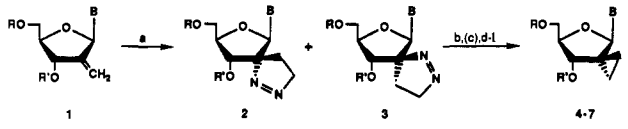
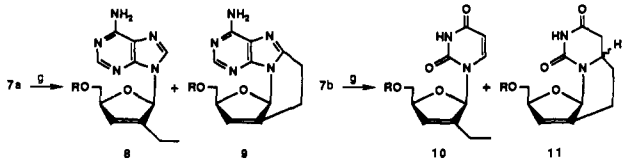
Scheme I[a]



1-4: R,R' = TPDS; 5: R = R' = H; 6: R = TBDMS, R' = H; 7: R = TBDMS, R' = C(S)OPh; a: B = adenin-9-yl; b: B = uracil-1-yl; c: B = 3-*N*-benzoyluracil-1-yl; 8-11: R = TBDMS.



[a](a) CH_2N_2/Et_2O. (b) $h\nu$/PhC(O)Ph/MeCN/C_6H_6. (c) NH_3/MeOH. (d) $Bu_4N^+F^-$/THF. (e) TBDMSCl/imidazole/DMF. (f) PhOC(S)Cl/DMAP/MeCN. (g) Bu_3SnH/AIBN/C_6H_6/Δ.

2′-deoxynucleoside-2′-spiropyrazoline derivatives **2a** (88%) and **3a** (4%) (Scheme I). The stereochemistry of **2a**(2′*R*) and **3a**(2′*S*) was assigned from 2D ROESY NMR experiments with each compound. Thus, diazomethane cycloaddition occurred preferentially from the less hindered α-face to give **2a** as the major isomer, analogous with our results with protected 3′-ketonucleosides and a bulky reducing agent[10a] or methyltriphenylphosphorane.[10b] Benzophenone-sensitized photolysis[11] of **2a**/**3a** in acetonitrile/benzene (1:1) provided the 2′-spironucleoside **4a** (92%). Deprotection (TBAF/THF) gave microcrystalline 2′-deoxyadenosine-2′-spirocyclopropane (**5a**, 90%).[12]

Analogous treatment of **1c**[13] with diazomethane/ether gave spiropyrazolines **2c** (63%) and **3c** (28%). Photolysis of **2c**/**3c** and deprotection (NH_3/MeOH, TBAF/THF) gave crystalline 2′-deoxyuridine-2′-spirocyclopropane (**5b**, 50% from **2c**/**3c**).[12] Compounds **5a** and **5b** are the first examples of nucleoside analogues containing the novel spirocyclopropane–sugar moiety.

Protection of **5a** with *tert*-butyldimethylsilyl chloride/imidazole/DMF gave the 5′-*O*-TBDMS (**6a**, 90%) and 3′,5′-bis-*O*-TBDMS (5%) derivatives. Treatment of **6a** with phenyl chlorothionoformate/DMAP/MeCN[14] gave 5′-*O*-TBDMS-2′-deoxy-3′-*O*-(phenoxythiocarbonyl)adenosine-2′-spirocyclopropane (**7a**, 90%).[12] The uridine analogue **7b** was prepared from **5b** in an analogous manner.

Our first biomimetic model reaction utilized the Barton radical-mediated deoxygenation[14,15] (Bu_3SnH/AIBN/benzene/80 °C) of **7a**. We were gratified to discover that 2′-ethyl-2′,3′-unsaturated (**8**, 65%) and 8,2′-ethano-2′,3′-unsaturated cyclonucleoside (**9**, 25%) derivatives were formed. The structure of **8** was apparent from its ^1H NMR spectrum, which had an ethyl triplet (δ 1.09) as expected in the product of hydrogen transfer to the primary radical intermediate. Its UV (λ_{max} 260 nm) and MS data and elemental analysis were compatible with those of **8**. Structure **9** was in harmony with its ^1H and ^{13}C NMR, UV (λ_{max} 264 nm) and mass spectral data, elemental analysis, and known chemistry involving the preferential addition of radicals at the 8-position of purine nucleosides.[16] Analogous treatment of **7b** gave the 3-butenyl nucleoside **10** (71%)[12] and the UV-transparent 5,6-dihydrouracil cyclonucleoside **11** (25%).[12] These results demonstrate a rational new approach to investigate the proposed radical-mediated conversion of ribonucleotides to their 2′-deoxy analogues by ribonucleotide reductases.

