chemical shifts or coupling constants. However, at low concentrations (10^{-3} M) of oxytocin, the hydroxyl proton of tyrosine-2 appeared. The failure to observe this signal in earlier studies of oxytocin and related compounds has been attributed to rapid exchange of this proton with water impurities in Me_2SO.[17,18] The amino terminal group of the half-cystine-1 was also believed to be involved in intramolecular catalysis of this exchange, since usually the tyrosine-2 hydroxyl resonance is observed in deaminooxytocin and analogues. However, our observation that at low concentrations of oxytocin in $[^2H_6]$-Me_2SO this hydrogen becomes observable, strongly indicates that at higher concentrations the catalytic effect which produces the rapid exchange of this proton with water has primarily an intermolecular rather than intramolecular origin, and offers perhaps the strongest evidence for an intermolecular interaction or association of oxytocin in this solvent. In this regard, it is interesting that even in deaminooxytocin the presence of the tyrosine-2 hydroxyl group is concentration dependent since at 5×10^{-2} M it was present,[17] but a 7×10^{-2} M[19] it was nearly absent. Indeed, examination of the literature[15,17-24] provides further indications of this phenomena for related analogues and derivatives of neurohypophyseal peptides. On the other hand, it appears that the formation of a complex of oxytocin with Ni^{2+} competes with this effect since addition of Ni^{2+} to an oxytocin solution in Me_2DMSO renders the tyrosine-2 hydroxyl hydrogen observable.[20]

We also conducted dilution experiments with $[^2H_6]Me_2SO$ solutions of [Pen^1]oxytocin, but even at 8×10^{-4} M, the hydroxyl proton of tyrosine-2 did not appear suggesting that even at this concentration, intermolecular interactions or association are important for this compound as was also suggested by the broad lines and featureless nature of the spectrum[14] even at concentrations of 1-5 mg/ml.

The results from the viscosity, carbon-13 T_1, and proton FT-NMR reported here suggest that some form of intermolecular interaction or association obtains for oxytocin in Me_2SO at high concentrations (>10 mg/ml) and for [Pen^1]-oxytocin throughout the concentration range examined. In the FT-NMR studies no significant changes in chemical shift or coupling constants for peptide backbone (NH and αCH) protons were observed, suggesting that whatever the interaction it does not cause a significant backbone conformational perturbation. No evidence was obtained to suggest that such an interaction occurs in aqueous solution. On the other hand, the carbon-13 T_1 results in Me_2SO solution imply that any interpretation of these data will be dependent on the experimental conditions chosen, and indicate that caution should be taken in interpretation of T_1 studies in concentrated organic solutions.

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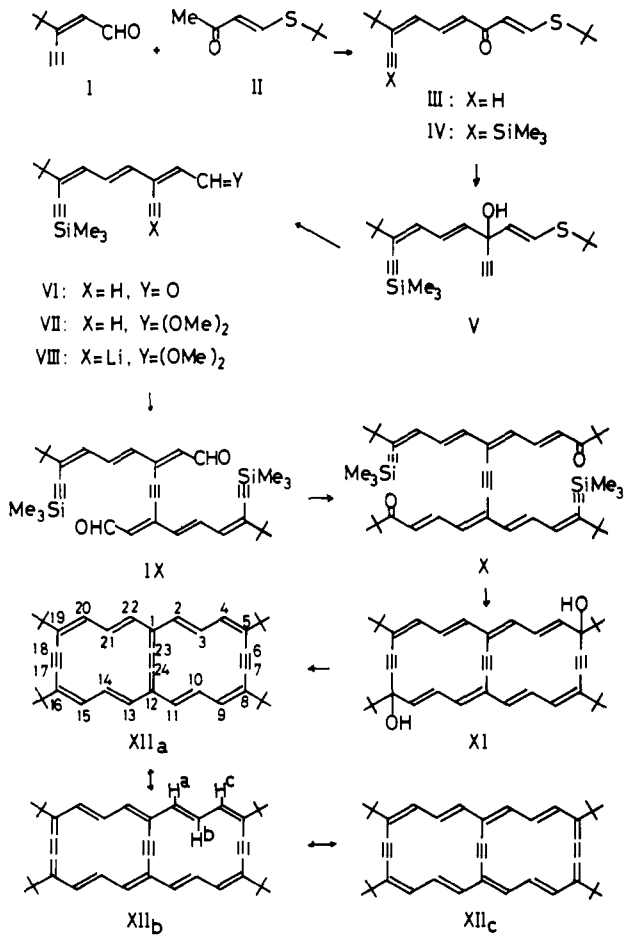
5,8,16,19-Tetra-*tert*-butyl-6,17,23-trisdehydro[22]-bi[10.10.2]annulene.[1] A Condensed Nonbenzenoid Aromatic System Consisting of Two 14π-Electron Systems

