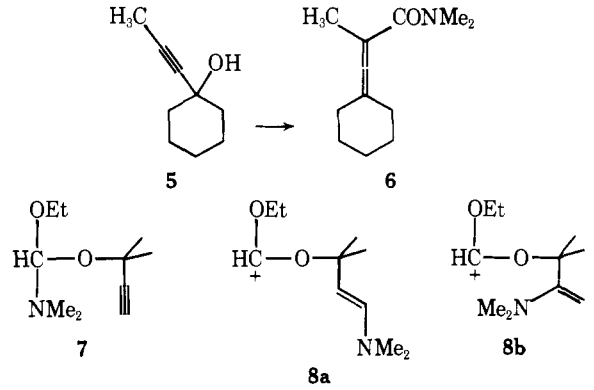
reactions; under typical reaction conditions (7.0 mmol in 2 ml of DMF diethyl acetal and 3 ml of ethanol containing 26 mg of pivalic acid) 1-(1-propynyl)cyclohexanol (**5**) is slowly converted to the allenic amide **6** (approximately 60% conversion after 38 h at reflux). When heated with the formamide acetal in toluene (10 mmol of **5**, 3 ml of DMF diethyl acetal, 10 ml of toluene, reflux) the conversion of **5** to **6** was more efficient; a 72% yield of **6** was obtained after 4 h (along with a 12% recovery of **5**). This transformation is analogous to the reaction of allylic alcohols with DMF acetals to form β,γ-unsaturated amides.[5]



The reaction of 4-phenyl-2-methyl-3-butyn-2-ol (**1e**), although slower than those of alcohols in which the acetylene is terminal, affords reasonable yields of the enamine orthoformate **4e**. Alcohol **1f**, which is both propargylic and allylic, afforded no detectable products resulting from rearrangement involving the olefinic bond.

We assume that this reaction proceeds by way of the mixed amide acetal **7**, which undergoes an intramolecular migration of the dimethylamino group, leaving a carbonium ion **8a** or **8b** (or the corresponding carbene) which subsequently eliminates (**8a** → **3**) or adds ethanol (**8b** → **4**). The mechanism and scope of this reaction as well as possible uses of the enamine products in synthesis are being investigated.

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References and Notes

(1) See P. F. Hudrlik and A. M. Hudrlik, *J. Org. Chem.*, **38**, 4254 (1973), and references therein.
(2) K. A. Parker and R. W. Kosley, Jr., *Tetrahedron Lett.*, 341 (1976).
(3) K. A. Parker and R. W. Kosley, Jr., *Tetrahedron Lett.*, 3039 (1975).
(4) See G. L. Olson, K. D. Morgan, and G. Saucy, *Synthesis*, 25 (1975), and references therein.
(5) G. Büchi, M. Cushman, and H. Wüest, *J. Am. Chem. Soc.*, **96**, 5563 (1974).
(6) W. Benn, *J. Org. Chem.*, **33**, 3113 (1968).

Kathlyn A. Parker,* Raymond W. Kosley, Jr.
Stephen L. Buchwald, Joseph J. Petraitis
Department of Chemistry, Brown University
Providence, Rhode Island 02912
Received June 21, 1976

A New Method for the Preparation of Sequential Polypeptides Using Matrix-Controlled Thermal Polymerization

Sir:

We wish to report a new method for the preparation of sequential polypeptides which is based on our synthesis of sequential polydepsipeptides.[1] We employ a thermal polymerization of trifluoroacetate salts of tripeptide pentachlorophenyl esters[2] deposited on a celite matrix. The polymerization is rapid compared to solution techniques. High yields of optically pure, high molecular weight polymers are obtained. In this communication, we also report a general approach to assess racemization in the preparation of sequential polypeptides.

We synthesized a sequential polypeptide by this technique from the trifluoroacetate salt of L-valyl-L-valyl-L-alanine pentachlorophenyl ester (F_3CCOOH·Val-Val-Ala-OPcp). A second polymer was synthesized by the same technique from the polymerization of the trifluoroacetate salts of L-valyl-L-alanyl-glycine pentachlorophenyl ester (F_3CCOOH·Val-Ala-Gly-OPcp) and glycyl-L-valyl-L-alanine pentachlorophenyl ester (F_3CCOOH·Gly-Val-Ala-OPcp), both of which yield the same sequence polymer. However, the former contains a C-terminal glycine residue which cannot racemize during polymerization while the latter contains an optically active L-alanine residue which may racemize.[3] By comparison of the optical purity of the L-alanyl residue from the hydrolysis products of both polymers, it is possible to deduce the extent of racemization during polymerization.