In summary, 2′-deoxynucleoside-2′-spirocyclopropanes have been prepared for the first time, as mechanistic probes for ribonucleotide reductases. A cycloaddition/photolysis route provided these analogues in good yields. Biomimetic radical reactions have yielded products resulting from ring opening of cyclopropylcarbinyl radicals. Studies with other nucleosides and collaborative enzymatic evaluations[7] with 5′-di- and triphosphate esters are in progress.

Acknowledgment. We thank the American Cancer Society (Grant No. CH-405) for support and Mrs. Kathryn Rollins for assistance with the manuscript.

Supplementary Material Available: Listings of experimental details and spectral data for compounds **2a,c**, **3a,c**, **4a,b**, **5a,b**, **6a,b**, **7a,b**, and **8–11** (9 pages). Ordering information is given on any current masthead page.

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(11) Beard, A. R.; Butler, P. I.; Mann, J.; Partlett, N. K. *Carbohydr. Res.* **1990**, *205*, 87–91.

(12) Elemental analyses (C, H, N) within ±0.3% of theory were obtained for compounds **5a**, **5b**, **7a**, **8–11**.

(13) Prepared by 3-N-benzoylation of **1b**[10b] by the procedure of Sekine, M.; Fujii, M.; Nagai, H.; Hata, T. *Synthesis* **1987**, 1119–1121.

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Novel Synthetic Route to Isolable Pentacoordinate 1,2-Oxaphosphetanes and Mechanism of Their Thermolysis, the Second Step of the Wittig Reaction

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Although there have been many mechanistic studies on the Wittig reaction, most of them have dealt with the formation process of 1,2-oxaphosphetanes for the purpose of elucidating the origin of stereochemistry of the Wittig reaction.[1,2] Attempts to investigate independently the second step of the Wittig reaction have been carried out only by using in situ generated 1,2-oxaphosphetanes,[2,3] in spite of the synthesis of several isolable 1,2-oxaphosphetanes.[4]

In the course of our study to trap an intermediate of the Horner–Emmons reaction, an oxidophosphorane, we have found a novel and general synthetic route to isolable pentacoordinate 1,2-oxaphosphetanes bearing the Martin ligand. We now report on a mechanistic study of their thermolysis, the second step of the Wittig reaction.

Sequential treatment of phosphine oxide **1** with 2 equiv of *n*-BuLi and then with *p,p*′-disubstituted benzophenones (**2**) in THF at 0–50 °C led to the isolation of a good yield of 1,2-oxaphosphetanes **3** via the corresponding dihydroxy derivatives **4** (Scheme I, Table I).[5] Compound **3a** formed as colorless needles, mp 179 °C dec. The structure of **3a** was strongly supported by its ^{31}P (δ_P −35.8) and ^{19}F NMR spectra (double quartet with centers of δ_F −79.6 and −76.5 (J_{FF} = 9.8 Hz)). In the ^1H NMR spectrum the signal due to the ortho proton of the Martin ligand[6] was

(1) Recent reviews: McEwen, W. E.; Beaver, B. D.; Cooney, J. V. *Phosphorus Sulfur* **1985**, *25*, 255. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. Recent examples: Ward, W. J., Jr.; McEwen, W. E. *J. Org. Chem.* **1990**, *55*, 493. Vedejs, E.; Marth, C. F.; Ruggeri, R. *J. Am. Chem. Soc.* **1988**, *110*, 3940.

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(5) Aldehydes and aliphatic ketones can also be used instead of benzophenones. If carbonyl compounds are unsymmetric, compounds **3** are obtained as a mixture of diastereomers.

(6) Granoth, I.; Martin, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 4618.

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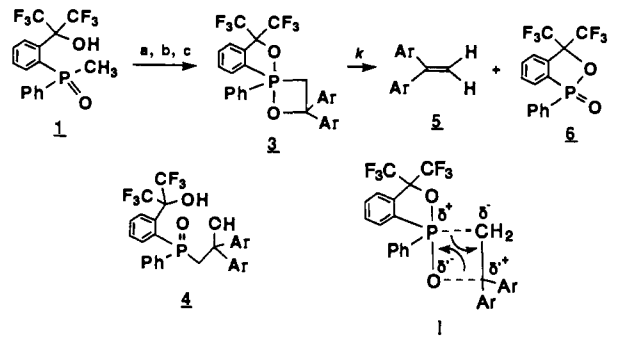
Table I. Yields, Melting Points, ^{31}P NMR Data, and Rate Constants of Thermolysis of **3**

3	X	yield,[a] %	mp,[b] °C	δ_P[c]	k,[d] 10^{-5} s^{-1}
a	H	94	179	−35.8	1.18
b	CH_3O	87	70	−35.9	14.5
c	CH_3	88	107	−35.9	3.11
d	F	75	183	−36.5	1.38
e	Cl	70	148	−36.5	0.75

[a] Isolated yields based on **1**. [b] Decomposition. [c] Measured in $CDCl_3$. [d] In d_8-toluene at 111 °C.

