45 mmol) of **18** was dissolved in 4 ml of dry methanol (by distillation from calcium hydride) and 2 ml of dry ether. After cooling to −4° with an ice-salt bath, dry hydrogen chloride gas was bubbled in until the solution was saturated. The methanol solution was carefully sealed from moisture and refrigerated (−4°) for 2 days. Dry ether (100 ml) was then added and the cloudy solution was kept chilled at 0°. The white needles of product **17** were quickly filtered off, washed with ether, and vacuum dried at room temperature: yield, 478 mg (1.71 mmol, 70%); mp 124–125°. *Anal.* ($B_{10}C_7H_{22}NOCl$) B, C, H, N, Cl.

***N*-[4,5-(1,2-Orthocarboranyl)pentyl]-*N*-(*p*-cyanobenzyl)-*N,N*-dimethylammonium Iodide (19).** To 40 ml of benzene was added 5.00 g (16.0 mmol) of γ-iodopropylorthocarborane (compound **9**) and 3.62 ml (22.5 mmol) of *p*-(dimethylaminomethyl)-benzonitrile. The solution was refluxed for 4 days. After cooling, the solution was filtered, and the solvent was removed from the filtrate. The residue was recrystallized from ethanol–water to yield 5.50 g (73%, 11.7 mmol) melting at 200° with decomposition. *Anal.* ($B_{10}C_{15}H_{29}N_2I$) B, C, H, N, I.

Methyl Imido Ester (20) of *N*-[4,5-(1,2-Orthocarboranyl)-pentyl]-*N*-(*p*-cyanobenzyl)-*N,N*-dimethylammonium Iodide (19). To an ice-cooled solution of 3.0 ml of anhydrous MeOH and 3.0 ml of methyl acetate was added 0.75 g (1.94 mmol) of the chloride salt of **19**. [The chloride salt of **19** was prepared by dissolving **19** in MeOH–water (9:1) and passing the mixture through an exchange column of Mallinckrodt IR-400 in the chloride form. The solvent was then removed by rotary evaporation.] The solution was saturated with dry HBr and refrigerated for 1 day. The solvent was removed with a filter stick, and the product was twice recrystallized from 5 ml of MeOH and 3.5 ml of ether to give 772 mg (74%, 1.44 mmol) of crystals showing gas evolution at 150°. *Anal.* ($C_{16}B_{10}H_{34}N_2Br_2$) C, B, H, N, Br.

***N*-[4,5-(1,2-Orthocarboranyl)pentyl]-*N*-benzyl-*N,N*-dimethylammonium Iodide (21).** To 90 ml of benzene was added 6.0 g (19.2 mmol) of γ-iodopropylorthocarborane (**9**) and 5.7 ml (38.4 mmol) of benzyldimethylamine. The solution was refluxed for 3 days, and the precipitate was filtered off. The 7.88 g (18.2 mmol) of precipitate (92%) was recrystallized from ethanol–water and melted with decomposition at 204°. *Anal.* ($B_{10}C_{14}H_{30}NI$) B, N.

***N*-[4,5-(1,2-Orthocarboranyl)pentyl]-*N,N*-dimethylamine Hydrogen Bromide Salt (22).** An amount of 7.0 g (15.7 mmol) of **21** in MeOH–water (9:1) was converted to its chloride form through IR-400. The solvent was evaporated and the residue was added to a solution containing 50 ml of HOAc, 25 ml of water, and 1.4 g of 5% palladium on carbon. The salt was hydrogenated at 1 atm until the reaction ceased. The solution was filtered and the solvent removed. The product was taken up in 1 *N* NaOH and extracted with ether. The ether extracts were dried over $MgSO_4$ and filtered. The product was then precipitated by bubbling HBr into the dried ether. The 4.40 g (14.2 mmol) or 90% yield of salt melted at 208°. *Anal.* ($B_{10}C_7H_{24}NBr$) C, H, N.