Sir:

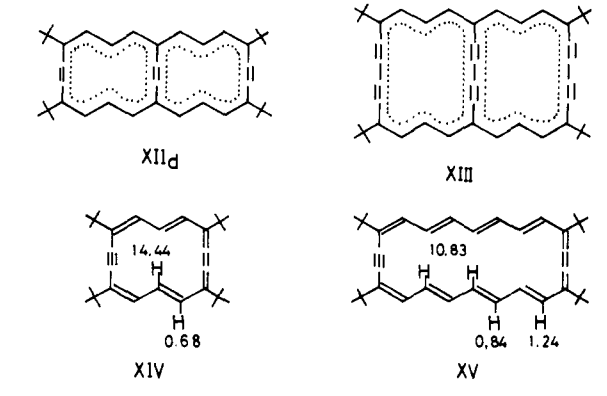
In a previous paper,[2] we have reported the synthesis of a condensed nonbenzenoid aromatic hydrocarbon (XIII), which can be regarded as a fused system of two tetrakisdehydro[18]-annulene derivatives. At the same time, the synthesis of an ortho-fused 26π-electron [14]annuleno[14]annulene derivative was reported by Cresp and Sondheimer.[3] In this communication, we wish to report the synthesis and properties of the third instance of a fused nonbenzenoid aromatic hydrocarbon (XII), a lower analogue of XIII consisting of two 14π-electron systems.

Treatment of the ethynyl ketone (III: yellow crystals; mp 104.5-105.0 °C; 83%; Anal. ($C_{17}H_{24}OS$) C, H, S),[4] obtained by the aldol condensation of II[5] with I[6] (NaOH-H_2O-EtOH, 0 °C, 4 h), with Et_2NLi in THF at −78 °C followed by the reaction with Me_3SiCl gave trimethylsilyl derivative (IV: yellow liquid; 78%). Product (V) of the reaction of IV with lithium acetylide in THF[7] (−65 °C, 1 h; −55 °C, 1.5 h) was treated without isolation with 2 N H_2SO_4 (30 °C, 1 h) to yield VI (orange yellow liquid; 72%; 2,4-dinitrophenylhydrazone: red crystals; mp 225-227 °C; Anal. ($C_{24}H_{28}N_4O_4Si$) C, H, N). VI was converted into dimethyl acetal (VII) in the usual way, and treated with BuLi in THF (−78 °C) to give lithio derivative (VIII). The reaction of VIII with IV (−65 °C, 1 h; −45 °C, 1 h) followed by rearrangement and hydrolysis with 2 N H_2SO_4 (30 °C, 0.5 h) yielded dialdehyde (IX: yellow crystals; mp 142-143 °C dec; 39% based on IV; Anal. ($C_{34}H_{46}O_2Si_2$) C, H).[8] After several unsuccessful trials, conversion of IX into diketone (X: yellow crystals; mp 212-213 °C dec; 81%; Anal. ($C_{46}H_{66}O_2Si_2$) C, H) could be achieved



by the reaction of carbanion derived from diethyl 3,3-dimethyl-2-oxobutanephosphonate (t-BuCOCH$_2$(O)P(OEt)$_2$).[9,10] Although the cleavage of trimethylsilyl groups in X was found to be difficult under the usual conditions, the cyclization of X without removal of the protective groups could be realized on a slow addition of a solution of X in THF into a suspension of finely powdered KOH in liquid NH_3[11] (−50 °C, 24 h). A mixture of diastereomers of the cyclic glycol (XI; yellow crystals; mp ca. 250 °C dec; Anal. ($C_{40}H_{50}O_2$) C, H) was obtained in a yield of 94%.