Two independent routes were employed to prepare F_3CCOOH·L-Val-L-Val-L-Ala-OPcp (I). In the first synthesis, L-alanine was allowed to react with L-valine *N*-carboxyanhydride to yield the free dipeptide L-valyl-L-alanine[4] which was coupled in situ with *tert*-butoxycarbonyl-L-valine *N*-hydroxysuccinimide ester.[5] The resulting *N*-*tert*-butoxycarbonyl-protected tripeptide free acid was esterified with pentachlorophenol at −20 °C in dimethylformamide by treatment with dicyclohexylcarbodiimide in the presence of *N*-hydroxysuccinimide.[6] The *tert*-butoxycarbonyl group was removed in trifluoroacetic acid to yield the desired tripeptide derivative I. The esterification of the tripeptide free acid can conceivably involve some racemization of the C-terminal L-alanyl residue. To avoid this side reaction, we employed a so-called "backup route".[1,7] In this approach, *tert*-butoxycarbonyl-L-alanine was esterified with pentachlorophenol and the *tert*-butoxycarbonyl protecting group removed by trifluoroacetic acid. This amino acid pentachlorophenyl ester was coupled by the repetitive excess mixed carbonic–carboxylic acid anhydride method[8,9] to *tert*-butoxycarbonyl-L-valine and, after deprotection with trifluoroacetic acid, with *tert*-butoxycarbonyl-L-valine again. Deprotection yielded the optically pure tripeptide derivative Ia.

The polymerizable tripeptide derivative, F_3CCOOH·Gly-Val-Ala-OPcp (II) was synthesized by the same step-by-step backup technique using appropriate repetitive excess mixed anhydride couplings and deprotections. The remaining tripeptide, F_3CCOOH·Val-Ala-Gly-OPcp (III), was prepared by allowing glycine to react with *tert*-butoxycarbonyl-L-alanine *N*-hydroxysuccinimide ester. After deprotection with trifluoroacetic acid, the free dipeptide was treated with *tert*-butoxycarbonyl-L-valine *N*-hydroxysuccinimide ester. Esterification with pentachlorophenol and deprotection with trifluoroacetic acid yielded the desired polymerizable tripeptide derivative III. All the tripeptide active esters were pure by TLC and gave satisfactory elemental and amino acid analysis as well as NMR and ir spectra.

Preliminary attempts at bulk polymerization of pentachlorophenyl ester were unsuccessful, even at high temperature, because of trapping of the liberated pentachlorophenol in the reaction mass.[1] Deposition of the monomers on an inert matrix accelerates the sublimation of liberated pentachlorophenol and allows the polymerization to proceed rapidly at temperatures well below the melting point of the monomer.

The polymerization was accomplished by dissolving the tripeptide active ester in a dimethylformamide/dioxane mixture (1:3 v/v), adding 66% by weight of micron-size celite

Table I. Matrix-Controlled Thermal Polymerization of Tripeptide Pentachlorophenyl Esters

Starting material	Polymer	Yield, %	$\nu_{sp/c}$[a]	$\overline{M}_v$
F_3CCOOH·Val-Val-Ala-OPcp (I)	Poly(Val-Val-Ala)[b]	91[c]	0.3[d]	40 000
		42[e]	0.48	80 000
F_3CCOOH·Gly-Val-Ala-OPcp (II)	Poly(Gly-Val-Ala)[f]	60[g]	0.19[h]	30 000
F_3CCOOH·Val-Ala-Gly-OPcp (III)	Poly(Val-Ala-Gly)[i]	80[g]	0.25	40 000

[a] Polymer concentration 0.5 g/100 ml of dichloroacetic acid. [b] Amino acid analysis Val 2.00, Ala 1.00. [c] Crude. [d] Reported 0.16 via solution polymerization.[5] [e] Reprecipitated from dichloroacetic acid/water. [f] Amino acid analysis Gly 0.96, Val 1.06, Ala 1.00. [g] Reprecipitated from methyl alcohol/ether (1:1). [h] Reported 0.158 via solution polymerization.[11] [i] Amino acid analysis Gly 1.01, Ala 1.00, Val 0.97.