γ-Cyanopropyl-1,2-dicarbaundecaborate (23). An amount of 2.0 g (9.5 mmol) of **18** was refluxed with 1.2 g (21.4 mmol) of KOH in 20 ml of ethanol for 3 hr. Then, 20 ml of ethanol was added after cooling, and CO_2 was bubbled in to precipitate the excess KOH. After filtration and solvent removal, the residue was dried by azeotropic distillation.[42] The yield of the crude potassium salt of **23** was 2.05 g (8.55 mmol, 90%). The tetramethylammonium salt of **23** was prepared for analysis by recrystallizing from ethanol–water. The melting point is above 300°. *Anal.* ($C_{10}B_9H_{29}N_2$) C, B, H, N.

Methyl Imido Ester (24) of γ-Cyanopropyl-1,2-dicarbaundecaborate (23). To 4.0 g (16.75 mmol) of the crude potassium salt of **23** was added 40 ml of dry MeOH (distilled from CaH_2). After chilling to 0°, dry HCl was passed in to saturate the MeOH solution. The liquid was sealed and refrigerated at −4° overnight. Crystalline KCl was formed and after filtration, the solvent was removed by evaporation to give a yellow oil. This was redissolved in 2 ml of MeOH. Addition of 150 ml of water gave an immediate yield of fine needles of **24** (1150 mg, 4.9 mmol or 29%), mp 153–154° dec. *Anal.* ($B_9C_7H_{22}NO$) B, C, H, N.

A propylamine derivative **25** was synthesized from the reaction of **24** with excess propylamine. After precipitation as the tetramethylammonium salt **25**, the derivative was recrystallized from CH_3CN–water: mp 65°. *Anal.* ($C_{13}B_9H_{38}N_3$) C, H.

1′,2′-(2-Methylenepropylene)orthocarborane (27). Under anhydrous conditions, 8.0 g (55.4 mmol) of orthocarborane in 20 ml of ether was added dropwise to an ice-cooled solution containing BuLi (166.2 mmol) in a mixture of 75 ml of ether and 25 ml of hexane. After stirring for 0.5 hr, the solvent was removed with a filter stick, and the precipitate was twice washed with petroleum ether. To the residue was added 50 ml of ether and then 6.5 ml of 3-chloro-2-chloromethyl-1-propene (61 mmol). The solution was allowed to warm to room temperature and stirred for 5 hr. Then, 200 ml of dilute HCl was added and the ether layer was removed and dried over $MgSO_4$. After filtration, the ether was removed, and the volatiles were removed under vacuum (0.1 mm) overnight. There remained 9.8 g (50 mmol or 91%) of product. Following recrystallization from hexane, the melting point was at 60°. *Anal.* ($B_{10}C_6H_{16}$) B, C, H.

3,4-(1,2-Orthocarboranyl)pentanolactam (26). To a mixture of 6.25 g of trichloroacetic acid and 0.12 ml of concentrated H_2SO_4 at 75° was added 0.50 g (2.53 mmol) of 1,2-(2-oxopropylene)orthocarborane (compound **6**) and then 0.180 g (2.80 mmol) of NaN_3. After 40 min 0.105 g (1.62 mmol) more of NaN_3 was added, and stirring continued for another hour. To the hot solution was added 60 ml of ice-cold water. The cold solution was filtered, and the precipitate was dissolved in 30 ml of ether. The ether layer was twice extracted with aqueous K_2CO_3. After drying over $MgSO_4$, the ether layer was removed. The product was recrystallized from toluene–heptane to give 0.417 g (1.96 mmol, 77%), mp 198°. *Anal.* ($B_{10}H_{15}C_5NO$) B, C, H, N.

Imino Ether (28) of 3,4-(1,2-Orthocarboranyl)pentanolactam (26). To 2 ml of methylene chloride containing 0.163 g (0.86 mmol) of triethyloxonium fluoroborate was added 100 mg of 3,4-(1,2-orthocarboranyl)pentanolactam (**26**). After stirring for 2 hr, 3 ml of water and 3 ml of ether were added. The ether layer was removed, and the aqueous layer was again washed with 3 ml of ether. The combined ether extracts were dried over $MgSO_4$. After filtration, the ether was removed by rotary evaporation. The product was sublimed (0.1 mm) at 60°. The 89 mg (0.38 mmol, 79%) of sublimate melted at 113°.

