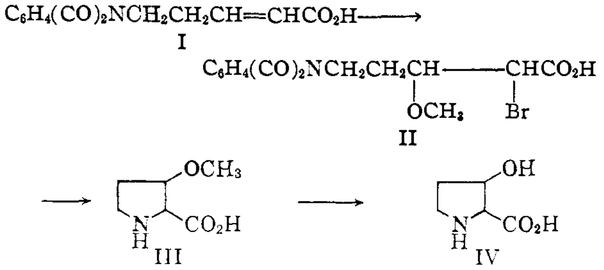
THE ISOLATION, CHARACTERIZATION AND SYNTHESIS OF 3-HYDROXYPROLINES

Sir:

Among the acidic hydrolysis products of the antibiotic Telomycin[1] we have found two amino acids not previously encountered in nature[2] or known synthetically. These two amino acids are designated as "slow moving" and "fast moving" hydroxyprolines, which relates to the difference in their behavior upon electrophoresis. Each amino acid has an analysis corresponding to $C_5H_9NO_3$ and affords proline upon reduction with red phosphorus and hydrogen iodide.[3] We also wish to report the synthesis of two racemates of 3-hydroxyproline, which correspond in chemical and physical properties to the two amino acids from Telomycin.



$C_6H_4(CO)_2NCH_2CH_2CH{=}CHCO_2H \longrightarrow$

I

$C_6H_4(CO)_2NCH_2CH_2\underset{OCH_3}{CH}-\underset{Br}{CHCO_2H}$

II

III

IV

5-Phthalimido-2-pentenoic acid (I)[4] was converted to 2-bromo-3-methoxy-5-phthalimidopentanoic acid (II) by a modification of the procedure of Carter and West[5a] for the preparation of 2-bromo-3-methoxybutyric acid from crotonic acid. The racemates of II were separated by fractional crystallization from toluene (IIA, 15%; m.p. 150–153°; *Anal.* Found: C, 47.44; H, 3.99; N, 4.26; Br, 23.25) (IIB, 13%; m.p. 112–114°; *Anal.* Found: C, 47.46; H, 3.95; N, 3.96; Br, 22.16).

The phthaloyl group was removed from IIA by titration with base at 0°,[6] then hydrolysis (1 hour in *N* hydrochloric acid at reflux). Phthalic acid, in almost quantitative yield, was separated by extraction into ether and, after concentration, the amine hydrochloride was treated with base to effect cyclization.[7] Neutralization followed by separation from sodium chloride on a sulfonic acid type cation exchange resin (ammonia elution) afforded one racemate of 3-methoxyproline (IIIA) in 34% over-all yield from IIA, m.p. 205.5–206.5°; *anal.* Found: C, 49.47; H, 7.54; N, 9.16.

Treatment of IIIA with constant-boiling hydrobromic acid, under reflux,[5a,b] afforded a single racemate of 3-hydroxyproline (IVA), 84%; m.p. 225–235° dec.; *anal.* Found: C, 45.76; H, 6.75; N, 10.73.

When the foregoing reaction sequence was carried out on IIB, a mixture of racemates of 3-methoxyproline (IIIA and IIIB) was obtained. These were separated by fractional crystallization of the copper salts (copper salt of IIIA is water-soluble; copper salt of IIIB is sparingly water-soluble) and regenerated on a cation exchange resin[8] (IIIA, 23%; m.p. 205.5–206.5°; mixture m.p. with IIIA (from IIA) undepressed) (IIIB, 13%; m.p. 184–185°; *anal.* Found: C, 49.65; H, 7.56; N, 9.54.) Compound IIIB afforded a single racemate of 3-hydroxyproline (IVB) in 84% yield, m.p. 223–230° dec.; *anal.* Found: C, 45.77; H, 6.85; N, 10.39.

The "fast moving" and "slow moving" hydroxyprolines from Telomycin were shown to correspond to IVA and IVB, respectively, by electrophoresis,[9a] paper chromatography[9b,c] and color reactions.

The relative mobilities (taking 4-hydroxyproline as unity) were: electrophoresis: 4-Hypro (1), *allo*-4-Hypro (1.15), IVA (1.15), IVB (0.83), "fast moving" Hypro (1.15), "slow moving" Hypro (0.83); paper chromatography (9b,9c): 4-Hypro (1,1), *allo*-4-Hypro (1.35, 1), IVA (1.80, 1.29), IVB (1.16, 1.08), "fast moving" Hypro (1.80, 1.29), "slow moving" Hypro (1.16, 1.08).

"Fast moving" hydroxyproline, "slow moving" hydroxyproline, IVA and IVB all gave a yellow color with ninhydrin spray but only "fast moving" hydroxyproline and IVA gave a color (blue) with isatin spray.

