by pulse radiolysis are also given on the same relative scale. An absolute comparison of the rates in the two phases has not been made. The semiquantitative correlation of the rates for e_{aq}^- and e_m^- is extremely striking and supports the conclusion that entropic effects are responsible for the rate differences between different solutes. The correlation also implies that one may properly describe e_m^- as a mobile solvated electron in ice.

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Synthesis of Human Angiotensin I[1,2]

Sir:

Human angiotensin has recently been purified from the incubation mixture of human serum protein and renin.[3] The amino acid sequence of isolated human angiotensin appears to be identical[4] with that of horse angiotensin I,[5] *i.e.*, L-Asp-L-Arg-L-Val-L-Tyr-L-Ile-L-His-L-Pro-L-Phe-His-L-Leu, which has not been synthesized before. We wish to report the synthesis of this decapeptide and its identity with the human natural peptide in chemical and biological properties.

L-Leucine *p*-nitrobenzyl ester *p*-toluenesulfonate (I), mp 201–202°, $[\alpha]^{22}D$ +10.2° (ethanol), was prepared in 67% yield by heating a mixture of L-leucine, nitrobenzyl alcohol, toluenesulfonic acid, and benzene. *Anal.* Calcd for $C_{20}H_{26}O_7N_2S$: C, 54.78; H, 5.98; N, 6.39. Found: C, 54.42; H, 5.98; N, 6.41. Condensation of benzyloxycarbonyl-*im*-benzyl-L-histidine (II)[6] with I by the dicyclohexylcarbodiimide method[7] gave oily Z-His(*im*-Bzl)-Leu-OBzl(NO_2) (III), 89%, R_f 0.76.[8] Debenzyloxycarbonylation of III with HBr in acetic acid yielded oily H-His(*im*-Bzl)-Leu-OBzl(NO_2)·2HBr (IV), 95%, R_f 0.76.[8] Condensation of II with H-Pro-Phe-OEt·HCl[9] by the dicyclohexylcarbodiimide method gave oily Z-His(*im*-Bzl)-Pro-Phe-OEt in 75% yield, R_f 0.73,[8] which was treated with hydrazine to afford semicrystalline Z-His(*im*-Bzl)-Pro-Phe-$NHNH_2$ (V), 85%, R_f 0.73.[8] Oily Z-His(*im*-Bzl)-Pro-Phe-His(*im*-Bzl)-Leu-OBzl(NO_2), R_f 0.84,[8] obtained in 46% yield from the azide derived from V with IV, was converted to oily H-His(*im*-Bzl)-Pro-Phe-His(*im*-Bzl)-Leu-OBzl(NO_2)·3HBr (VI), 95%, R_f 0.76.[8] Condensation of benzyloxycarbonyl-O-benzyl-L-tyrosine[10] with L-isoleucine ethyl ester by the mixed anhydride method with isobutyl chloroformate[11] gave Z-Tyr(O-Bzl)-Ile-OEt (VII), 82%, mp 127–128°, $[\alpha]^{20}D$ +10.7° (acetic acid). *Anal.* Calcd for $C_{32}H_{38}O_6N_2$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.43; H, 7.03; N, 5.18. Hydrogenolysis of VII yielded oily H-Tyr-Ile-OEt·HCl (VIII), 94%, R_f 0.77.[8] Condensation of benzyloxycarbonyl-L-valine with VIII by the mixed anhydride method[11] gave Z-Val-Tyr-Ile-OEt in 82% yield, mp 190–191°, $[\alpha]^{22}D$ −20.2° (acetic acid) (*Anal.* Calcd for $C_{30}H_{41}O_7N_3$: C, 64.84; H, 7.44; N, 7.56. Found: C, 64.68; H, 7.30; N, 7.75), which was converted to Z-Val-Tyr-Ile-$NHNH_2$ (IX) in 97% yield, mp 278–280°. *Anal.* Calcd for $C_{28}H_{39}O_6H_5 \cdot 0.5H_2O$: C, 61.07; H, 7.32; N, 12.71. Found: C, 60.98; H, 7.26; N, 12.59. Condensation of the azide derived from IX with VI yielded acyloctapeptide ester, Z-Val-Tyr-Ile-His(*im*-Bzl)-Pro-Phe-His(*im*-Bzl)-Leu-OBzl(NO_2) (X), 34%, mp 130–134°, $[\alpha]^{18}D$ −41.0° (acetic acid). *Anal.* Calcd for $C_{81}H_{95}O_{14}N_{13} \cdot H_2O$: C, 65.17; H, 6.55; N, 12.20. Found: C, 65.06; H, 6.95; N, 12.05. Oily octapeptide trihydrobromide obtained from X in 97% yield, R_f 0.60,[8] was condensed with a mixed anhydride[11] of benzyloxycarbonyl-nitro-L-arginine[12] to yield Z-Arg(NO_2)-Val-Tyr-Ile-His(*im*-Bzl)-Pro-Phe-His(*im*-Bzl)-Leu-OBzl(NO_2) (XI), 78%, mp 138–142°, $[\alpha]^{18}D$ −32.5° (acetic acid). *Anal.* Calcd for $C_{87}H_{106}O_{17}N_{18} \cdot 6H_2O$: C, 58.57; H, 6.67; N, 14.13. Found: C, 58.29; H, 6.57; N, 14.44. Coupling of oily nonapeptide trihydrobromide, obtained from XI in 96% yield, with a mixed anhydride[11] of benzyloxycarbonyl-β-benzyl-L-aspartic acid[13] yielded Z-Asp(β-Bzl)-Arg(NO_2)-Val-Tyr-Ile-His(*im*-Bzl)-Pro-Phe-His(*im*-Bzl)-Leu-OBzl(NO_2) (XII), 79%, mp 140–144°, $[\alpha]^{18}D$ −30.0° (acetic acid), R_f 0.90.[8] *Anal.* Calcd for $C_{98}H_{117}O_{20}N_{19} \cdot 6H_2O$: C, 59.17; H, 6.54; N, 13.39. Found: C, 58.82; H, 6.34; N, 13.38. XII (200 mg) in a solvent of methanol–acetic acid–water (60:20:15) was hydrogenated with palladium black at room temperature for 48 hr.[14] The filtrate from the catalyst was evaporated, and the residue, 130 mg, was collected with the aid of a mixture of acetone and ether. This material was purified by subsequent column chromatography using carboxymethylcellulose, DEAE-Sephadex A-25, and Bio-Gel P-2 which have proved to be most effective in isolating natural human angiotensin I.[4] The active fractions from the Bio-Gel column with 0.1 N acetic acid as a developing solvent were lyophilized, leaving a white powder, 8.6 mg; amino acid ratios in acid hydrolysate, were $Asp_{0.98}Arg_{1.03}Val_{1.12}Tyr_{0.88}Ile_{0.92}His_{1.98}Pro_{1.10}Phe_{1.03}Leu_{1.06}$. In-