(which is a Johns-Manville registered trademark for diatomaceous silica products) and then removing the solvent at low temperature in vacuo. The resulting matrix–monomer preparation was then polymerized at 125 °C under high vacuum (0.025 mm) in a sublimator. The progress of the polymerization was monitored by quantitative infrared spectroscopy. Samples from the polymerization mixture were extracted with trifluoroethanol and the extracts were evaporated to dryness and pressed into a KBr pellet. After 24 h, the extent of the reaction was calculated to be 90% based on the ratio of ν(C=O) of the pentachlorophenyl ester (1776 cm^{-1}) to the 1380, 1360 cm^{-1} doublet of the valyl *gem*-dimethyl absorption.[10] Below 125 °C, the reaction was very slow. The reaction was terminated after 24 h and the polymer was eluted from the matrix with trifluoroethanol and precipitated with ether. Results are presented in Table I.

To ensure that polymers prepared by matrix-controlled thermal polymerization maintain the optical purity of the constituent tripeptide unit, we subjected polymers and trifluoroacetate salts of the tripeptide pentachlorophenyl esters to racemization analysis. The method used for determination of the amount of D-amino acids is based on the method of Manning and Moore,[12] namely, hydrolysis of the peptide and derivatization of the free amino acids by reaction with L-leucine *N*-carboxyanhydride. The resulting dipeptide mixture is separated by ion exchange chromatography and the amount of any diastereomeric dipeptide assessed quantitatively.

Hydrolysis of poly(Val-Val-Ala) and the corresponding polymerizable tripeptide pentachlorophenyl ester under normal conditions (6 M HCl, 110 °C for 22 h)[13] is incomplete as shown by amino acid analysis of the hydrolyzate. Complete hydrolysis occurs after 24 h at 165 °C in propionic acid:12 M HCl (1:1).[14] Since total racemization of the amino acid controls, L-alanine and L-valine, occurs, these hydrolysis conditions could not be used to measure racemization. We employed the conditions of 72 h at 110 °C in 6 M HCl, where hydrolysis is complete and racemization of the L-alanine and L-valine controls is not found. Results are presented in Table II. As can be seen from Table II, the activation step for the preparation of tripeptide active ester I caused the formation of 4.5% D-Ala.[15] This figure was calculated by subtracting the amount of D-Ala in tripeptide active ester Ia (4.5%) which was prepared by the nonracemizing backup route from the amount of D-Ala found in tripeptide active ester I (9%).

It is known that racemization may occur during hydrolysis of peptides or treatment of some free amino acids under the same conditions.[16] Since the tripeptide active ester Ia was prepared by the nonracemizing backup technique, the formation of 4.5% D-Ala in Ia is thus attributed to hydrolysis. However, this last value cannot be taken as a standard for racemization during hydrolysis of poly(Val-Val-Ala) because the alanine residue of the tripeptide active ester is linked to a pentachlorophenyl residue whereas in the polymer it is bonded to a valine residue.

An appropriate standard for the degree of racemization during hydrolysis is a polymer which has exactly the same primary structure as the polymer in question but is not able to racemize during tripeptide active ester synthesis or polymerization. Thus, poly(Val-Ala-Gly) is an appropriate standard for the degree of racemization during hydrolysis of poly(Gly-Val-Ala) because both polymers have identical primary structures. As can be seen from Table II, both polymers show the same D-Ala content (9%). Therefore racemization of poly(Gly-Val-Ala) occurs during hydrolysis and is not due to the tripeptide active ester synthesis or polymerization.

Table II. Results of Racemization Analysis

Material analyzed[a]	% D-Ala[b]
F_3CCOOH·Val-Val-Ala-OPcp (I)	9.0
F_3CCOOH·Val-Val-Ala-OPcp (Ia)	4.5
Poly(Val-Val-Ala)[c]	15.0
Poly(Gly-Val-Ala)	9.0
Poly(Val-Ala-Gly)	9.0

[a] Hydrolysis in 6 M HCl for 72 h at 110 °C. [b] Accuracy 0.42%[12] (1% of D-Ala residue is the lower detectable limit in the polymers because of the extent of racemization during hydrolysis). [c] Prepared by polymerization of tripeptide active ester I.