Acknowledgments.—J. G. W. was aided by a National Institutes of Health Predoctoral Fellowship (GPM 12,279 Cl): We are indebted to Bristol Laboratories (Division of Bristol-Myers Company) of Syracuse, N. Y., for a supply of Telomycin.

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(3) J. C. Sheehan, P. E. Drummond, J. N. Gardner, K. Maeda, D. Mania, A. K. Sen and J. A. Stock, in preparation.

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(5) (a) H. E. Carter and H. D. West, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons., Inc., New York, N. Y., 1955, p. 813. (b) Refluxing hydrobromic acid converted O-methylthreonine to threonine.

(6) Reference 5a, p. 774, by a similar procedure methyl 2-bromo-3-methoxypropionate was saponified without loss of the bromine group.

(7) N. F. Albertson and J. L. Fillman, *J. Am. Chem. Soc.*, **71**, 2818 (1949). By this same procedure 2-chloro-5-aminopentanoic acid hydrochloride was cyclized to proline.

(8) M. Sato, K. Okawa and S. Akabori, *Bull. Chem. Soc. Japan*, **30**, 937 (1957).

(9) (a) pH 1.9; 3 kv.; 3 hours. (b) *n*-Butyl alcohol saturated with water with 10% v./v. of diethylamine; 120 hours; Whatman no. 1 paper; T. L. Hardy and D. O. Holland, *Chemistry and Industry*, 855 (1952). (c) *n*-Butyl alcohol–water–acetone–concentrated ammonium hydroxide (8:6:1:1); 116 hours; Whatman no. 1 paper; N. F. Shaw and S. W. Fox, *J. Am. Chem. Soc.*, **75**, 3421 (1953).

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RECEIVED AUGUST 6, 1962

ON THE STRAIN ENERGY IN CYCLOPROPENE AND THE HEAT OF FORMATION OF THE $C_3H_3^+$ ION

Sir:

The cyclopropenyl cation is predicted by the simple molecular orbital theory to have a significant delocalization energy.[1] For some time, we have been trying to obtain the ion by reactions such as the hydride abstraction from cyclopropene[2] *via* the

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(1) J. D. Roberts, A. Streitwieser, Jr., and C. M. Regan, *J. Am. Chem. Soc.*, **74**, 4579 (1952).

(2) K. B. Wiberg, Abstracts 131st Meeting of the Am. Chem. Soc., Miami, April 7–12, 1957, p. 39-O. Aryl and alkyl substituted cyclo-

trityl cation.[3] It has not been possible to obtain the ion from these reactions, and thus we have been led to examine the heat of formation of the ion in the gas phase.

It is first necessary to know the heat of formation of cyclopropene. This now has been determined using a flame calorimeter,[4] giving a heat of combustion, ΔH_c^{298} (g, 1 atm.) 485 ± 0.6 kcal./mole. This corresponds to a heat of formation (298°) of 66.6 ± 0.6 kcal./mole.[5] There are several interesting numbers which may be derived from this. First, the heat of hydrogenation to cyclopropane (ΔH_f^{298} 12.7 kcal./mole)[6] should be −53.9 kcal./mole as compared to a "normal" value of about −27 kcal./mole.[7] The extra strain energy in cyclopropene, over that in cyclopropane, is then on the order of 27 kcal./mole. Similarly, the heat of isomerization to methylacetylene is −22 kcal./mole as compared to the heat of isomerization of cyclopropane, −7.9 kcal./mole.[6]

The appearance potential for the process

$$RH + e^- \longrightarrow R^+ + H\cdot + 2e^-$$

may be determined mass spectrometrically. The values are available for methylacetylene and allene,[8] and one now has been obtained for cyclopropene. The data are given in Table I.

TABLE I

APPEARANCE POTENTIAL FOR VARIOUS $C_3H_3^+$ IONS

Hydrocarbon	ΔH_f	A.P. (ion), e.v.	ΔH_f(ion), kcal./mole
Cyclopropene	66.6 ± 0.6	11.15 ± 0.06	272 ± 2
Methylacetylene	44.3 ± .02	12.06 ± .06	270 ± 1
Allene	45.9 ± .22	12.02 ± .03	271 ± 1

There are three alternative conclusions which may be derived from these data: (1) The ions have two or more different structures, and the identity of the heats of formation is accidental. (2) All ions have the same structure, that of the propargyl cation. (3) All ions have the same structure, that of the cyclopropenyl cation.

At the present time, there are no data which permit one to dismiss the first possibility. However, it would be remarkable if these three compounds and several others[8] should give $C_3H_3^+$ ion with different structures and the same energy. The similarity of the mass spectra of the three compounds at higher ionizing potentials also suggests that the ions have the same structure.