(1) This work was supported in part by U. S. Public Health Service Grant No. HE 09429-02.

(2) The abbreviation followed are from *J. Biol. Chem.*, **241**, 2491 (1966): Z, benzyloxycarbonyl; Bzl, benzyl; OBzl(NO_2), *p*-nitrobenzyl ester; $NHNH_2$, hydrazide.

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(8) The R_f on thin layer chromatography refers to the system 1-butanol–acetic acid–pyridine–water (4:1:1:2, v/v). Compounds possessing a free amino group were detected by spraying with ninhydrin, and those with a blocked amino group by spraying with 47% hydrobromic acid and then with ninhydrin.

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(14) The reaction was followed at various times with the chromatographic properties and the bioassay of the pressor activity, and the highest activity was observed after the hydrogenation of some 48 hr. However, chromatography indicated that the considerable part of the imidazoyl benzyl groups remained untouched, and this fact might be one of the reasons that the yield of pure product (8.6 mg) was poor. Treatment of the hydrogenated material of XII with sodium–liquid ammonia did not give a product bearing strong pressor activity.

cubation of the sample with carboxypeptidase A[15] caused the liberation of Leu, His, and Phe, while with leucine aminopeptidase,[16] the sample was degradated completely to nine amino acid residues, leaving no decapeptide. These data confirm the stereochemical purity of the product.

The preparation was chromatographed on Toyo Roshi No. 51 paper (solvent: 1-butanol–acetic acid–water, 7:1:2) and on Serva tlc thin layer (solvent: *sec*-butyl alcohol–3% ammonium hydroxide, 100:44); the R_f values, 0.51 and 0.71, respectively, were identical with those of natural human angiotensin I.[4] The chemical identity was confirmed further by the cochromatography of a mixture of the preparations from the synthesis and the human origin with the Bio-Gel column (solvent: 0.1 *N* acetic acid). The rat pressor activity[4] of the synthetic decapeptide was identical with that of natural human angiotensin I and 48% of that of synthetic octapeptide (Ile^5-angiotensin II).[17] Both synthetic and natural human angiotensin I thus showed quite identical chromatographical and biological properties.

