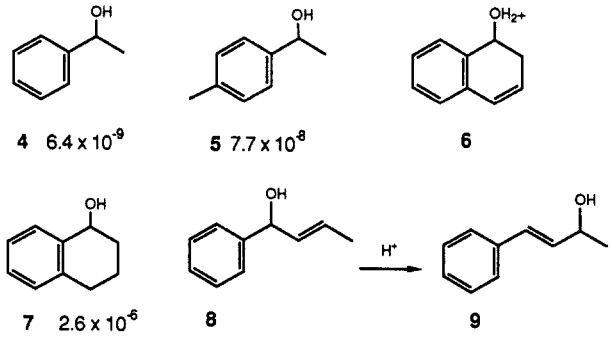

According to Scheme I, aromatic stabilization of the products could influence the reactivity of the hydrates in two ways. The first is by increasing the rate of proton loss from the carbocation. As may be seen from the potential energy profiles in Figure 1, however, the magnitude of this increase is limited by the difference in barrier heights (Δ) for formation and reaction of the phenylethyl cation which, if we extrapolate from Jencks and Richard's results for the *p*-methyl derivative,[10] amounts to a factor of only 500 in reaction rates (in water). A more radical role for aromatic stabilization would be implied if the naphthalene were formed directly from the protonated hydrates (e.g., **6**) in a concerted reaction, as shown in the lower pathway of Scheme I and the lower dashed line in Figure 1.

The two possibilities may be distinguished because the concerted but not the stepwise reaction involves proton transfer in the rate-determining step and should be subject to catalysis by buffer acids. Since, in practice, measurements in acetic acid buffers (up to 0.4 M acid, I = 0.5) failed to reveal such catalysis, even for the reactive 1,4-hydrate **3**, it follows that proton transfer is not rate-determining and hence that breaking of the C–H and C–O bonds of the protonated hydrates is not concerted.

The absence of buffer catalysis further suggests that, in contrast to α-phenylethanol, deprotonation of the carbocation is also not rate-determining, consistent with the expectation that the rate of this step *is* increased by the aromatic stabilization. This conclusion is not unequivocal because buffer catalysis of deprotonation of reactive carbocations is weak.[10] It is confirmed, however, by (i) failure to observe rearrangement of the 1,4- to the more stable (and more strongly absorbing) 1,2-hydrate in competition with dehydration, despite the reactions sharing a common benzallylic carbocation intermediate; (ii) absence of diminished product absorption that would indicate trapping by azide ion when the 1,4-hydrate is reacted in the presence of 2 M sodium azide (9:1 NaN_3/HN_3 buffer, pH 5.5); and (iii) reasonable agreement between the spectrophotometrically measured rate constant for dehydration of **1** (0.35 M^{-1} s^{-1}) and an approximate polarimetric rate constant (0.7 ± 0.2 M^{-1} s^{-1}) for loss of optical activity from a small amount of chiral **1** [(*R*)-(+)-1-hydroxy-1,2-dihydronaphthalene, $[\alpha]^{25}_D$ +52° ($CHCl_3$)], both measured in 50% (v/v) aqueous trifluoroethanol.[11]

It follows that dehydration rate constants for **1–3** refer to rate-determining carbocation formation, in contrast to those for **4** and **5**, which are for rate-determining deprotonation. The aromatic stabilization of the product does increase the reactivity of the hydrates, therefore, but as already noted, this accounts for only 500-fold of the rate differences of 5 × 10^7 between **1** and **4** and 5 × 10^{10} between **3** and **4**. Apparently, other factors also contribute to the differences.

One further contribution to the high reactivity of **1–3** is that reaction occurs more readily in the cyclic than open-chain phenethyl structure. This is apparent from measurements of rate constants for dehydration and carbocation formation from the dihydro derivative of **1** and **3**, α-tetralol (**7**), which show that these reactions occur respectively 400 and 200 times more rapidly than the corresponding reactions of α-phenylethanol. The rate constant for carbocation formation was measured polarimetrically, from racemization of the *R*-(+) substrate, as ~6 × 10^{-4} M^{-1} s^{-1} (extrapolated to water from aqueous trifluoroethanol mixtures), which is 230 times greater than for the dehydration reaction and only 500 times slower than dehydration of the 1,2-naphthalene hydrate **1**. Solvolyses of open-chain alkyl and cyclohexyl substrates lacking a phenyl substituent show little difference in rates.[12] The high reactivity of the tetralol therefore probably reflects an absence of steric[12] and entropic inhibition of resonance stabilization of the carbocation by the phenyl group.