γ-Aminopropyl-1,2-dicarbaundecaborate (29). To 30 ml of MeOH and 0.1 ml of water was added 2.10 g (6.7 mmol) of γ-iodopropylorthocarborane (compound **9**). The solution was saturated with ammonia and heated to 70° for 2 days. After cooling, the solvent was removed. The residue was dissolved in 30 ml of 0.01 *M* HCl and filtered. Then, NH_4OH was added to the filtrate until the pH was 10.5, and then the filtrate was refrigerated overnight. The solution was filtered and the precipitate dried under vacuum (0.1 mm) over P_2O_5 to yield 0.37 g (1.92 mmol or 28%) of **29** melting at 297°. *Anal.* ($B_9C_5H_{20}N$) B, N.

***N*-Diethylpropylacetal-*N,N′*-dimethylamine (31).** An amount of 10 g (0.06 mol) of diethyl 3-chloropropylacetal and 4.05 ml (0.09 mol) of dimethylamine in 25 ml of ethanol was sealed in a 60-ml thick-walled tube and then heated to 110° for 16 hr. The resulting liquid was stripped of solvent and treated with excess aqueous KOH. The liberated amine was taken up in ether and, after drying and evaporation of solvent, distilled under reduced pressure (25 mm, bp 85–90°) to give 3.0 g (17.2 mmol, 29%) of a clear, foul-smelling liquid. *Anal.* ($C_9H_{21}NO_2$) C, H, N.

***N*-[4,5-(1,2-Orthocarboranyl)pentyl]-*N*-(3-diethylpropylacetal)-*N,N*-dimethylammonium Iodide (30a).** An amount of 1.0 g (5.7 mmol) of **31** and 1.6 g (5.1 mmol) of γ-iodopropylorthocarborane[31] in 10 ml of ether was stirred at 25° for 1 week. Some 1.7 g (3.5 mmol or 61%) of **30a** precipitated as a white powder. Recrystallization was from ethanol–water; mp 130° dec. *Anal.* ($C_{14}B_{10}H_{38}NO_2I$) C, B, H, N, I.

An amount of 170 mg (0.35 mmol) of **30a** was converted into the chloride form (**30b**) by ion exchange and concentrated at 30° into a viscous liquid. Concentrated HCl was added with cooling and after 6 hr the solution was thoroughly evacuated. The resulting viscous liquid was characterized by the CHO ^1H shift in DMSO-d_6 (τ 0.3) and the ir peak at 1725 cm^{-1}. The compound was not isolated due to its instability. A 2,4-dinitrophenylhydrazone derivative **33** having a melting point of 91° dec was synthesized. *Anal.* ($C_{16}B_{10}H_{32}N_5O_4Cl$) C, B, H, N.

1-Dimethylsulfonium-6-isocyanatodecaborate Anion (34). An amount of 103 mg (0.5 mmol) of 1-dimethylsulfonium-6-carbonyldecaborate[61] in 2 ml of CH_3CN was added dropwise to a stirred slurry of 100 mg (1.54 mmol) of NaN_3 in 2 ml of CH_3CN. After the reaction had subsided, the CH_3CN solution was concentrated into a viscous oil and diluted with 3 ml of water. Addition of tetramethylammonium chloride gave a white precipitate of **34**. Recrystallization was effected from warm water. The yield was 90

mg (0.306 mmol 61%); mp 222-224°. *Anal.* ($C_7B_{10}H_{26}N_2SO$) C, B, H, N, S.

A propylamineureido derivative was made from the sodium form of 34 and propylamine in water. The reaction was complete at room temperature after 6 hr. Concentrated Me_4NCl was then added to precipitate the tetramethylammonium salt **35**. This salt was recrystallized from CH_3CN-water; mp 193-194°. *Anal.* ($C_{10}B_{10}H_{35}N_3SO$) C, H, N.

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