Scheme I[a]



[a] Ar = *p*-X-C_6H_4. (a) 2 *n*-BuLi, THF, 0 °C; (b) Ar_2CO (**2**), 0–50 °C; (c) H_3O^+.

observed at δ 8.64 (dd, $^3J_{HH}$ = 7.7 Hz, $^3J_{PH}$ = 11.9 Hz), this chemical shift being characteristic of a TBP (trigonal bipyramid) structure. In the ^{13}C NMR spectrum, the quaternary C-4 resonates at δ_C 75.93 (d, $^2J_{CP}$ = 16.2 Hz) and two sets of signals of aromatic rings at the 4-position are observed separately, because of the presence of a chiral phosphorus. The X-ray crystallographic analysis carried out for **3d** has indicated that it has a distorted TBP structure (Figure 1).[7]

Compounds **3** were heated around 100 °C under argon to give 1,1-diarylethylenes (**5**) and the corresponding cyclic phosphinate **6** quantitatively. A kinetic study on the olefin formation from **3** by ^1H and/or ^{19}F NMR spectroscopy showed that the reaction was first order in **3**; the rate constants (k) obtained in d_8-toluene at 111.3 °C are shown in Table I. The rates show a good correlation with σ_p^+, log $(k/k_0) = -0.709$ $(2\sigma_p^+)$ $(r = 0.999)$.[8] In the Wittig reactions using substituted aromatic carbonyl compounds, ρ values have been reported to range from +1.0 to +2.8 for both nonstabilized[9] and stabilized ylides,[10] indicating that the formation of oxaphosphetanes is a rate-determining step.[11] We have now clarified for the first time that the ρ value for the second step is negative. The rate constants of the reactions in d_8-toluene (ε 2.38),[12] d_3-acetonitrile (36.2), and d_6-dimethyl sulfoxide (49) were 1.18 × 10^{-5}, 1.5 × 10^{-5}, and 1.8 × 10^{-5} s^{-1}, respectively, showing a very small solvent effect.

The temperature dependence of the rate constants for **3a** led to the estimation of the activation parameters ($\Delta H^{\ddagger}$ = 29.1 ± 0.29 kcal/mol and $\Delta S^{\ddagger}$ = −5.7 ± 0.75 eu).[13]

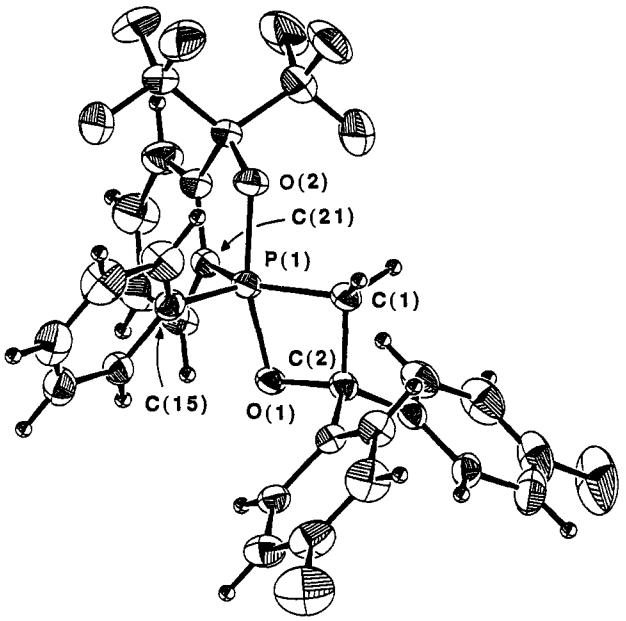


Figure 1. ORTEP drawing of **3d**. Selected bond lengths (Å) and bond angles (deg): P(1)–O(1), 1.728 (2); P(1)–O(2), 1.754 (3); P(1)–C(1), 1.808 (4); O(1)–P(1)–O(2), 163.3 (1); C(1)–P(1)–C(15), 111.8 (2); C(1)–P(1)–C(21), 136.0 (2); C(15)–P(1)–C(21), 112.1 (2); O(1)–P(1)–C(1), 77.4 (1); O(2)–P(1)–C(21), 87.4 (2).