The remaining difference between **7** and **1** is sensibly ascribed to stabilization of the carbocation by a vinyl substituent. Thus, comparison of the 1,4-hydrate **3** with its open-chain vinyl analogue **8**, for which the rate of carbocation formation is measured as 0.58 M^{-1} s^{-1} by monitoring rearrangement to its stable isomer **9**, shows a rate difference of 400 (k_3/k_8), which is close to the difference (170) between the cyclic and open-chain structures **7** and **4** (k_7/k_4). The 130-fold difference between **2** and **3** can be attributed to the lower energy of a conjugated than unconjugated double bond in the reactants and corresponds roughly to the energy difference between 1,2- and 1,4-dihydronaphthalene.[13] Finally, the small (5-fold) difference between **1** and **2** presumably reflects a difference in stability of their carbocations.

In summary, the higher reactivity of naphthalene hydrates than α-phenylethanol may be understood in terms of contributions from a number of factors, none of which, individually, is unusually large and all of which have straightforward explanations. Aromatic stabilization is one of these (contributing a factor of 5 × 10^2), but enhanced resonance in the cyclic cation (2 × 10^2), the effect of a vinyl substituent (5 × 10^2), and deconjugation of the double bond in the reactants (1.5 × 10^2) are also important.

Acknowledgment. We thank the Department of Education for Northern Ireland (R.A.S.McM.) and the British Science and Engineering Research Council (N.D.S.) for financial support.

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Novel Heterocycles Comprising Alternating Phosphorus Atoms and Alkyne Units[1]

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As part of our program directed toward synthesis of the unknown cage compounds **1**, **2**, and related "phosphocarbons" (C_nP_m), we have prepared the first heterocycles comprising alternating phosphorus atoms and alkyne units. Herein we report our syntheses and some properties of 1,4,7-tri-*tert*-butyl-1,4,7-triphospha[3]pericyclyne (**3**) and 1,4,7,10-tetra-*tert*-butyl-1,4,7,10-tetraphospha[4]pericyclyne (**4**).[2] Such heterocycles and phosphocarbons are expected to exhibit a variety of unusual structural and electronic properties.

Our syntheses began with *tert*-butylphosphonous dichloride (**5**), prepared in 48% yield by the addition of *tert*-butylmagnesium chloride to phosphorous trichloride.[3] Treatment of **5** with excess

(1) Part 8 in the series "Cyclynes". This work was first presented at the International Meeting of Pacific Basin Chemical Societies (PACIFICHEM 89) in Honolulu, Hawaii, Dec 1989. Part 7: Scott, L. T.; Cooney, M. J.; Johnels, D. *J. Am. Chem. Soc.* **1990**, *112*, 4054–4055.
(2) All-carbon [*N*]pericyclynes have previously been reported: Scott, L. T.; DeCicco, G. J.; Hyun, J. L.; Reinhardt, G. *J. Am. Chem. Soc.* **1985**, *107*, 6546–6555.

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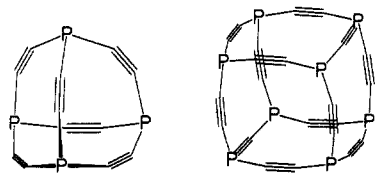
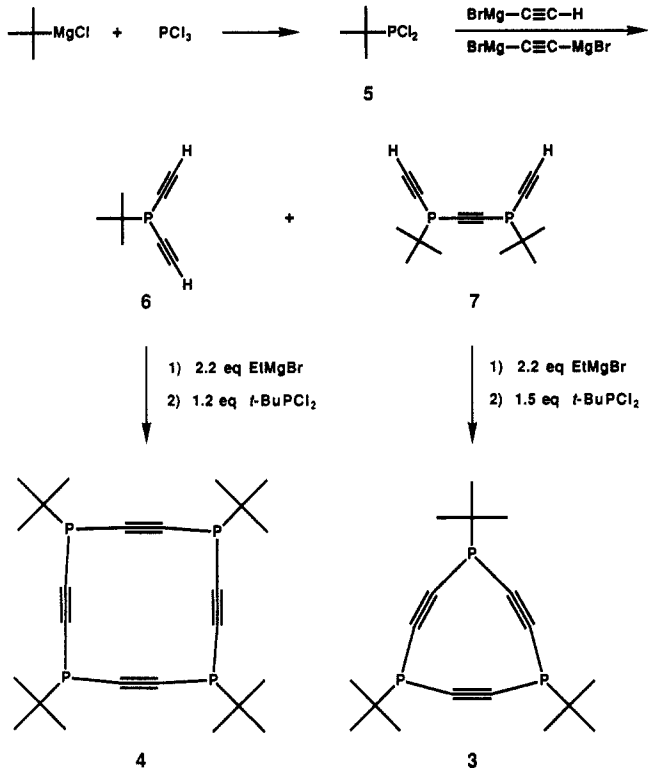


