Table III[a]

	$\left(\frac{\delta_C - \delta_B}{\delta_A - \delta_B}\right)_{H(2)}$	$\left(\frac{\delta_C - \delta_B}{\delta_A - \delta_B}\right)_{H(4)}$
AcHm	0.40 ±0.03	0.51 ±0.08
AcHis	0.22 ±0.03	0.11 ±0.08

[a] Comparison of chemical shift changes of imidazole ring protons caused by Cu^+ and H^+ for AcHm and AcHis. The ratios of such changes, as defined in the headings of the table, are proportional to the charge fraction carried by the imidazole ring. Errors are maximum errors calculated on the basis of an average error of 0.02 ppm in the individual chemical shifts.

Cu(II) specific, can take part in Cu(I) complexation if coupled with a nonspecific ligand such as the imidazole ring of histidine. This finding should be taken into account for the identification of active sites of Cu proteins with redox activity; spatial proximity of an histidyl residue (present in nearly all such proteins) and of the ubiquitous carboxylate group may be considered as a sufficient requirement for a redox active site. (2) The negligible tendency of the amide group toward Cu(I) complexation[4] is confirmed also for cases in which it is coupled with the imidazole ring. (3) The simple application of nmr spectroscopy used in this study turned out to be very effective in revealing a complexation to Cu(I) that would probably be undetectable by techniques such as potentiometry, commonly employed in the study of complexes with poor optical spectral properties. In fact, in the specific case of $(AcHis)_2Cu^I$, a hypothetical potentiometric study of the Cu^+-carboxylate interaction should be performed in a pH range in which the whole complex is not stable owing to protonation of the imidazole nitrogen atoms.

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Preparation of a New *o*-Nitrobenzyl Resin for Solid-Phase Synthesis of *tert*-Butyloxycarbonyl-Protected Peptide Acids

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Abstract: A new resin—3-nitro-4-bromomethylbenzoylamide polystyrene resin—was prepared. This resin is suitable for the synthesis of Boc-protected peptides possessing a free C-terminal carboxyl group. The protected peptide acid is removed from the resin by photolysis at 3500 Å. These conditions do not cleave acid-labile protecting groups nor decompose aromatic amino acids. The application of this resin to the synthesis of Boc-Leu-Arg(Tos)-Pro-Gly, Boc-Ser(Bzl)-Tyr(Bzl)-Gly-Leu-Arg(Tos)-Pro-Gly, pGlu-His(Tos)-Trp-Ser(Bzl)-Tyr(Bzl)-Gly-Leu-Arg(Tos)-Pro-Gly, and Boc-Ser(Bzl)-Tyr(Bzl)-Gly is described.

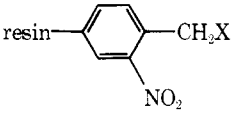
The solid-phase method of peptide synthesis, introduced by Merrifield in 1963,[1] has proven to be an effective method for the rapid synthesis of peptides. However, the products prepared by this method are often difficult to purify. Impurities, such as failure sequences[2] which are caused by changes in the physical-chemical properties of the polymer,[3] accumulate during a stepwise synthess and can be difficult to remove. Several authors[4-7] have suggested that a more homogeneous final product might be isolated by coupling pure protected peptide fragments on the solid support. Failure sequences formed during a synthesis using fragment coupling would differ substantially from the desired product and would be more readily removed during purification. The basic trypsin inhibitor from bovine pancreas, synthesized by fragment coupling on a polymer, was reported to be purer[8] than the product obtained by stepwise synthesis.[9] However, if the fragment coupling approach is to become generally useful, a convenient method for preparing Boc peptide acids is needed. These derivatives have been prepared by solid-phase synthesis but either transesterification[10,11] or hydrazinolysis[12] reactions were required to remove the Boc-protected peptides from the resin and these conditions are not always applicable. In this paper we describe the synthesis and use of a new resin **7** from which protected peptide acids can be removed by photolysis under conditions which do not destroy aromatic residues nor cleave acid- or base-labile protecting groups.