The glycol (XI) in ether was mixed at −55 °C with a solution of tin(II) chloride dihydrate in the same solvent saturated with hydrogen chloride. Resulting deep reddish violet reaction mixture was worked up in the usual way to yield 5,8,16,19-tetra-*tert*-butyl-6,17,23-trisdehydro[22]bi[10.10.2]annulene[1] (XII: reddish purple crystals; mp ca. 280 °C dec; 77%; Anal. ($C_{40}H_{48}$) C, H; *m/e* 528 (M^+)). The annulenoannulene (XII) was found to be a stable compound and has a higher solubility than XIII. XII forms 1:1 CT complex with 2,4,7-trinitrofluorenone (purple crystals; mp >280 °C dec; Anal. ($C_{53}H_{53}N_3O_7$) C, H, N). The electronic spectrum of XII (λ_{max} (THF) 216 (ϵ 12 300), 244 (15 300), 250 (17 500), 263 (20 400), 274.5 (32 700), 322.5 (12 600), 371 (37 300), 384 (114 000), 401 (563 000), 468 (4390), 492 sh (6470), 518 (19 000), 553 (39 900), 637 (480), 676 (1020), 742 (2140) nm) clearly shows characteristic features of [4n + 2]annulenes; i.e., the spectrum of XII was found to be closely related with that of 3,7,10,14-tetra-*tert*-butyl-1,8-bisdehydro[14]annulene (XIV)[11] except for a bathochromic shift and a hyperchromism in XII.



The 100-MHz ^{1}H NMR spectrum in $CDCl_3$ reveals that XII is strongly diatropic showing the inner proton signals at τ 12.85 dd (H^b, J = 13, 14 Hz) and those of the outer protons at τ −0.16 d (H^a, J = 14 Hz) and at τ 0.39 d (H^c, J = 13 Hz). The signal of *tert*-butyl protons was observed at τ 7.99 s. The difference in chemical shifts ($\Delta\tau = \tau_i - \tau_o$) between inner ($\tau_i$) and outer ($\tau_o$) proton signals can be regarded as an approximate measure of the magnitude of ring current. As pointed out previously,[2,12] the $\Delta\tau$ values for a series of conformationally stable tetra-*tert*-butylbisdehydro[4n + 2]annulenes decrease markedly with an increase of ring size. The value for tetra-*tert*-butylbisdehydro[22]annulene (XV)[12,13] has been found to be $\Delta\tau$ = 9.99. However, a much larger value ($\Delta\tau$ = 12.46 and 13.01) was found for XII. The increase in the $\Delta\tau$ value of XII cannot be ascribed to an enhanced planarity of XII caused by the bridging between 1- and 12-positions with an acetylenic linkage, because XV showed essentially temperature independent NMR spectra, and a highly planar structure of XV has been revealed by an x-ray crystal structure analysis.[14] Furthermore, it may be noted that the outer protons in XII resonate too low-field (τ −0.16 and 0.39) with respect to the chemical shift of inner protons (τ 12.85), because in spite of a much higher-field signal of the inner protons (τ 14.44) of XIV, the signal of outer protons (τ 0.68) appears at a higher field than those of XII.

The electronic spectrum of XII showed a considerable hypsochromic shift as compared with that of 3,11,14,22-tetra-*tert*-butyl-1,12-bisdehydro[22]annulene (XV),[13] although the periphery of XII is the same 22π-electron system.

The electronic and NMR spectral behavior of XII seems to suggest that the bicyclic annulene (XII) is a higher analogue of naphthalene being a resonance hybrid of valence-bond structures ($XII_a \leftrightarrow XII_b \leftrightarrow XII_c$),[15] which may be better represented by a symmetrical formula (XII_d).

References and Notes

(1) IUPAC nomenclature: 5,8,16,19-tetra-*tert*-butylbicyclo[10.10.2]tetracosa-1(23),2,4,8,10,12(24),13,15,21,23-undecaen-6,17-diyne.
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chemical shifts of these signals indicate that all the sp-hybridized carbon atoms in XII have a hybrid character of an acetylene and a cumulene. Cf. S. Nakatsuji and M. Nakagawa, *Tetrahedron Lett.*, 3927 (1975).

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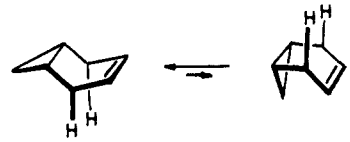
Reversal of Stereospecificity during Allylic Hydroperoxidation of 3-Norcarene and Bicyclo[4.2.0]oct-3-ene Derivatives Arising from Structurally Enforced Quenching of Singlet Oxygen by the Hydrazide Functionality

Sir:

The importance of the singlet ($^1\Delta_g$) state of oxygen to synthetic, mechanistic, and environmental chemistry is now well recognized. The wide ranging reactivity of $^1O_2$ is witnessed in its ability to effect allylic hydroperoxidation of simple olefins, 1,2-cycloaddition to alkenes of low ionization potential, and 1,4-endoperoxidation of conjugated dienes.[1] Without exception, the first of these reactions has been found to proceed with cis stereochemistry, being characterized by an exacting dependence on steric factors and the availability of an in-plane allylic hydrogen. The other pair of transformations proceed with equally impressive stereocontrol, full retention of stereochemistry occurring in every reported example.

