Table II

No.	Reactions: Starting material	Reactions: Reagents	Product ratios: *trans–trans*	*cis–trans*	*cis–cis*	*trans–tert*	*cis–tert*
1	Geraniol	$TiCl_3$–MeLi	1.00	0.82	0.24	0.77	0.32
2	Nerol	$TiCl_3$–MeLi	1.00	1.23	0.44	0.72	0.43
3	Linalool	$TiCl_3$–MeLi	1.00	1.20	0.40	0.80	0.50
4	Geraniol	$TiCl_3$–C_6H_5Li	1.00	1.24	0.31	0.85	0.34
5	Geraniol	$TiCl_3$–NaNp	1.00	0.90	0.23	0.75	0.33
6	Geraniol	$TiCl_3$–MeLi (uv photolysis)	1.00	0.66	0.10	0.63	0.15
7	Geranyl chloride	NaNp	1.00	0.04	None	1.20	None
8	Geranyl chloride	Geranyl MgCl	1.00	0.74	0.22	2.20	0.67
9	Geranyl chloride	$(C_6H_5)_3SnH$ (product: $(CH_3)_2C{=}CH(CH_2)_2C(CH_3){=}CHCH_3$)	$\frac{cis}{trans}$ = 0.38–0.48; $\frac{tert}{cis + trans}$ = 0.14–0.16				

$$RO^- + TiCl_4 \rightarrow \left\{ (RO)_2TiCl_2 \xrightarrow[NaNp]{K^0 \text{ or}} \left[(RO)_2Ti \right]_n \rightleftharpoons n(RO)_2Ti \xrightarrow{\Delta} (TiO_2)2R\cdot \right\} \rightarrow R{-}R$$

In the case of the aryllithium–titanium trichloride modification, no chlorobenzene was detectable as product when phenyllithium was employed; however, biphenyl and benzene were observed. Since titanium(III) and -(IV) alkyls and aryls are known to generate carbon radicals, the following view of this modification is thought reasonable.

$$TiCl_3 + 2ROH \xrightarrow{2R'Li} \left\{ (RO)_2TiCl \xrightarrow{R'Li} (RO)_2TiR' \xrightarrow{-R'} (RO)_2Ti \xrightarrow[(\text{as in a})]{\Delta} \right\} \underline{R{-}R}$$

The pertinence of this coupling chemistry to the titanium-induced nitrogen fixation–reduction phenomena currently under study in this laboratory is evident (see preceding communication).

Acknowledgment. The authors are indebted to the National Science Foundation for financial support (GP 5556).

(9) Fellowship provided by Swedish Council for Applied Research, 1967–1968.

(10) National Institutes of Health Predoctoral Fellow, 1965–1967.

E. E. van Tamelen, B. Åkermark,[9] K. B. Sharpless[10]
Department of Chemistry, Stanford University
Stanford, California 94305

Received December 9, 1969

The Effects of Metal Components and Acids on Racemization in the Synthesis of Peptides by the Oxidation–Reduction Condensation

Sir:

In our previous paper[1] we reported that Z-Phe-Gly-OEt can be synthesized without racemization by way of an oxidation–reduction condensation starting from the NPS-amino acid ester (A) or from a free amino acid ester (B), respectively, according to the following equations.

(1) T. Mukaiyama, M. Ueki, H. Maruyama, and R. Matsueda, *J. Am. Chem. Soc.*, **90**, 4490 (1968).

$$(\text{Z-L-Phe})_2Cu + 2\text{NPS-Gly-OEt} + 4Ph_3P \rightarrow 2\text{Z-L-Phe-Gly-OEt} + [Cu(SC_6H_4NO_2)_2 \cdot Ph_3P] + 3Ph_3P{=}O \quad (A)$$

$$\text{Z-L-Phe-OH} + \text{H-Gly-OEt} + HgCl_2 + (o\text{-}O_2NC_6H_4S)_2 + Ph_3P + 2Et_3N \rightarrow \text{Z-L-Phe-Gly-OEt} + Hg(SC_6H_4NO_2)_2 + Ph_3P{=}O + 2Et_3N\cdot HCl \quad (B)$$

This communication reports the further examination of racemization during peptide bond formation by the more sensitive Young test[2] and its prevention.