Recently we reported that protected amino acids and

Table I. Swelling Characteristics of Resins as a Function of Solvent

Resin, 200 mg	$CHCl_3$, ml	DMF, ml
Chloromethylated polystyrene (1% DVB)	2.0	1.2
Chloromethylated polystyrene (2% DVB)	1.5	0.9
1 (2.4 mmol of Cl/g)	0.4	1.4
1 (0.4 mmol of Cl/g)	0.5	1.2
6 (0.4 mmol of NH_2/g)	2.0	1.2
7 (0.3 mmol of Br/g)	2.0	1.2
8 (0.3 mmol of Boc-Gly/g)	1.8	1.2

peptides could be removed from the *o*-nitrobenzyl resin **1** by photolysis.[13] Using this method the purified protected tripeptide, Boc-Ser(Bzl)-Tyr(Bzl)-Gly (**16**), was obtained in 62% yield based on starting Boc-Gly-resin.[13] However, the synthesis of longer peptides by this method was less successful. Thus, the protected tetrapeptide Boc-Leu-Arg(Tos)-Pro-Gly (**10**) was obtained in only 32% yield after purification.



1a, X = Cl-
b, X = Boc-Gly-O-
c, X = Boc-Ser(Bzl)-Tyr(Bzl)-Gly-O-

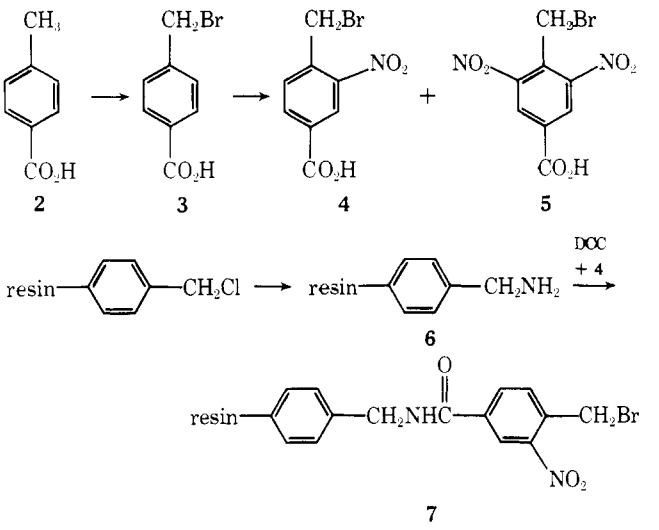
Further study showed that resin **1** (prepared by nitration of 1% crosslinked chloromethylated polystyrene resin) had poor swelling characteristics in some organic solvents. In chloroform resin **1** was found to swell only one-fourth as much as chloromethylated polystyrene resin (Table I). The low extent of swelling of polystyrene resins reduces penetration of solvents and rates of reactions[1] and therefore may have caused the poor yields of the longer chain protected peptides. Each phenyl ring of resin **1** contains a nitro group[1] which greatly increases the polarity of the resin. A more polar resin should swell less in organic solvents with low dielectric constants. In highly polar solvents such as DMF the swelling of resin **1** was found to be identical with that of unnitrated polystyrene resin (Table I) which indicates that the swelling properties of resin **1** are being altered by polarity of the resin and not by an increased crosslinking between polymer chains.

These results led us to synthesize a new nitro resin containing only those nitro groups essential for the photochemical reaction. This resin was expected to retain the swelling characteristics of the chloromethylated polystyrene polymers generally in use and yet possess the photochemically labile *o*-nitro group. In the following section the synthesis of a 3-nitro-4-bromomethylbenzoylamide resin (**7**) is described. Peptides can be synthesized on resin **7** using *tert*-butyloxycarbonylamino acids and conditions commonly employed for solid-phase peptide synthesis.[1] The synthesis of protected fragments of LH-RH[14] is described to illustrate the application of resin **7** to the general problem of solid-phase synthesis of protected peptide fragments suitable for coupling in solution or on a solid support.[10,15-24]

