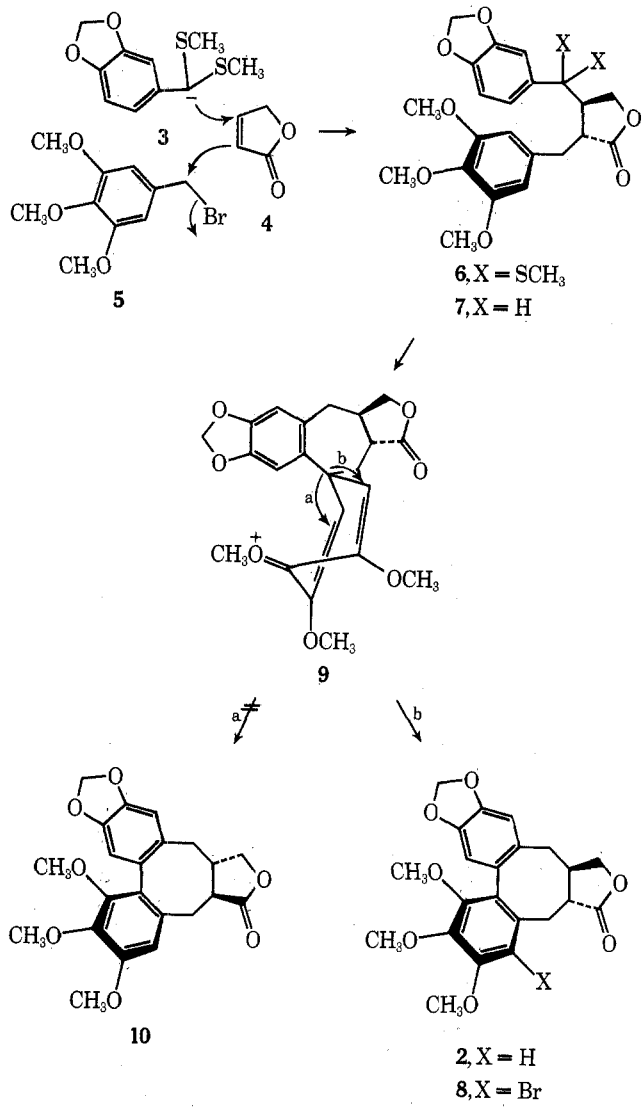

pulse height discrimination). The size of the crystal used for data collection was approximately 00.2 × 0.25 × 0.30 mm; the data were corrected for absorption (μ = 34.5 cm^{-1}). Of the 2706 independent reflections with $\theta < 57°$, 1859 were considered to be observed. The structure was solved by a multiple solution procedure[13] and was refined by full matrix least squares. In the final refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R = 0.059 and wR = 0.056 for the 1859 observed reflections. The final difference map has no peaks greater than ±0.4 e A^{-3}. The computer drawing of compound **8** (Figure 1) clearly indicates that **8**, and therefore compound **2**, possess the unnatural biphenyl configuration.[14]

The exclusive formation of **2** as opposed to compound **10** (the natural biphenyl configuration) must occur during the VOF_3 cyclization of compound **7**. One possible explanation for this stereochemical result involves the intermediacy of the spirodiene **9**.[15] Phenyl migration in **9** via path a leads to stegane (**10**) whereas phenyl migration via path b gives rise to isostegane (**2**). Inspection of molecular models indicate path b is considerably more favored on the basis of configurational interactions than is path a.[16]