Poly(Val-Val-Ala) was found to contain 15% D-Ala (see Table II), of which, as we discussed above, 4.5% can be attributed to racemization during the activation of the tripeptide. The remaining 10.5% D-Ala is close to the 9% found in poly(Val-Ala-Gly) and poly(Gly-Val-Ala), and is therefore attributable to hydrolysis. The difference of 1.5% probably arises from the greater hydrophobic character and steric hindrance towards hydrolysis of poly(Val-Val-Ala) compared with poly(Val-Ala-Gly).

We are extending this general method for the preparation of sequence polypeptides to other systems with more complex structures. It is our hope that we can prepare a broad series of sequence polymers which can be used as accurate models of proteins or other biopolymers.

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References and Notes

(1) D. Nissen, C. Gilon, and M. Goodman, *Makromol. Chem.*, **1**, 23 (1975).
(2) J. Kovacs and A. Kapoor, *J. Am. Chem. Soc.*, **87**, 118 (1965).
(3) J. Kovacs, G. L. Mayers, R. H. Johnson, R. Giannotti, M. Cortegiano, and J. Roberts in "Progress in Peptide Research", Vol. 2, S. Lande, Ed., Gordon and Breach, New York, N.Y., 1972, p 185.
(4) M. Oya, K. Uno, and Y. Iwakura, *Prog. Polym. Sci. Jpn.*, **6**, 97 (1973).
(5) R. Katakai, M. Oya, F. Toda, K. Uno, and Y. Iwakura, *Macromolecules*, **6**, 827 (1973).
(6) E. Wünsch and F. Drees, *Chem. Ber.*, **99**, 110 (1966).
(7) M. Goodman and K. C. Stueben, *J. Am. Chem. Soc.*, **81**, 3980 (1959).
(8) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Am. Chem. Soc.*, **89**, 5012 (1967).
(9) M. A. Tilak, M. L. Hendrichs, and D. S. Wedel, ref 3, p 351.
(10) K. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, San Francisco, Calif., 1962.
(11) K. Katakai, M. Oya, and Y. Iwakura, *Biopolymers*, **14**, 1315 (1975).
(12) J. M. Manning and S. Moore, *J. Biol. Chem.*, **243**, 5591 (1968).
(13) S. Moore and W. H. Stein, *Methods Enzymol.*, **6**, 819 (1963).
(14) F. Westall and H. Hesser, *Anal. Biochem.*, **61**, 610 (1974).

(15) D-L. F. DeTar and N. F. Estrin, *Tetrahedron Lett.*, **48**, 5985 (1966).
(16) J. M. Manning, *J. Am. Chem. Soc.*, **92**, 7449 (1970).

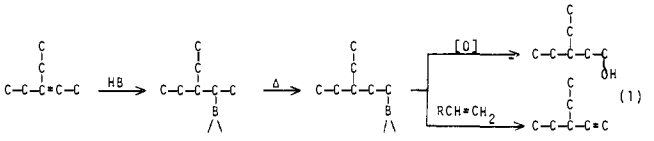
Maria Sakarellos-Daitsiotis, Chaim Gilon
Constantinos Sakarellos, Murray Goodman*
Department of Chemistry B-014
University of California, San Diego
La Jolla, California 92093
Received June 28, 1976

Remarkably Stable Organoboranes Derived from the Hydroboration of Olefins with 9-Borabicyclo[3.3.1]nonane. Utilization to Achieve the Successful Synthesis of Stereospecific Derivatives in 1-Substituted Cyclooctenes and Similar Related Derivatives

Sir:

Trialkylboranes derived from olefins via hydroboration with 9-borabicyclo[3.3.1]nonane are remarkably resistant to thermal isomerization. Thus the *B*-alkyl-9-BBN derived from *cis*-3-hexene requires heating at 150 °C for 168 h to attain the equilibrium distribution of boron along the hexyl chain. At the same temperature, the isomerization of the alkylborane from *cis*-3-hexene and borane is complete in only 1 h.[1c] This unusually sluggish migration of the 9-BBN moiety along the carbon skeleton makes possible the successful stereoselective hydroboration of certain labile systems not readily handled by earlier hydroborating reagents. For example, the hydroboration of 1-methylcyclooctene and 1-phenylcyclooctene with borane:THF produces mixtures of compounds arising from the facile isomerization of the borane intermediates. However, these olefins are readily hydroborated with 9-BBN and the intermediates oxidized to *trans*-2-methylcyclooctanol and *trans*-2-phenylcyclooctanol, isomerically pure.