Discussion

The preparation of resin **7** is outlined in Scheme I. Treatment of *p*-toluic acid (**2**) in dry benzene with *N*-bromosuccinimide and benzoyl peroxide under reflux gave α-bromo-*p*-toluic acid (**3**) which upon reaction in 90% nitric acid at $-10°$ was converted to 3-nitro-4-bromomethylbenzoic acid (**4**). At slightly higher temperatures the dinitro acid **5** became the major product. Treatment of chloromethylated polystyrene resin (1% divinylbenzene, 0.40 mmol of chloride/g) with anhydrous ammonia in methylene chloride at 0° for 96 hr gave the aminomethyl resin **6.** After one treatment with the ammonia solution only 60% of chlorine had been replaced. After a second ammonation at 5° all chlorines were replaced by amino groups. The degree of crosslinking of resin **6** was determined to be essentially unchanged judging by the extent of swelling of the resin in chloroform (Table I). At higher temperatures or in different solvent systems such as methanol, methanol–dioxane, or DMF the ammonation step greatly increased the degree of crosslinking. Treatment of the amino resin **6** (0.4 mmol of NH_2/g) with the nitro acid **4** and dicyclohexylcarbodiimide in dimethylformamide followed by acetylation of the residual amino groups by acetic anhydride and diisopropylethylamine gave the nitro resin **7.** The light yellow product contained 0.3 mmol of bromine/g of resin and no detectable free amino groups. The high bromine content and correct nitrogen analysis indicated that little or no alkylation of resin amino groups by bromomethyl groups had occurred. The nitro resin **7** swells in chloroform and all other solvents used in solid-phase synthesis to the same extent as does the chloromethylated polystyrene starting material (Table I).