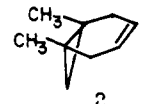
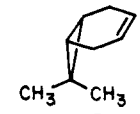
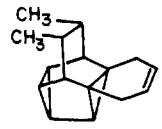
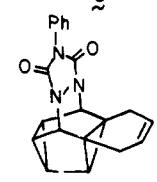
We have now investigated a heretofore unexplored parameter of singlet oxygen behavior, viz., rigid fixing of a functional group capable of quenching the $^1\Delta_g$ state within suitable proximity to the favored site of oxygenation. Since the observed end result is unprecedented redirection of $^1O_2$ attack to the more sterically congested surface of the molecule, the synthetic value of such a scheme is made evident, particularly if the functionality which causes singlet oxygen deactivation can later be extruded from the molecule. In this communication, attention is given to the allylic hydroperoxidation of 3-norcarene and bicyclo[4.2.0]oct-3-ene ring systems. The accompanying paper[2] describes a comparable assessment of the $^1O_2$ endoperoxidation of related norcaradienes and presents a unifying molecular orbital basis for the markedly contrasting observations made. The reader should recognize that our treatment is extra-mechanistic and therefore independent of the precise mechanistic details of the specific type of oxygenation, some of which remain highly controversial.

^{1}H NMR studies have indicated 3-norcarene to be capable of facile interconversion between boat conformations **1a** and **1b**.[3] These two forms are clearly not isoenergetic and stereochemical considerations suggest that **1a** with its quasi-equatorial cyclopropane ring should be somewhat favored over **1b**. However, models reveal the conformational equilibrium to be rather delicately balanced and to be expectedly sensitive to substitution on the cyclopropane ring and elsewhere. Of importance to the photooxygenation reaction, **1a** and **1b** share the common stereoelectronic feature of having two equivalent allylic C–H bonds properly aligned with the pπ orbitals of the double bond, as emphasized in the formulas. On a more general note, electrophilic attack on **1a** and **1b** from the less hindered



1a **1b**

Table I. Product Distribution Data

Compd	Percentage composition (syn:anti)[a] Epoxidation[b]	Bromohydrin formation[c]	Photooxygenation[d]
 **1**	61.6:38.4	87.4:12.6	100:0
 **2**	25.6:74.4	16.5:83.5	0:100
 **3**	0:100	0:100	0:100
 **4**	69:31	93:7	100:0
 **5**	35:65	—	0:100[f]
 **6**	7:84[e]	15:70[e]	91:0[e,g]

[a] The points of stereochemical reference are the cyclopropane ring and the attacking reagent. [b] *m*-Chloroperbenzoic acid in CH_2Cl_2 buffered with solid sodium bicarbonate, 25 °C; yields determined by VPC analysis except where noted. [c] *N*-Bromosuccinimide in aqueous glyme, 25 °C; yields determined by VPC analysis after conversion to epoxides with sodium hydride in refluxing tetrahydrofuran. [d] 10% Methanol in CH_2Cl_2 containing 10^{-3} M rose bengal; product analysis made subsequent to $NaBH_4$ reduction of the hydroperoxides. [e] Isolated yields determined after column chromatography on silica gel. [f] Lack of epimeric contamination determined by TLC analysis. [g] Independent synthesis achieved by phenylselenide anion promoted opening of the stereochemically related epoxide and H_2O_2 treatment.

direction leads unambiguously to different products, **1a** serving as progenitor to the syn isomer and **1b** to the anti counterpart. These expectations need not be borne out, however, in more highly substituted derivatives where additional steric factors may gain subtle importance.[4]

The stereochemical consequences of direct epoxidation and bromohydrin formation of several 3-norcarenes (Table I) reveal **1** and **4** to be more disposed to attack from the direction syn to the cyclopropane ring. In contrast, the structural features in **2, 3, 5,** and **6** are such that approach of the electrophile from the anti direction is kinetically preferred. That epoxidation and bromohydrin formation proceed with like stereoselectivity (although generally more accentuated when Br^+ is the electrophile) was established by base-promoted cyclization of the bromohydrins. The major epoxide isolated from each of these experiments was invariably the epimer of that obtained by the more direct procedure. Structural assignments to the individual epoxides follow from their respective ^{1}H NMR spectra and supportive Eu(fod)$_3$ pseudocontact shifting in selected cases.