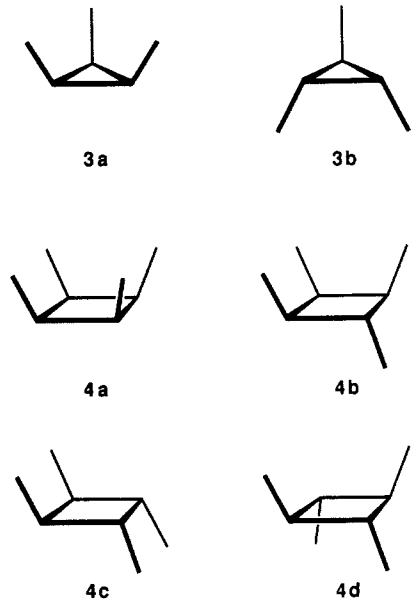
1 2

ethynylmagnesium bromide[4] gave *tert*-butyldiethynylphosphine (**6**), accompanied by a lesser amount of 3,6-di-*tert*-butyl-3,6-diphospha-1,4,7-octatriyne (**7**). The 3:2 adduct (**7**) presumably arises from the reaction of **5** with bis(bromomagnesium) acetylide, a byproduct from the preparation of ethynylmagnesium bromide.[5] Dry column chromatography on silica gel gave **6** and **7** in 53% and 3% isolated yields, respectively.



Double deprotonation of **7** (2.2 equiv of EtMgBr, THF, 50 °C, 30 min) followed by slow addition to 1.5 molar equiv of *tert*-butylphosphonous dichloride (**5**, THF, −10 °C, then room temperature for 3 h) produced the nine-membered-ring heterocycle **3** in 16% isolated yield.[6] The 12-membered-ring heterocycle **4** was likewise prepared in 11% isolated yield by double deprotonation of **6** followed by slow addition to 1.2 molar equiv of *tert*-butylphosphonous dichloride (**5**).[6] This latter ring assemblage involves four C–P bond-forming reactions!

The pyramidal configuration of phosphorus atoms at the vertices of heterocycles **3** and **4** adds an element of stereochemistry to these compounds. For the nine-membered ring, one can envision two possible stereoisomers, represented graphically here as **3a** and **3b**, whereas four stereoisomers (**4a–d**) are possible for the 12-membered ring.



The proton-decoupled ^{31}P NMR spectrum of crude triyne **3** consists of a doublet (δ −22.32, $^3J_{PP}$ = 14.1 Hz) and a triplet (δ −25.87, $^3J_{PP}$ = 14.1 Hz) in a ratio of 2:1, which establishes the structure of this triyne as the cis,trans isomer (**3b**). No additional singlet could be found for the all-cis diastereomer (**3a**). Recrystallization from methanol gave pure *cis,trans*-1,4,7-tri-*tert*-butyl-1,4,7-triphospha[3]pericyclyne (**3b**, mp 141.2–141.6 °C), the three-dimensional structure of which was confirmed by X-ray crystallography.[7] We see no evidence for equilibration of **3b** with **3a** by pyramidal inversion of phosphorus at temperatures up to +50 °C on the ^{31}P NMR time scale or on standing in solution at room temperature.