Scheme I

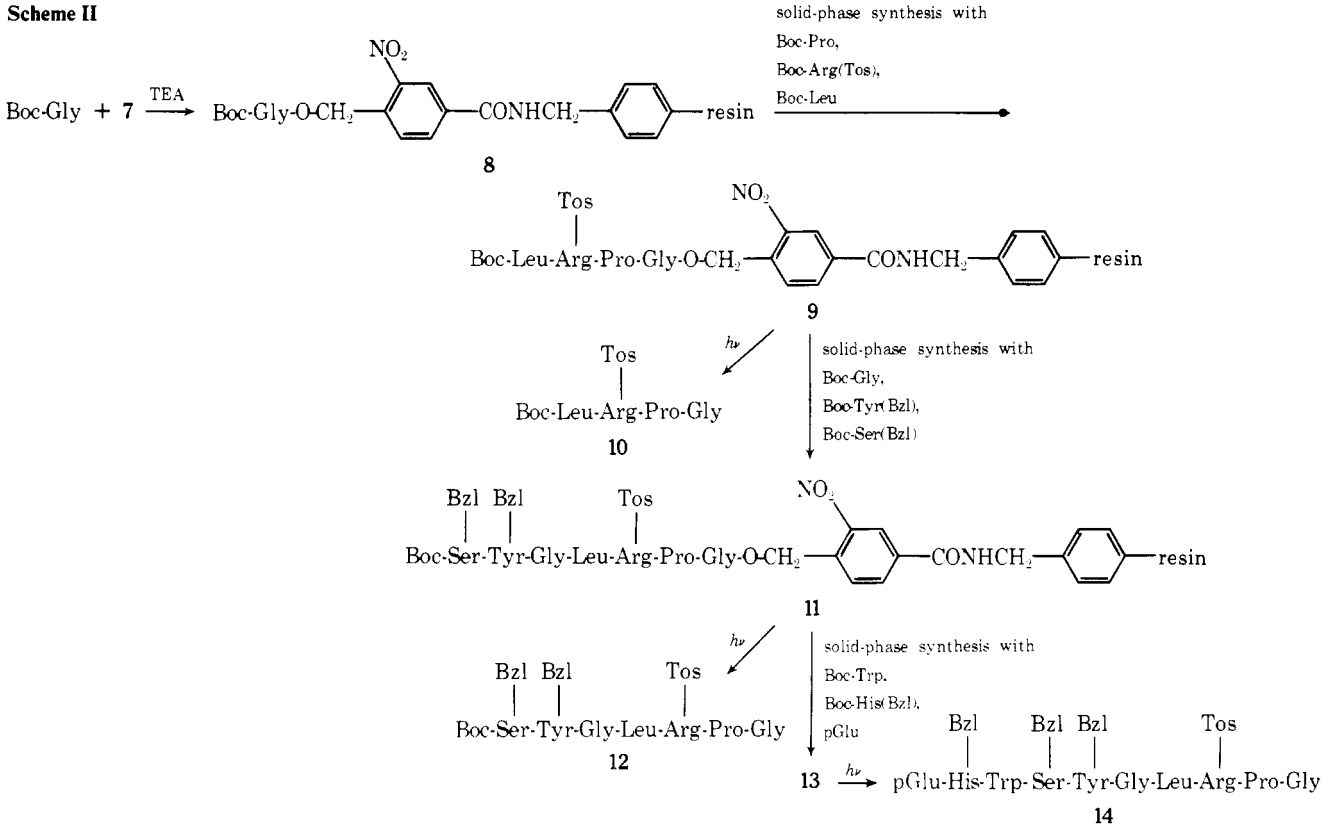


tert-Butyloxycarbonylamino acids can be attached to nitro resin **7** by heating under reflux with triethylamine or diisopropylethylamine in ethyl acetate (Scheme II). The latter amine is preferred since it reduces quaternization of the resin.[11] No racemization has been detected either during attachment or photochemical removal of the amino acid derivatives.[13] The extent of substitution of Boc-Gly resin **8** was 0.3 mmol/g in amino acid. No bromine remained. Treatment of resin **7** with tetramethylammonium salts of *tert*-butyloxycarbonylamino acids[25] or with other strong bases caused some decomposition as seen by a pronounced darkening of the resin. *o*-Nitrobenzyl halides are known to undergo chemical reactions in the presence of strong base.[26]

The *tert*-butyloxycarbonylamino acids and peptides can be released from resin **7** by photolysis in methanol under strictly anaerobic conditions as previously described.[13] The presence of oxygen reduces both the yield and purity of product.

The protected decapeptide **14** was synthesized using the nitroresin **7** (Scheme II). Peptide **14** was chosen for synthesis because it contains a number of photosensitive amino acids such as His, Trp, and Tyr. Esterification of Boc-Gly to resin **7** was achieved as described (vide supra) and Boc-Pro, Boc-Arg(Tos), Boc-Leu, Boc-Gly, Boc-Tyr(Bzl), Boc-Ser(Bzl), Boc-Trp, Boc-His(Bzl), and pGlu were then coupled to the resin in stepwise fashion following the general

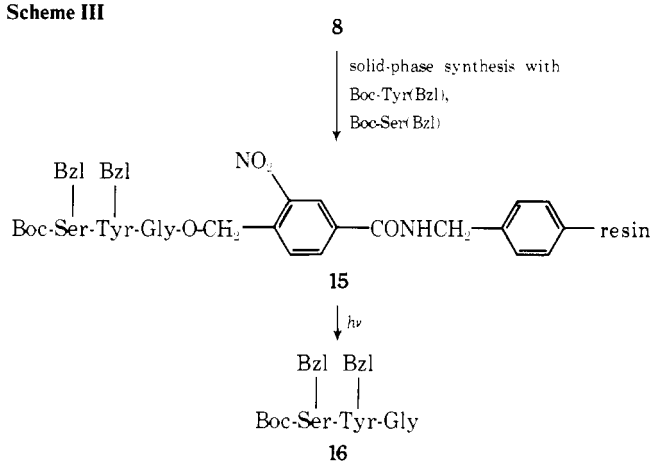
Scheme II



method of Merrifield[1] as modified by Hancock et al.[27] to include a second coupling step for each amino acid in a second solvent system. The coupling step was monitored for completion using the ninhydrin method.[28] The protected decapeptide **14** was removed from resin **13** by photolysis in methanol and purified by gel filtration on Sephadex LH-20 in methanol. After crystallization the analytically pure protected decapeptide **14** was obtained in 64% yield based on starting Boc-Gly resin **8.**

In a similar manner the nitro resin **7** was used to synthesize Boc-Leu-Arg(Tos)-Pro-Gly (**10**) in 56% yield, Boc-(Ser)-Tyr(Bzl)-Gly-Leu-Arg(Tos)-Pro-Gly (**12**) in 50% yield, and Boc-Ser(Bzl)-Tyr(Bzl)-Gly (**16**) in 50% yield (Scheme III).

Scheme III



These yields represent overall yields, based on starting Boc-Gly-resin **8,** of analytically pure products obtained after LH-20 chromatography followed by crystallization.

These results establish that protected peptide acids suitable for fragment coupling in solution or on a solid support can be synthesized in good yield on a preparative scale using resin **7.**

The Boc, Bzl, and tosyl protecting groups are stable to the photolysis conditions. A tosyl group also remains on the imidazole ring of histidine during photolysis. However, dinitrophenyl protection cannot be used on histidine since it will also be photolyzed.