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References and Notes

(1) We suggest the name isostegane instead of deoxyisosteganone to denote both the lack of ketonic oxygen and the unnatural biphenyl twist. The name stegane is used instead of deoxysteganone.
(2) S. M. Kupchan, R. W. Britton, M. F. Ziegler, C J. Gilmore, R. J. Restivo, and R. F. Bryan, *J. Am. Chem. Soc.*, **95**, 1335 (1973).
(3) (a) L. R. Hughes and R. A. Raphael, *Tetrahedron Lett.*, 1543 (1976); (b) A. S. Kende and L. S. Liebeskind, *J. Am. Chem. Soc.*, **98**, 267 (1976); (c) F. E. Ziegler and J. A. Schwartz, *Tetrahedron Lett.*, 4643 (1975); (d) D. Becker, L. R. Hughes, and R. A. Raphael, *Chem. Commun.*, 430 (1974).
(4) We have been involved with this type of multi carbon–carbon bond forming reaction sequence using two electrophiles and one nucleophile for some time. See for example (a) J. L. Herrmann, M. H. Berger, and R. H. Schlessinger, *J. Am. Chem. Soc.*, **95**, 7923 (1973); (b) R. F. Romanet and R. H. Schlessinger, *ibid.*, **96**, 3701 (1974). A similar conjugate addition alkylation reaction has been reported in ref 3c.
(5) This compound was prepared in essentially quantitative yield from piperonal using standard reaction conditions.
(6) Prepared in 75% overall yield starting from butyrolactone using a modified procedure based on the reported by C. C. Price and J. M. Judge, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 255.
(7) Compound **5** (mp 73 °C) was prepared in 62% overall yield from gallic acid using standard reaction procedures.
(8) It is important to note that the alkylation segment of this reaction sequence occurs in good yield only if tetramethylethylenediamine is added, and, further, only if this reagent is added after the alkylating agent.
(9) All new compounds exhibited satisfactory spectral and physical data.
(10) Transformation **7** to **2** represents the second example of this type of cyclization successfully applied to the preparation of a cyclooctadiene system; the first example of this reaction type is described in ref 3b. It should be noted however, that the conversion of **7** into **2** is the only example of this cyclization reaction which leads directly to a tetracyclic cyclooctadiene system.
(11) This reaction may be carried out at significantly higher concentrations with a minimal loss in yield (5 to 10%). The remainder of the reaction mixture consists of phenolic substances which have not been fully characterized. A wide variety of other two-electron-transfer oxidants failed to bring about the conversion of **7** into **2**.
(12) Compound **8** (mp 173–174 °C) was prepared from **2** using pyridinium hydrobromide perbromide in chloroform: procedure of L. S. Liebeskind.
(13) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr.*, **A27**, 368 (1971).
(14) A similar phenomenon has been observed by Kende and coworkers. We thank Professor Kende for a preprint describing these results.
(15) Intermediates like **9** have been suggested for other nonphenolic coupling reactions. For examples see (a) S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *J. Am. Chem. Soc.*, **95**, 6861 (1973); (b) S. M. Kupchan, V. Kameswaran, J. T. Lynn, D. K. Williams, and A. J. Liepa, *ibid.*, **97**, 5622 (1975); and (c) S. M. Kupchan and C. Kim, *ibid.*, **97**, 5623 (1975).
(16) Molecular models strongly suggest that the configuration depicted in structure **9** represents an energy minimum for this species.

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Anhydrocholine

Summary: Choline, $(CH_3)_3N^+CH_2CH_2OH\ OH^-$, was found to exist in water-poor media mainly in the form of anhydrocholine, $(CH_3)N^+CH_2CH_2O^-$.

Sir: A characteristic feature of enzyme systems appears to be the existence of highly reactive regions on the enzyme surface. In these regions acidic or basic groups often function as if their pK's were much greater (or smaller) than they are in aqueous solution.[1] It is likewise possible that some small biomolecules might be particularly susceptible to such changes in acidity, either on an enzyme surface or in some other cellular environment, and that this variability might be a vital part of their function.

The effect of polar, water-poor mixed solvents on the binding of various substrates to an enzyme cavity model has been reported recently.[2] We wish to report a remarkable

Table I. Equilibrium Constants and Thermodynamic Parameters for the Reaction

$(CH_3)_3N^+CH_2CH_2OH + OH^- \rightarrow (CH_3)_3N^+CH_2CH_2O^- + H_2O$

Solvent[a]	T, K	K[b]	ΔH, kcal/mol	ΔS, cal/mol K
H_2O	291.15	13.9 ± 0.2	4.39 ± 0.22	20.3 ± 0.8
H_2O	322.90	29.3 ± 1.6		
0.60 aqueous ethanol	273.15	27.5 ± 1.0	2.58 ± 0.02	15.9 ± 0.1
0.60 aqueous ethanol	291.15	33.3 ± 1.3		
0.60 aqueous ethanol	322.90	55.9 ± 2.1		
0.85 aqueous ethanol	291.15	141.7 ± 6.7	−1.47 ± 0.08	4.79 ± 0.18
0.85 aqueous ethanol	322.90	110.4 ± 3.7		
0.60 aqueous DMSO	273.15	1766 ± 57	−2.35 ± 0.21	6.27 ± 0.87
0.60 aqueous DMSO	291.15	1397 ± 54		
0.60 aqueous DMSO	322.90	911.7 ± 84		

[a] Solvent composition indicated as mole fraction of organic solvent. [b] See ref 4.

change in the acidity of choline ion relative to water on going from water solvent to such a polar, water-poor medium.

The customary formulation of choline,[3] $(CH_3)_3N^+CH_2CH_2OH$ OH^-, is no doubt based on the fact that the choline ion, $(CH_3)_3N^+CH_2CH_2OH$, has a pK_a sufficiently close to that of water so that in dilute aqueous solution reaction 1

$$(CH_3)_3N^+CH_2CH_2OH + OH^- \rightleftarrows (CH_3)_3N^+CH_2CH_2O^- + H_2O \quad (1)$$

can be neglected. While following the rate of the base-catalyzed hydrolysis of acetylcholine conductometrically we observed that the conductance of solutions of choline were substantially lower than would be required by the customary formulation. Comparison of the conductance of a solution of choline with the conductances of separate solutions of NaOH, choline chloride, and NaCl yielded the equilibrium constants[4-6] listed in Table I.