Theoretical calculation shows that ring formation and ring opening of the oxygen-apical oxaphosphetane and its pseudorotamer (carbon-apical oxaphosphetane) occur through a [2s + 2s] concerted mechanism.[14] From the fact that polarity of the solvent did not significantly affect the rate it can be concluded that Bestmann's proposal, i.e., a P–C bond heterolysis mechanism from a carbon-apical oxaphosphetane,[15] which agrees with the apical-entrance and apical-departure principle,[16] is unlikely in the second step of the Wittig reaction.

In order to explain not only the solvent effect but also the substituent effect and the negative $\Delta S^{\ddagger}$, we propose a slightly polar transition state as shown in I (Scheme I) for the ring-opening reaction. In the transition state the P–C and C–O bonds are slightly elongated to a different extent,[17] so that C-3 and C-4 are polarized as δ^- and δ'^+, respectively, whose positive charge can be stabilized by more electron donating groups, leading to the rate acceleration. The small solvent effect is attributed to the slightly polar transition state. The negative activation entropy can be interpreted to arise from the reduction of freedom of the solvent induced by reorientation of the solvent toward the slightly polar transition state.

In summary, we have succeeded in the isolation of stable pentacoordinate 1,2-oxaphosphetanes bearing substituted phenyl groups at the 4-position and elucidated that the second step of the Wittig reaction proceeds via a concerted mechanism involving a slightly polar transition state.

Acknowledgment. This work was partially supported by Grant-in-Aid for Scientific Research on Priority Area of Organic Unusual Valency No. 02247205 (T.K.) from the Ministry of Education, Science and Culture. We are grateful to Dr. N. Tokitoh, The University of Tokyo, for the determination of the

(7) $C_{29}H_{19}F_8O_2P$, fw = 582.43, crystal size (mm) 0.75 × 0.50 × 0.50, monoclinic, space group $P2_1/C$, a = 10.450 (5) Å, b = 9.737 (1) Å, c = 25.766 (4) Å, β = 96.17 (4)°, V = 2607 (1) Å^3, Z = 4, D_{calcd} = 1.484 g/cm^3, R = 0.048 (R_w = 0.046). Full details of the crystallographic structure analysis are provided in the supplementary material.

(8) Although these two aryl groups affect the rate differently, we assume here that their effects are the same.

(9) (a) Speziale, A. J.; Bissing, D. E. *J. Am. Chem. Soc.* **1963**, *85*, 3878. (b) Rüchardt, C.; Panse, P.; Eichler, S. *Chem. Ber.* **1967**, *100*, 1144. (c) Giese, B.; Schoch, J.; Rüchardt, C. *Ibid.* **1978**, *111*, 1393. (d) Donxia, L.; Dexian, L.; Yaozhong, L.; Huaming, Z. *Tetrahedron* **1986**, *42*, 4161.

(10) (a) Yamataka, H.; Nagareda, K.; Takai, Y.; Sawada, M.; Hanafusa, T. *J. Org. Chem.* **1988**, *53*, 3877. (b) Yamataka, H.; Nagareda, K.; Hanafusa, T.; Nagase, S. *Tetrahedron Lett.* **1989**, *30*, 7187.

(11) There is a case wherein the positive ρ value supports single electron transfer as the rate-determining process in the formation of 1,2-oxaphosphetanes (see ref 10b).

(12) Dielectric constants at 25 °C. Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1988; p 408.

(13) Rate constants: 0.58 × 10^{-5} s^{-1} (104.2 °C), 1.18 × 10^{-5} s^{-1} (111.3 °C), 2.15 × 10^{-5} s^{-1} (116.2 °C), 3.38 × 10^{-5} s^{-1} (120.9 °C), 8.37 × 10^{-5} s^{-1} (131.3 °C), 22.0 × 10^{-5} s^{-1} (141.3 °C), and 30.4 × 10^{-5} s^{-1} (146.2 °C).

(14) Volatron, F.; Eisenstein, O. *J. Am. Chem. Soc.* **1987**, *109*, 1.

(15) Bestmann, H. J. *Pure Appl. Chem.* **1980**, *52*, 771. Bestmann, H. J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 85. This mechanism has been questioned. For examples, see refs 2b and 17.

(16) Dennis, E. A.; Westheimer, F. H. *J. Am. Chem. Soc.* **1966**, *88*, 3432. The calculation supports this principle: Boyd, D. B. *Ibid.* **1969**, *91*, 1200.

(17) Such an asynchronous bond cleavage has been proposed: Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1989**, *111*, 1519.