In the type A reaction, an unsatisfactory result was obtained with the Young test, probably because of the generation of ethyl glycinate anion as an intermediate.

For example, when copper(II) benzoyl-L-leucinate (5 mmol), N-(*o*-nitrophenylsulfenyl)glycine ethyl ester (10 mmol), and triphenylphosphine (20 mmol) were allowed to react in methylene chloride for 8 hr, Bz-Leu-Gly-OEt was obtained by chromatography on silica gel in 77% yield, mp 148–149°, $[\alpha]^{20}D$ −17.4° (*c* 3.1, EtOH), L isomer[2] 57% [lit.[2] L isomer mp 156–157°, $[\alpha]^{20}D$ −34° (*c* 3.1, EtOH)].

As to the Young test, the racemization intermediate is known to be 4-isobutyl-2-phenyloxazolone whose formation is catalyzed by bases.[3] A base-catalyzed enolization mechanism which involved two possible proton abstraction steps from the amide hydrogen and from the oxazolone hydrogen was also reported by Kemp and his associates.[4]

The effect of acidic additives was studied on the assumption that racemization could be prevented by keeping the reaction medium neutral or acidic. For example, when copper(II) benzoyl-L-leucinate (5 mmol), NPS-glycine ethyl ester (10 mmol), and triphenylphosphine (10 mmol) were allowed to react in the presence of 2,4-dinitrophenol (10 mmol) for 8 hr, Bz-Leu-Gly-OEt was obtained in 81% yield, 77% L isomer.[2]

Of six acidic additives, 2,4-dinitrophenol (81% yield, 77% L isomer), picric acid (48%, 80% L isomer), and N-hydroxysuccinimide[5] (63%, 82% L isomer) proved to be

(2) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963). The per cent of L isomer was calculated from $[\alpha]^{20}D$ −34° as in Young's report.

(3) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 3701 (1964).

(4) D. S. Kemp and S. W. Chien, *J. Am. Chem. Soc.*, **89**, 2746 (1967).

(5) J. E. Zimmerman and G. W. Anderson, *ibid.*, **89**, 7151 (1967). Favorable results were obtained by adding N-hydroxysuccinimide in the DCCD method but not obtained by pivalic acid. The major reason is reported to be the formation of N-hydroxysuccinimide ester.

Table I

MX_2	$(R^2S)_2$	Crude Bz-Leu-Gly-OEt Yield, %	Crude Bz-Leu-Gly-OEt $[\alpha]^{20}D$, deg[a]	Crude Bz-Leu-Gly-OEt L isomer, %
Di-*p*-anisylmercury	$(p\text{-}ClC_6H_4S)_2$	88	−30.5	90
Di-*p*-anisylmercury	$(o\text{-}O_2NC_6H_4S)_2$	92	−32.4	95
2*p*-Anisylmercuric bromide	$(o\text{-}O_2NC_6H_4S)_2$	92	−32.0	94

[a] *c* 3.1, EtOH.

effective in maintaining optical purity, but phenol (75%, 0% L isomer), *p*-nitrophenol (90%, 11% L isomer), and pivalic acid[5] (57%, 39% L isomer) were ineffective.

In reactions of type B, HCl is produced along with the peptide by the reaction of the supposed key intermediate of acyloxyphosphonium salt $(Ph_3P^+OCOR^1)\text{-}{}^-SR^2$, ethyl glycinate, and mercuric chloride. Therefore, a basic substance such as triethylamine must be used as a HCl scavenger.

In order to eliminate bases from the reaction system, reactions were tried using various kinds of metal compounds in place of the metal halide and triethylamine. These compounds should yield mercaptides and chemical species which are not concerned with the deprotonation.

For this purpose, two kinds of metal compounds can be considered, namely (a) mercuric salts of urea, succinimide, *p*-nitrophenol, etc., and (b) di-*p*-anisylmercury and *p*-anisylmercuric bromide. It was found that the former group of compounds rapidly affords mercaptides on treatment with triphenylphosphine and disulfide probably through the direct attack of the R^2S^- anion of the phosphonium salt produced, while the latter compounds can react only with R^2SH to yield mercaptides and anisole, but cannot react with the R^2S^- anion.