The results obtained here further confirm the correctness of the structure of human angiotensin I as the decapeptide of the amino acid sequence mentioned above.

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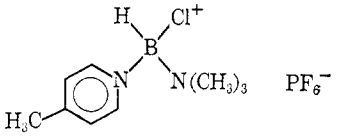
An Optically Active Boron Cation

Sir:

We wish to report the synthesis of a salt containing an asymmetric boron atom and the first resolution of a boron cation into optically active isomers.

Trimethylamine monoiodoborane was prepared by a modification of the method of Noeth[1] by adding solid iodine (0.050 mole) in portions to a cooled and stirred benzene solution of trimethylamine borane (0.110 mole). Reaction of the resulting solution with dry 4-picoline (94 ml) in an ice bath gave within 5 min a precipitate of the iodide salt of the picolinetrimethylaminedihydroboron cation (0.096 mole, mp ~150° dec). The water-soluble iodide was readily converted to the less soluble hexafluorophosphate by addition of excess NH_4PF_6.[2] Recrystallization from hot water gave pure $CH_3C_5H_4N(CH_3)_3NBH_2PF_6$ (93% yield, mp 146.5–147.0°). *Anal.* Calcd for $C_9H_{18}BF_6N_2P$: C, 34.87; H, 5.85; B, 3.49; F, 36.77; N, 9.04; P, 9.99. Found: C, 34.92; H, 5.96; B, 3.39; F, 36.56; N, 8.92; P. 9.80. The dihydro compound reacted with chlorine[3] in methylene chloride solution at room temperature producing the asymmetric boron compound (I) in nearly quantitative



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yield. Recrystallization from methylene chloride–tetrahydrofuran–diethyl ether gave 97% recovery of pure product, mp 119.8–120.3°. *Anal.* Calcd for $C_9H_{17}BClF_6N_2P$: C, 31.38; H, 4.97; B, 3.14; Cl, 10.29; F, 33.09; N, 8.13. Found: C, 31.52; H, 5.02; B, 3.06; Cl, 10.44; F, 33.30; N, 8.15.

The ^{11}B resonance spectra are in agreement with the expected structures, showing a triplet for the dihydro compound (δ 17.8 ± 0.5 ppm,[4] J_{B-H} = 90 ± 5 cps) and a doublet for the monochloro compound (δ 9.3 ± 0.8 ppm, J_{B-H} = 140 ± 15 cps). The proton nmr spectra of the PF_6^- salts, obtained in CH_2Cl_2 and referred to external tetramethylsilane, gave resonances at δ (ppm) 2.67 (9 H), 2.63 (3 H), 7.78 (2 H, doublet, J = 7 cps), and 8.55 (2 H, doublet, J = 7 cps) and for the monochloro compound at δ (ppm) 2.78 (9 H), 2.70 (3 H), 7.87 (2 H, doublet, J = 6 cps), and 8.75 (2 H, doublet, J = 7 cps). Boron-attached hydrogens could not be detected because of excessive line broadening.

Attempts to resolve the asymmetric boron cation with the ammonium salt of *d*-α-bromocamphor-π-sulfonic acid or with potassium *d*-antimonyl tartrate were unsuccessful because of unfavorable solubility relationships and because the boron compound slowly reduces the antimonyl complex in hot water. However, partial resolution was achieved without an optically active resolving agent in the following manner. Two grams of the hexafluorophosphate salt was dissolved in 50 ml of hot methylene chloride, and enough cyclohexane was added to cause a slight precipitate which was redissolved by the addition of 2–3 ml of acetone. On very slow cooling and evaporation there were produced relatively large crystals.

A few crystals were well defined having relatively sharp edges and rhombohedral faces. These crystals were weighed individually and then dissolved separately in methylene chloride. Optical rotations were measured on a digital readout polarimeter. Both negative and positive readings were observed. As an example, a crystal weighing 84 mg was dissolved in 1.2 ml of methylene chloride. The observed rotation was −0.315 ± 0.003°. In another case, a solution containing 257 mg of optically active boron compound per milliliter of methylene chloride gave a rotation of +1.120 ± 0.003°. Specific rotations of solutions of single crystals varied from $[\alpha]^{24}_{365m\mu}$ −5.1 to +4.1; the samples were therefore not optically pure. These rotations did not change significantly upon standing in stoppered tubes for periods as long as 5 days. For a given solution the amount of rotation was found to decrease with increasing wavelength. Nmr spectra taken before and after recrystallization showed no change other than a trace of acetone which apparently occluded during the crystallization process. We are now attempting large-scale and complete resolution

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