Experimental Section

Material and Equipment. The solvents used for photolysis and synthesis were purchased from Aldrich and were dried and redistilled. Chloromethyl methyl ether, *p*-toluic acid, and *N*-bromosuccinimide were obtained from Aldrich, benzoyl peroxide from Mallinkrodt, and polystyrene resin Bio-Beads S-X1 200–400 mesh from Bio-Rad Laboratories. *tert*-Butyloxycarbonylamino acids were obtained from Beckman. The solid-phase synthesis was done on a Beckman peptide synthesizer Model 990. All photolyses were done in an RPR100 apparatus (Rayonet, The Southern Co., Middletown, Conn.) equipped with RPR 3500-Å lamps. The ^{1}H NMR spectra were obtained on a Bruker HX 90 E spectrometer. The uv spectra were obtained on a Cary 15; infrared spectra obtained on a Perkin-Elmer Model 257 spectrophotometer and optical rotations on a Perkin-Elmer Model 241 polarimeter. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The elemental analyses were done by Galbrith Laboratories, Knoxville, Tenn. Amino acid analyses were obtained on a Beckman Model 120 amino acid analyzer.

General Method for Solid-Phase Synthesis. The solid-phase synthesis was carried out on a Beckman Model 990 peptide synthesizer using the following modified procedure of Yamashiro and Li.[29] (1) Deprotection was achieved by two successive washes (5 and 30 min) of 25% TFA in CH_2Cl_2 which contained 1 mg/ml of indole.[30] (2) Two equivalents of each *tert*-butyloxycarbonylamino acid per equivalent of *tert*-butyloxycarbonylglycine resin was used. (3) A second coupling of each amino acid in 50% DMF–CH_2Cl_2 was performed.[27] (4) The resin was washed with ethanol and dried with nitrogen at the end of each synthesis.

Removal of Protected Peptides from Nitro Resins. A suspension of resin in anhydrous MeOH or EtOH was placed in a flask surrounded by a jacket containing a 40% $CuSO_4$ solution. Dissolved air was removed from the suspension by passing prepurified, O_2-free nitrogen for 2 hr through the solution which was under a slight vacuum. The suspension was then irradiated at 3500 Å for 18–24 hr. Upon completion of photolysis the suspension was filtered and

the resin washed three times for 2 min with 20-ml portions of each of the following solvents: EtOH, CH_2Cl_2, 50% CH_2Cl_2–EtOH, EtOH. The filtrate and washings were evaporated in vacuo. The crude product was purified by chromatography over a Sephadex LH-20 column in methanol (100 g, 2.5 × 80 cm, flow rate 30 ml/hr, fraction volume of 5 ml each). The elution was monitored by a dual beam uv detector from Instrumentation Specialties Co. The products were checked for homogeneity in the following thin-layer chromatography (tlc) solvent systems: 1 (acidic), 1-butanol–acetic acid–water–ethyl acetate (1:1:1:1); 2 (basic), 1-butanol–NH_4OH (7:3); 3, 1-butanol–acetic acid–water (4:1:5 upper layer); 4, chloroform–methanol (7.5:25); 5, chloroform–methanol (1:1).

Aminomethyl Resin (6). The chloromethylated resin (1% DVB) (5.0 g, 0.42 mmol of Cl/g) was suspended in 50 ml of CH_2Cl_2 in a pressure bottle. Dry liquid ammonia (75 ml) was added under nitrogen after 30 min and the suspension was stirred slowly for 96 hr at 5°. The reaction vessel was cooled to −78° and opened, and the suspension was filtered. The resin was washed three times for 2 min with 20-ml portions of each of the following solvents: CH_2Cl_2, MeOH, H_2O, MeOH, MeOH. The resin was air-dried for 1 hr and then dried in vacuo to give a partially ammonated resin (0.16 mmol of Cl/g). The resin was resuspended in 100 ml of CH_2Cl_2 in a pressure bottle. Dry liquid ammonia (25 ml) was added and the suspension was stirred at 5° for 48 hr. The resin was washed and dried as described vide supra to give fully ammonated resin **6** in quantitative yield (5.1 g): ir (KBr) 3400, 1600 cm^{-1}. It contained 0.4 mmol/g of free amine (Dorman method)[31] and no detectable chlorine; 100 mg of resin swelled to 1.0 ml in 10 ml of dry $CHCl_3$.