If one considers the other two possibilities, one datum favors the third. Collin and Lossing[8] have shown that the ratio of $C_3D_3^+$ to $C_3D_2H^+$ peaks in the mass spectrum of methyl-d_3-acetylene is 1:3 indicating equivalence of the C–H and C–D bonds before the loss of a hydrogen atom. This suggests that the carbons also become equivalent, leading to a cyclic structure.

It is of interest to compare the delocalization energies of the $C_3H_3^+$ ion and the allyl cation. To a first approximation this is given by the difference in the ionic bond dissociation energies of the species formed by removing an electron from propylene and from cyclopropene. This is given by

$$D(\text{allyl}^+\text{–H}) - D(C_3H_3^+\text{–H}) = \Delta H_f(\text{allyl}^+) - \Delta H_f(C_3H_3^+) - \Delta H_f(\text{propylene}^+) + \Delta H_f(\text{cyclopropene}^+)$$

The heat of formation of the allyl cation may be obtained from the C–H bond dissociation energy of propylene (79 kcal./mole)[9] and the ionization potential of the allyl radical (8.16 e.v.)[10] giving ΔH_f (allyl+) = 220 kcal./mole.[11] Using I(propylene) = 9.84 ev.,[12] I(cyclopropene) = 9.95 ev.[13] and $\Delta H_f(C_3H_3^+)$ = 271 kcal./mole, one finds

$$D(\text{allyl}^+\text{–H}) - D(C_3H_3^+\text{–H}) = 14 \text{ kcal./mole}$$

The difference in the ionic bond dissociation energies does not include the difference in the energies of the reference structures. The reference structure for the allyl cation would have a primary carbonium ion and a terminal double bond whereas that for the cyclopropenyl cation (if that were the structure of the ion) would have a secondary carbonium ion and an internal double bond. Rough corrections may be made using Franklin's group equivalents[11] which will reduce the value by about 4 kcal./mole.

The value thus obtained, about 10 kcal./mole, is considerably less than might be expected based on the simple molecular orbital method which gives a difference of 1.2 β between the allyl and cyclopropenyl cations. It may, however, be reasonable if one considers the probable increase in strain in going from cyclopropene to the cyclopropenyl cation, and remembers that the inclusion of the electron repulsion integrals will reduce the calculated delocalization energy of the cyclic ion more than that of the linear ion. Alternately, one may consider the small difference in delocalization energy as indicating the propargyl cation structure.

Financial support from the U. S. Army Research Office is gratefully acknowledged.

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RECEIVED AUGUST 16, 1962

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propenyl cations have been obtained by R. Breslow and his co-workers (*J. Am. Chem. Soc.*, **79**, 5318 (1957); **80**, 5991 (1958); **82**, 2644 (1960)).

(3) In analogy with the formation of the cycloheptatrienyl cation: H. J. Dauben, Jr., F. A. Gadecki, K. M. Harmon and D. L. Pearson, *ibid.*, **79**, 4557 (1957).

(4) The procedure described by F. D. Rossini, *et al.*, *J. Research Natl. Bur. Standards*, **6**, 1 (1931); **19**, 249 (1937); **42**, 269 (1949), was used. As a check, the heat of combustion of propylene was determined giving ΔH_c^{298} (g, 1 atm.) 491.9 ± 0.4 kcal./mole as compared with the literature value, 491.8 ± 0.15 kcal./mole (F. D. Rossini and J. W. Knowlton, *ibid.*, **19**, 249 (1937).

(5) The entropy and the variation of the thermodynamic functions with temperature are available elsewhere: K. B. Wiberg and W. J. Bartley, *J. Am. Chem. Soc.*, **82**, 6375 (1960).

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(8) J. Collin and F. P. Lossing, *ibid.*, **79**, 5848 (1957); **80**, 1568 (1958).

(9) C. A. McDowell, F. P. Lossing, I. H. S. Henderson and J. B. Farmer, *Can. J. Chem.*, **34**, 345 (1956).

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(11) A somewhat larger value, 228 kcal./mole, is obtained from the appearance potential (11.95 e.v.) of the $C_3H_5^+$ ion from propylene: F. H. Field and J. L. Franklin, "Electron Impact Phenomena," Academic Press, New York, N. Y., 1957.

(12) R. E. Honig, *J. Chem. Phys.*, **16**, 105 (1948).

(13) J. Collin and F. P. Lossing, *J. Am. Chem. Soc.*, **81**, 2064 (1959).

(14) Department of Chemistry, Yale University, New Haven, Conn.