In the proton-decoupled ^{31}P NMR spectrum of crude tetrayne **4**, signals can be seen for all four stereoisomers; **4a**, **4c**, and **4d** give rise to singlets (δ −34.35, −35.57, and −38.20, respectively[8]), whereas **4b** shows three signals in a 1:2:1 ratio [δ −33.91 (t, 1 P, J_{PP} = 10.2 Hz), −36.46 (dd, 2 P, J_{PP} = 10.2 and 6.4 Hz), and −37.06 (t, 1 P, J_{PP} = 6.3 Hz)]. The ratio of **4a**:**4b**:**4c**:**4d** in this mixture was found to be 1.0:9.4:7.9:5.2. These stereoisomers are likewise configurationally stable on the NMR time scale at room temperature. Fractional crystallization from methanol gave the all-trans isomer (**4d**, mp 196.5–197.0 °C), the stereochemistry of which was determined by X-ray crystallography.[7]

Figure 1 shows the UV spectra of **3b** [λ_{max} (ϵ) 212 (sh) (13 400), 225 nm (15 800)][9] and **4d** [λ_{max} (ϵ) 215 (27 700), 226 (29 000), 236 (sh) (25 700), 258 nm (sh) (14 800)].[9] Both compounds exhibit strong absorption bands that extend out to nearly 300 nm. The spectrum of **3b**, however, lacks the prominent long-wavelength shoulders seen in the spectra of **4d** and the acyclic precursors **6** [λ_{max} (ϵ) 218 (4000), 248 nm (sh) (1320)][9] and **7** [λ_{max} (ϵ) 223 (10 700), 258 nm (sh) (2800)].[9] Though a detailed interpretation of these spectra must await theoretical analysis, it is clear that *these novel heterocycles are characterized by strong cyclic electronic interactions.*

The chemistry reported here was actually carried out first (with comparable results) on the corresponding compounds bearing phenyl substituents, rather than *tert*-butyl groups; however, the presence of phenyl chromophores complicated interpretation of the UV spectra. We are currently working on syntheses of compounds related to **3a** and **4a** which bear ethynyl groups in place

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(6) All the protons appear equivalent in the normal 300-MHz ^1H NMR spectrum of **3b** ($CDCl_3$) [δ 1.26 (d, $^3J_{HP}$ = 15.3 Hz)] and **4d** ($CDCl_3$) [δ 1.24 (d, $^3J_{HP}$ = 14.4 Hz)]. The ^{31}P NMR spectroscopic data in the text are reported in parts per million downfield from phosphoric acid. **3b**: IR (neat) 2362 and 2343 cm^{-1}. **4d**: IR (neat) 2363 and 2338 cm^{-1}.

(7) We thank P. Carroll and A. B. Smith, III, at the University of Pennsylvania for determining the X-ray crystal structures of **3b** and **4d**; details will be reported in the full paper on these compounds.

(8) The assignment for isomer **4d** was established by subsequent isolation of the pure compound; however, our assignments for **4a** and **4c** are based solely on the relative abundances of the two and could be reversed. We assume **4a** to be the less abundant isomer on both statistical and steric grounds.

(9) All UV spectra were recorded in cyclohexane.

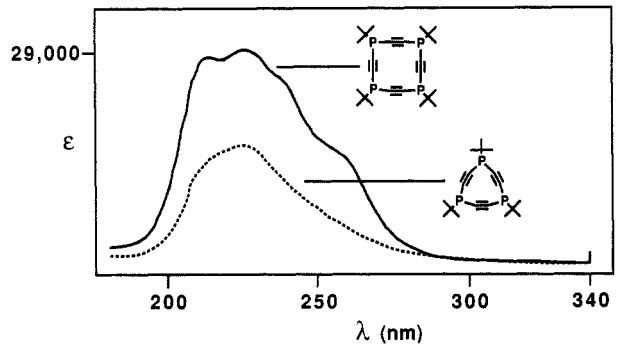

Figure 1. UV spectra of compounds **3b** and **4d** in cyclohexane.

of the *tert*-butyl groups for use as potential precursors to phosphocarbons **1** and **2**.

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DNA Cleavage and Antitumor Activity of Designed Molecules with Conjugated Phosphine Oxide–Allene–Ene–Yne Functionalities†

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Molecules with DNA-cleaving properties[1] and new anticancer agents[2] are of considerable current interest and value to molecular biology and medicine. As part of our program in these areas, we have designed, synthesized, and tested a series of compounds with conjugated phosphine oxide–allene–*cis*-ene–yne functionalities. In this communication we report our results, which include both of the above properties.