Examination of the equilibrium constants shows a dramatic change in the relative acidities of choline ion and water on going to progressively less H-bonding media. This change is accompanied by an even larger shift in the enthalpy of reaction 1. This very large shift to an exothermic ΔH of reaction (by almost 7 kcal/mol) as one goes to the less aqueous medium is opposed by an accompanying decrease in entropy, thus damping the effect on the equilibrium constant. As this damping entropic effect might be absent in the highly ordered biological environments in which the choline ion functions, the factors favoring anhydrocholine,[7] $(CH_3)_3N^+CH_2CH_2O^-$, as a viable biomolecule[8] may be even more pronounced.

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References and Notes

(1) E.g., lysozyme, where glutamic acid 35 appears to be protonated (i.e., a weak acid) in the enzyme, but then acts as a strong acid in the enzyme-substrate complex [D. C. Phillips, *Proc. Natl. Acad. Sci. U. S.*, **57**, 484 (1967)].
(2) B. Siegel and R. Breslow, *J. Am. Chem. Soc.*, **97**, 6869 (1975).
(3) For a recent review, see R. S. Harris, W. P. Griffith, J. F. Nyc, W. S. Hartcroft, and E. A. Porta in "The Vitamins", Vol. III, 2nd ed, W. H. Sebrell and R. S. Harris, Ed., Academic Press, New York, N.Y., 1971, pp 2–154.
(4)

$$K^{-1} = \left(\frac{L_{CholCl+NaOH} - L_{NaCl}}{L_{NaOH} + L_{CholCl} - L_{CholCl+NaOH}}\right) \times \left[C - \frac{C}{\left(\frac{L_{CholCl+NaOH} - L_{NaCl}}{L_{NaOH} + L_{CholCl} - L_{CholCl+NaOH}}\right) + 1}\right]$$

where L is the conductance of the indicated compound or compounds at concentration C. The equilibrium constant K was determined at at least three concentrations with C ranging from 10^{-4} to 10^{-2} M. These K values are defined using a value of unity for the concentration of H_2O in eq 1. Using the actual concentration of H_2O yields K values which are somewhat different and ΔH and ΔS values which are slightly different. It does not alter the picture represented by the values in Table I. In the two ethanolic media this calculation does not distinguish the relative contributions of OH^- and $C_2H_5O^-$ to the equilibrium, but rather measures the K of the equilibrium $(CH_3)_3N^+CH_2CH_2OH + SO^- \rightarrow (CH_3)_3N^+CH_2CH_2O^- + SOH$ (SOH = solvent).
(5) This yields the following values for the ionization of choline chloride in water [$(CH_3)_3N^+CH_2CH_2OH \rightarrow (CH_3)_3N^+CH_2CH_2O^- + H^+$]: pK_a (25 °C) = 12.8, ΔH° = 17.73 kcal/mol, ΔS° = 1.6 cal/mol deg. The only literature report on the acidity of choline chloride (based on the measurement of the pH of dilute solutions) gives a value of $pK_a = 9$ and is clearly in error [C. W. Lewis and W. C. M. Price, *Trans. Faraday Soc.*, **29**, 777 (1933)]. There is an interesting recent report on the anomalously low pH of aqueous KOH in concentrated solutions of choline salts, which can probably be accounted for by reaction 1 [J. Steigman and D. Sussman, *J. Am. Chem. Soc.*, **89**, 6400 (1967)].
(6) A far less convenient method of measuring equilibrium 1 is to observe the ^1H NMR spectrum of a mixture of choline chloride and sodium hydroxide. To check our results we did this in one case (water) and obtained substantially the same equilibrium constant as by the conductance method.
(7) Since the salt $(CH_3)_3N^+CH_2CH_2OH$ OH^- is called choline, the reasonable name for its dehydration product, $(CH_3)_3N^+CH_2CH_2O^-$, is *anhydrocholine*. Unfortunately, the use of the term choline for the cation, $(CH_3)_3N^+CH_2CH_2OH$, is also widespread. From this starting point one would arrive at the name *choline dipolar ion*, for $(CH_3)_3N^+CH_2CH_2O^-$. We prefer *anhydrocholine* as being shorter and more descriptive.
(8) Since anhydrocholine should be much more nucleophilic than the choline cation, it may, for example, be a good candidate for the reactive species at the active site of choline acetylase or choline kinase.
(9) Taken from the M.A. Thesis of Jeffrey Pessin, Brooklyn College of the City University of New York, 1975.

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