4-Bromomethylbenzoic Acid (3). Benzoyl peroxide (0.2 g) and *N*-bromosuccinimide (17.8 g, 100 mmol) (recrystallized from hot H_2O) were added to a suspension of *p*-toluic acid (13.6 g, 100 mmol) (recrystallized from $CHCl_3$–MeOH) in dry benzene (100 ml). The mixture was heated at reflux for 24 hr. Removal of the solvent in vacuo gave a white residue which was suspended in 100 ml of boiling H_2O, collected by filtration, and washed with boiling H_2O (4 × 100 ml). The crude product was dried and recrystallized from hot MeOH to give pure acid (17.5 g, 81.4%): mp 224–226°; ir (Nujol) 2800–2400, 1690 (COOH), 1560 cm^{-1} (aromatic); nmr ($CDCl_3$, DMSO-d_6) δ 4.61 (s, 2), 7.8 (8.4, J = 8 Hz), 10.4 (s, 1); uv max (MeOH) 232 mμ (ϵ 1.32 × 10^4), 285 (1166). Anal. Calcd for $C_8H_7BrO_2$: C, 44.68; H, 3.28; Br, 37.15. Found: C, 44.50; H, 3.18; Br, 37.02.

Synthesis of 3-Nitro-4-bromomethylbenzoic Acid (4). The bromo acid **3** (11.8 g) was added in portions over 0.5 hr to 100 ml of 90% HNO_3 (white fuming) at −10°. The suspension was stirred at −10° for an additional 2 hr when the solution became clear orange. This solution was poured onto crushed ice. The product was collected by filtration and washed with ice-cold H_2O (3 × 50 ml) until the washings were neutral. Drying in vacuo followed by crystallization twice from CH_2Cl_2–hexane gave pure nitro acid **4** (11.02 g, 85%): mp 125–126°; ir (Nujol) 2800–2300, 1690, 1610 (COOH), 1600 (aromatic), 1540, 1300 cm^{-1} (NO_2); NMR ($CDCl_3$, DMSO-d_6) 4.9 (s, 2), 7.8 (d, 1), 8.2 (dd, 1), 8.6 (d, 1), 10.8 (s, 1); TLC R_f (5) 0.55, R_f (1) 0.82; uv max (CH_3OH) 227 mμ (ϵ 2.13 × 10^4), 305 (4.1 × 10^3). Anal. Calcd for $C_8H_6NBrO_4$: C, 36.95; H, 2.32; N, 5.38; Br, 30.73. Found: C, 37.16; H, 2.46; N, 5.47; Br, 30.97.

3-Nitro-4-bromomethylbenzoylamide Resin (7). Aminomethylated polystyrene resin **6** (1.0 g, 0.4 mmol of NH_2/g) was added to a solution of the nitro acid **4** (0.52 g, 2 mmol) and DCC (0.42 g, 2 mmol) in DMF (10 ml). The suspension was stirred at room temperature for 18 hr and filtered. The resin was washed with MeOH, CH_2Cl_2, and MeOH (3 × 20 ml for 1 min each), dried in vacuo, and placed again in a solution of 0.260 g of nitro acid **4** and 0.206 g of DCC in 10 ml of DMF. After the same work-up (vide supra) the resin was suspended in CH_2Cl_2 (25 ml), and acetic anhydride (0.61 g, 6 mmol) and DIA (0.774 g, 6 mmol) were added. The suspension was stirred at room temperature for 1 hr, washed with CH_2Cl_2 and MeOH (3 × 20 ml for 1 min), and dried in vacuo to give the desired resin **7** (1.08 g): ir (KBr) 1600 (NH_2), 1560, 1350 cm^{-1} (NO_2). The resin contained 0.3 mmol/g of bromine and no free amine (Dorman);[31] 100 mg of resin swelled to 1.0 mg in dry $CHCl_3$. Anal. Calcd for 0.3 mmol of Br^-/g, 0.6 mmol of N/g: Br, 2.4; N, 0.84. Found: Br, 2.08; N, 0.70.

Glycine Resin (8). The 3-nitro-4-bromomethyl resin **7** (4.0 g, 0.3 mmol of Br^-/g) was added slowly to the solution of *tert*-butyloxycarbonylglycine (0.70 g, 4 mmol) in 20 ml of EtOAc. Diisopropylethylamine (0.52 g, 4 mmol) was added and the suspension was gently heated at reflux for 48 hr. The resin was collected by filtration, washed with EtOAc, MeOH, CH_2Cl_2, and MeOH (3 × 25 ml for 2 min), and dried in vacuo to give the desired product **8** (4.2 g). The resin contained 0.3 mmol/g of *tert*-butyloxycarbonylglycine and no detectable bromine (Dorman method).[31]