In the cases of group a compounds (MX), the acyloxyphosphonium mercaptide readily reacts with the metal compounds to produce metal mercaptides and the second acyloxyphosphonium salts by the reference anion exchange. The stabilities of X^- anions involved in the salts would be expected to have a great effect on racemization and, in accordance with this, the optical purity increased as the X^- anion stability increased, except in the case of N-hydroxysuccinimide: mercuric salt of urea, 81% yield (23% L isomer); succinimide, 91% (46% L isomer); phthalimide, 85% (47% L isomer); *p*-nitrophenol, 82% (51% L isomer); 2,4-dinitrophenol, 92% (73% L isomer); N-hydroxysuccinimide, 89% (59% L isomer).

More favorable results were obtained by the use of group b compounds as shown in Table I.

In a typical experiment, ethyl glycinate (10 mmol) in methylene chloride was added at room temperature to a stirred mixture of equimolar amounts of di-*p*-anisylmercury, triphenylphosphine, di-*o*-nitrophenyl disulfide, and N-benzoyl-L-leucine in methylene chloride. After stirring for 2 days, the precipitated mercury mercaptide was filtered off and the solvent was evaporated *in vacuo*. From the residue, Bz-Leu-Gly-OEt was separated by chromatography on silica gel, 2.94 g (92%), mp 142–148°, $[\alpha]^{20}D$ −32.4° (*c* 3.1, EtOH), and was recrystallized from ethyl acetate–petroleum ether (bp 30–50°), mp 156–157°, $[\alpha]^{20}D$ −34.2° (*c* 3.1, EtOH).

The high optical purity obtained in the above experiment may due to the absence of oxazolone formation. In this reaction system the intermediate acyloxyphosphonium salt is attacked only by ethyl glycinate to produce the peptide and R^2SH which yields mercaptide and anisole by reaction with mercuric compounds. Since anisole is produced directly by the protonation of R^2SH to the mercuric compound, anisyl anion is absent during this mercaptide formation reaction and oxazolone formation can be prevented.

Teruaki Mukaiyama, Rei Matsueda
Hiroshi Maruyama, Masaaki Ueki
Laboratory of Organic Chemistry, Tokyo Institute of Technology
Ookayama, Meguro-ku, Tokyo, Japan
Received December 7, 1968

Carbon Skeletal Rearrangement of Butene Ions

Sir:

The lability of the double bond in alkene ions, as suggested by the similarity of the mass spectra of isomeric C_4H_8 compounds,[1] has been well known for some time. The migration is usually written as a hydrogen randomization involving a 1,2 and/or a 1,3 hydride or hydrogen atom shift.[2] The randomness of deuterium atom retention in $C_3(H,D)_5^+$ from 1-butene-4-d_3 ion near its appearance potential excludes a pure 1,3-shift mechanism,[3] a conclusion supported by the mass spectrum of 2-butene-1,4-d_2 at a nominal ionizing voltage of 70 V.[4] The mass spectra of specifically deuterium-labeled pentenes can also be interpreted by a series of 1,2 shifts competing with dissociation without the participation of cyclic intermediates.[4] However, the mechanism of the deuterium atom randomization has not been established, and the possibility that carbon atom migration contributes has not been investigated.

We have examined this question using 1-butene-4-d_3 and 1-butene-4-^{13}C, prepared by the method of Regier and Blue.[5] The mass spectra of these compounds were determined on an Atlas CH4 mass spectrometer at 0.2-V intervals of nominal electron accelerating potentials between 9.0 and 15 V. Representative results for the deuterated compound are given in Table I; relative abundances compare well with those reported by Bryce and Kebarle,[3] confirming the conclusion that the hydrogens randomize. In our investigation the mass values shown in Table I can

(1) Catalog of Mass Spectra Data, American Petroleum Institute Project 44, Texas A&M College, College Station, Texas, 1964.
(2) K. Biemann, "Mass Spectrometry–Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 83; H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, p 55.
(3) W. A. Bryce and P. Kebarle, *Can. J. Chem.*, **34**, 1249 (1956).
(4) B. J. Millard and D. F. Shaw, *J. Chem. Soc., B*, 664 (1966).
(5) R. B. Regier and R. W. Blue, *J. Org. Chem.*, **14**, 505 (1949).