X-ray structure of **3d**. We also thank Central Glass and Tosoh Akzo Co. for gifts of hexafluorocumyl alcohol and alkyllithiums, respectively.

Supplementary Material Available: Physical and spectral data of **3a-e** and **6** and X-ray crystallographic data with tables of thermal and positional parameters, bond lengths, and bond angles for **3d** (18 pages). Ordering information is given on any current masthead page.

New Triply Hydrogen Bonded Complexes with Highly Variable Stabilities

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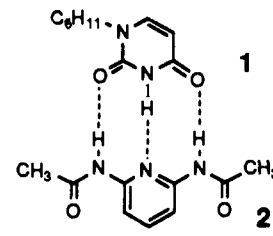
The use of hydrogen bonds to confer binding strength and selectivity has become a dominant theme in host-guest complexation studies.[1] As the number of reports on hydrogen-bonded complexes grows, so will the opportunities to discern patterns and, in turn, formulate rules for predicting the properties of unknown systems.[2] A case in point is the insightful analysis of triply hydrogen bonded systems recently reported by Jorgensen.[3] It notes that two complexes in which hydrogen bond donor (D) and acceptor (A) groups alternate (ADA·DAD; **1·2**, **3·4**) have $K_{assoc} \approx 10^2$ M^{-1},[4,5] while two DDA·AAD complexes (**5·6**, **7·8**) are significantly stronger with $K_{assoc} \approx 10^4$ M^{-1}.[6,7] Since the primary hydrogen bonds were similar in each system, the discrepancy was proposed to result from the different arrangement of the hydrogen-bonding sites and, in turn, different secondary electrostatic interactions. To test the generality of this analysis, we have experimentally examined four new triply hydrogen bonded complexes (**9·10**, **9·11**, **12·13**, **14·15**), of which one included the previously unknown DDD·AAA hydrogen-bonding motif (**12·13**). This latter arrangement contained four attractive secondary interactions and was predicted computationally to lead to the strongest complex.[3]



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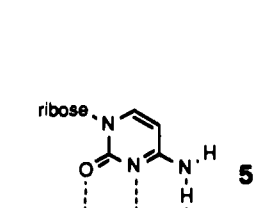

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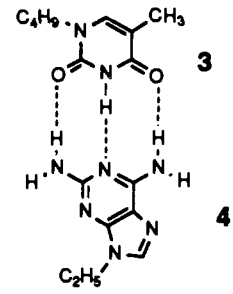

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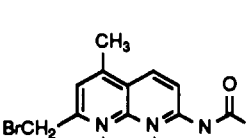

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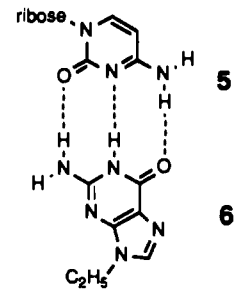

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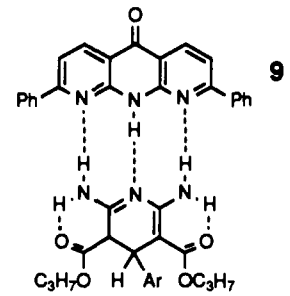

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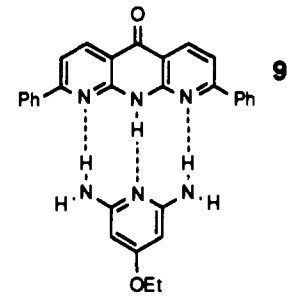

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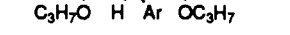
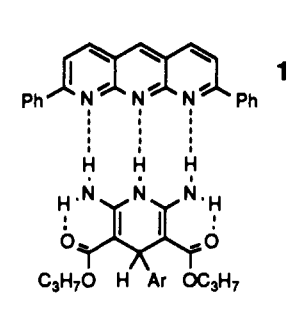


10 : Ar = 2-nitrophenyl

11



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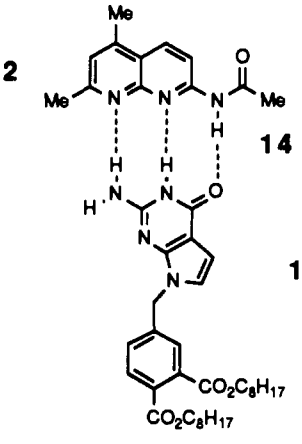
13 : Ar = 3-nitrophenyl



14

15

Most of the compounds used in this study were commercially available or were readily prepared using known procedures.[8-11]

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