It has been established that organoboranes undergo thermal isomerization under relatively mild conditions (75–160 °C in the presence of catalytic amounts of hydride).[1] This process apparently involves the migration of the boron atom along the carbon chain to yield products with boron attached predominantly to the least substituted carbon atom. The resulting mixture of organoboranes approaches thermodynamic equilibrium distribution. This isomerization reaction, combined with hydroboration of olefins, has opened up possibilities for useful synthetic transformations, such as the contrathermodynamic equilibration of olefins and the formation of primary alcohols from the corresponding tertiary or secondary isomers (eq 1).[1e] However, in some cases, the facile isomerization of



(1)

organoboranes constitutes an undesirable side reaction.[2] For example, early attempts to convert 1-methylcycloheptene and 1-methylcyclooctene into the corresponding *trans*-2-methylcycloalkanols via hydroboration–oxidation with diborane encountered difficulties because of the facile isomerization of the boron intermediates.[3] The availability of a reagent capable of forming thermally stable organoboranes would be highly desirable.

9-Borabicyclo[3.3.1]nonane (9-BBN)[4] possesses this particular quality. The relative rates of isomerization of borane vs. 9-BBN derived organoboranes (Table I) clearly indicate that the *B*-alkyl-9-BBN derivatives are far more resistant to isomerization than the parent organoboranes.

Table I. The Rates of Thermal Isomerization of the Organoboranes Derived from the Hydroboration of *cis*-3-Hexene Using 9-BBN and BH_3

Reagent	Ratio[a]	Temp, °C	Time, h	Distribution of hexanols,[b] % 3-ol	2-ol	1-ol
9-BBN	1.11	125	0	100	0	0
			1	90	10	Trace
			2	81	19	Trace
			4	69	31	Trace
			8	45	55	Trace
			25	27	70	3
		150	0	100	0	0
			1	51	48	1
			2	33	63	4
			4	25	67	8
			8	21	59	20
			25	15	34	51
			48	10	25	65
			168	4	8	88
BH_3[c]	1.20	125	0	100	0	0
			1	26	30	44
			2	18	25	57
			4	11	15	74
			8	9	9	82
			24	6	6	88
		150	0	100	0	0
			1	4	7	89
			2	3	6	91
			16	4	6	90

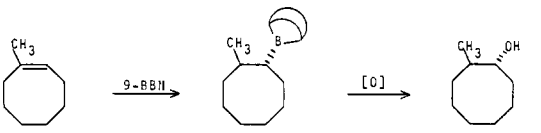
[a] Ratio of equivalent of hydride to 3-hexene. [b] From the alkaline hydrogen peroxide oxidation of the organoborane mixture. [c] H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **88**, 1433 (1966).

The distribution of the boron moiety on the carbons of the hexane chain was determined by gas chromatographic examination of the hexanols following alkaline hydrogen peroxide oxidation of the organoboranes.[5] The change in the isomeric distribution of the product from 3-hexene and 9-BBN (Table I) indicates that the boron moiety moves stepwise down the chain; consequently, it is possible to stop the reaction at an intermediate stage and obtain 2-hexanol in moderate yield.

Analogously, in a sluggish reaction, the *B*-alkyl-9-BBN compounds derived from 1- and 2-hexenes undergo slow isomerization to the same ultimate equilibrium mixture.

Even more striking results were obtained with the organoboranes derived from 1-methyl- and 1-phenylcyclooctene with 9-BBN. Previously, it was observed that the hydroboration of 1-methylcyclooctene with borane, followed by oxidation with alkaline hydrogen peroxide, did not yield the desired pure *trans*-2-methylcyclooctanol.[3,6] It was concluded that the intermediate organoborane must be undergoing a rapid isomerization around the cyclooctane ring, producing isomeric alcohols on oxidation.[6a] Similar results were realized in the present study in the hydroboration–oxidation of 1-phenylcyclooctene by the borane procedure.

However, application of 9-BBN solved the problem completely. Treatment of 1-methylcyclooctene with 9-BBN at 25 °C results in the clean hydroboration of the olefin (eq 2).



(2)

Oxidation of the intermediate with alkaline hydrogen peroxide yielded *trans*-2-methylcyclooctanol in 90% yield.[7] Only insignificant traces of isomeric material were observed in the GC examination of the product.