Scheme I depicts the mechanistic rationale for the formation and action of this new class of compounds. Thus, it was hypothesized that propargylic compounds of type I may be induced to rearrange to the conjugated allenic systems III under the influence of PhSCl or Ph_2PCl via intermediates II. Structures III were then expected to undergo a Myers[3] cyclization reaction[4] to

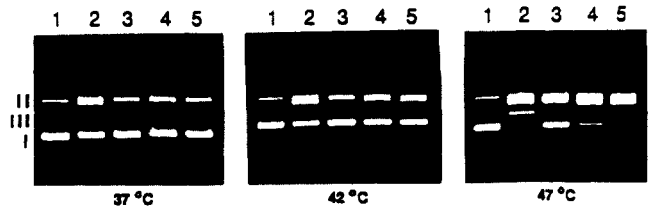
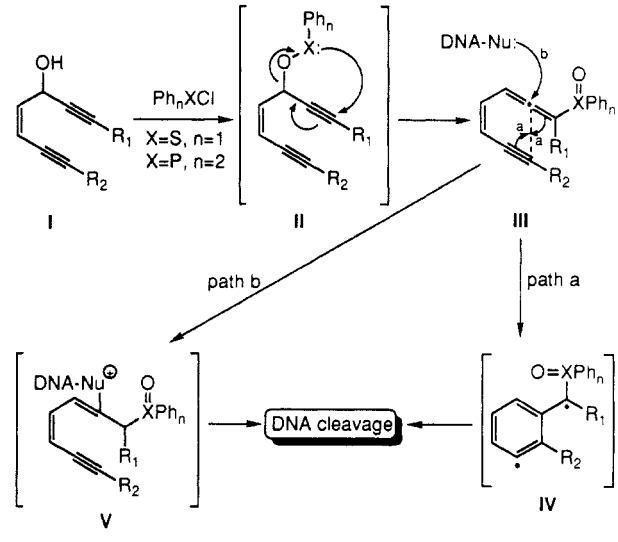


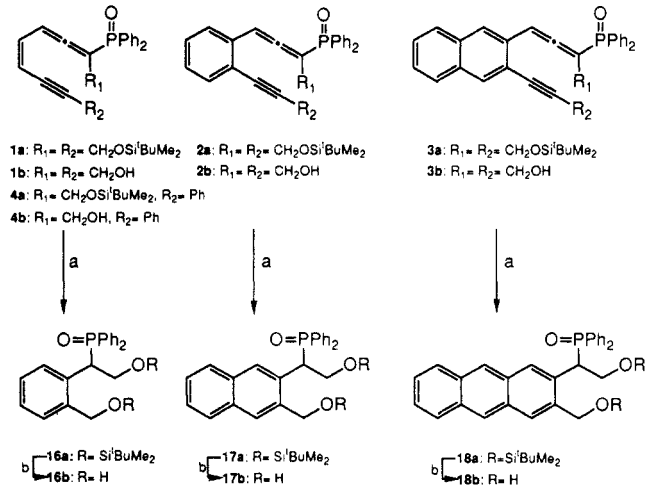
Figure 1. ΦX174 form I DNA (50 μM/base pair) was incubated for 48 h at the specified temperatures with various compounds (1 mM in 20% ethanol in phosphate buffers, pH 8.5, 50 mM) and analyzed by gel electrophoresis (1% agarose, ethidium bromide stain). Lane 1, DNA alone; lanes 2–5, compounds **1b**, **2b**, **3b**, and **4b**, respectively. I: form I DNA. II: form II DNA. III: form III DNA.

Scheme I[a]



[a] Mechanistic rationale for the design of DNA-cleaving molecules with, potentially, a dual mode of action: (a) radical mechanism; (b) alkylation mechanism.

Scheme II[a]



[a] Compounds synthesized and studied in this work: (a) 0.01 M in 1,4-cyclohexadiene, 37 °C, 0.01 M; **1a**, $t_{1/2}$ = 8 h; **2a**, $t_{1/2}$ = 23 h; **3a**, $t_{1/2}$ = 117 h; (b) 48% aqueous HF, acetonitrile, 20 °C, 15 min, quantitative.

form radicals IV (path a) or undergo nucleophilic attack originating from DNA to form species V (path b) as expected from our recent results with propargylic and allenic sulfones.[1d] Either pathway should cause cleavage of DNA. Sulfur compounds of

† This work was partly presented at the Pacifichem December 1989 Conference, Honolulu, HI.

‡ Recipient of a Ministerio de Educación y Ciencia Fulbright Fellowship, Spain, 1989–1990.

§ Department of Chemistry, The Research Institute of Scripps Clinic.

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