Boc-Leu-Arg(Tos)-Pro-Gly (10). The peptide resin **9** (Scheme II) was synthesized as described (vide supra) using *tert*-butyloxycarbonylglycine resin **8** (2.0 g, 0.23 mmol of glycine/g). Amino acid analysis gave Leu 1.0, Arg 0.92, Pro 0.91, Gly 1.01. A suspension of 1.0 g of **9** in absolute EtOH was photolyzed and purified as described under general methods. The purified tetrapeptide **10** was obtained in 56% yield (0.098 g): mp 122–124°; TLC R_f (1) 0.93, R_f (2) 0.29, R_f (3) 0.46, R_f (4) 0.24; uv max (MeOH) 255 mμ (ϵ 1200); NMR was consistent with structure; amino acid analysis gave Leu 1.04, Arg 1.0, Pro 1.0, Gly 1.03; $[\alpha]^{27}D$ −14° (*c* 1, CH_3CO_2H). Anal. Calcd for $C_{31}H_{49}N_7SO_9$: C, 53.51; H, 7.10; N, 14.09; S, 4.61. Found: C, 53.58; H, 7.20; N, 14.28; S, 4.63.

Boc-Ser(Bzl)-Tyr(Bzl)-Gly-Leu-Arg(Tos)-Pro-Gly (12). The synthesis of the peptide resin **11** (Scheme II) was done following the general method using *tert*-butyloxycarbonylglycine resin **8** (2.0 g, 0.3 mmol of glycine/g). Amino acid analysis gave Gly 2.0, Ser 1.3, Pro 1.2, Leu 1.1, Tyr 1.4, Arg 0.8. A suspension of 0.5 g of **11** in absolute MeOH was photolyzed and purified as described under methods. The purified heptapeptide **12** was obtained in 50% yield (0.057 g): mp 135–138°; TLC R_f (1) 0.86, R_f (2) 0.44, R_f (3) 0.87, R_f (4) 0.91; uv max (MeOH) 264 mμ (ϵ 3300); the NMR was consistent with the structure. The amino acid composition was Gly 2.0, Ser 1.06, Pro 0.88, Leu 1.12, Tyr 0.87, Arg 0.73; $[\alpha]^{27}D$ −12° (*c* 1, CH_3CO_2H). Anal. Calcd for $C_{59}H_{78}N_{10}SO_{14}$: C, 59.88; H, 6.64; N, 11.84; S, 2.71. Found: C, 59.96; H, 6.64; N, 11.69; S, 2.89.

pGlu-His(Bz)-Trp-Ser(Bzl)-Tyr(Bzl)-Gly-Leu-Arg(Tos)-Pro-Gly (14). The synthesis of the peptide resin **13** (Scheme II) was done according to the general method described using *tert*-butyloxycarbonylglycine resin **8** (2.0 g, 0.3 mmol of Gly/g). Amino acid analysis gave Gly 2.0, Ser 0.96, Pro 1.05, Glu 1.05, Leu 1.06, Tyr 1.13, Arg 1.10, Bzl(His) 0.86. A suspension of 1.1 g of **13** in absolute ethanol was photolyzed and purified as described (vide supra). The purified protected decapeptide **14** was obtained in 64% yield (0.257 g): mp 155–159°; TLC R_f (1) 0.80, R_f (2) 0.11, R_f (3) 0.75, R_f (4) 0.04; uv max (MeOH) 262 mμ (ϵ 6000); the NMR was consistent with the structure; $[\alpha]^{27}D$ −22° (*c* 1, CH_3CO_2H); the amino acid composition was Gly 1.90, Ser 0.92, Pro 1.0, Leu 1.0, Tyr 0.92, Arg 1.02, Glu 1.02, His(Bzl) 0.97. Anal. Calcd for $C_{83}H_{98}N_{16}CH_2Cl_2$: C, 59.56; H, 5.95; N, 13.23; S, 1.89. Found: C, 59.80; H, 5.44; N, 13.20; S, 1.80.

Boc-Ser(Bzl)-Tyr(Bzl)-Gly (16). The peptide resin **15** (Scheme III) was synthesized according to the general procedure (vide supra) using *tert*-butyloxycarbonylglycine resin **8** (2.0 g, 0.3 mmol of Gly/g). Amino acid analysis gave Ser 1.0, Tyr 0.74, Gly 1.26. A suspension of 0.5 g of **15** was photolyzed and purified as described in general method. The purified tripeptide **16** was obtained in 50% yield (0.045 g) and was found to be identical[13] with a sample prepared by solution procedure: mp 136–137°; TLC R_f (1) 0.71, R_f (2) 0.85, R_f (3) 0.56, R_f (4) 0.45; uv max (MeOH) 258 mμ (ϵ 1800); NMR spectrum was consistent with the structure; amino acid composition Gly 1.16, Tyr 0.89, Ser 1.0; $[\alpha]^{27}D$ −8° (*c* 1, CH_3CO_2H). Anal. Calcd for $C_{33}H_{39}N_3O_8$: C, 65.44; H, 6.49; N, 6.94. Found: C, 65.21; H, 6.39; N, 7.08.

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(14) Abbreviations used are Boc, *tert*-butyloxycarbonyl; Bzl, benzyl; Tos, *p*-toluenesulfonyl; DCC, dicyclohexylcarbodiimide; TFA, trifluoroacetic acid; DMF, dimethylformamide; DVB, divinylbenzene; LH-RH, luteinizing hormone-releasing hormone; TEA, triethylamine; DIA, diisopropylethylamine.
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Communications to the Editor

Stabilization in Cyclopentadienyl, Cyclopentenyl, and Cyclopentyl Cations

Sir:

Breslow and Hoffman[1] have reported the rate of the silver-assisted solvolysis of 5-cyclopentadienyl iodide to be at least 10^5 times slower than that of cyclopentyl iodide. They concluded that the c-$C_5H_5^+$ cation is therefore antiaromatic and exhibits conjugative destabilization. Recent gas-phase experiments in this laboratory provide striking support for their findings. Using an electron monochromator–mass spectrometer combination, described previously,[2,3] the ionization potentials of cyclopentyl, cyclopentenyl, and cyclopentadienyl radicals, produced in pyrolytic reactions, have been measured as follows (eV): cyclopentyl, 7.47; cyclopentenyl, 7.00; and cyclopentadienyl, 8.41. These electron impact ionization thresholds are probably not more than 0.1 eV above the adiabatic ionization potentials, owing to the energy resolution (0.07 eV fwhm) and high sensitivity available in this apparatus.[4]

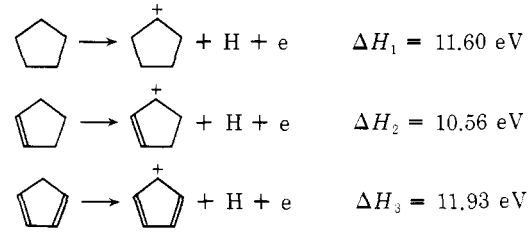
Production of the radicals was carried out in a fused-silica reactor at millisecond contact times[3] as follows: cyclopentyl from cyclopentyl methyl nitrite at 350°, cyclopentenyl from 3-allyl cyclopentane at about 800°, and cyclopentadienyl from allyl phenyl ether. In the latter reaction the phenoxy radical produced in the primary bond scission decomposed further to CO + cyclopentadienyl radical[5] at about 950°.

The heats of formation of the neutral radicals are reasonably well-established as follows (kcal/mol): cyclopentyl, 24.4;[6,7] cyclopentenyl, 37.8;[8] and cyclopentadienyl, 60.9 ± 1.2.[9] Combined with the ionization potentials given above, these give the following ionic heats of formation (kcal/mol): c-$C_5H_9^+$, 197; c-$C_5H_7^+$, 199; and c-$C_5H_5^+$, 255. These values are to be preferred to those derived from dissociative ionization thresholds, since they correspond to ionic structures of known identity and are probably good to within ±3 kcal/mol.

The relative stabilization of the three cations is most easily compared by reference to enthalpies of the general reaction

$$RH \rightarrow R^+ + H + e$$

calculated from $\Delta H_f(R^+)$ and standard heats of formation[10] of the hydrocarbons RH. The corresponding reactions are given below, together with the enthalpies calculated from the present data. It can be seen that while the intro-



duction of one double bond into the C_5 ring brings about a stabilization of 1.04 eV, the second double bond destabilizes the cyclopentenyl cation by 1.37 eV. The c-$C_5H_5^+$ ion is consequently destabilized by 0.33 eV (7.6 kcal/mol) with respect to the cyclopentyl cation. This is in close agreement with the solvolysis rate difference of 10^5 found by Breslow and Hoffman,[1] which corresponds to a difference in transition state energies of 7 kcal/mol.[11]

A fuller account of these results will form part of a later publication.[12]

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