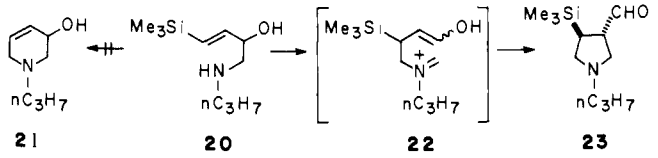
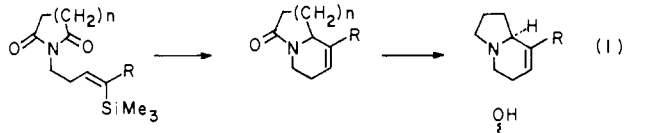
ring system is most commonly constructed by reduction of the corresponding pyridinium salt or from 4-piperidone precursors.[9,10] The cyclization approach reported here has the advantage of complete regiocontrol of the double-bond position and, moreover, should be of particular use for preparing 1-aryl-substituted tetrahydropyridines, which are not generally available from pyridine precursors.

Two mechanisms can be considered for these cyclization reactions (Scheme I). The simplest is direct cyclization of iminium ion **15** to **6**, presumably via a β-silyl cation intermediate **16**.[11] Alternatively, **15** could undergo cationic aza-Cope rearrangement[12] to allylsilane iminium ion isomer **17**, which then cyclizes to **6**.[11-14] Two experiments demonstrate that cationic aza-Cope equilibration occurs more rapidly than cyclization. First, treatment of (*Z*)-vinylsilane amine **14** in refluxing acetonitrile for 1.2 h with formaldehyde containing a trace of formic acid gave a 6:1:3 mixture of 1-isobutyl-1,2,5,6-tetrahydropyridine and the (*Z*)- and (*E*)-methylated amines **18**[4] and **19**,[4] respectively. Since **14** does not undergo $Z \rightarrow E$ isomerization in the absence of formaldehyde,[15] the loss of stereochemistry when formaldehyde is present implies equilibration of **15** and **17** (R = *i*-Bu). Conclusive evidence for the facile formation of a rearranged allylsilane comes from treatment of **20** with paraformaldehyde and camphorsulfonic acid (0.95 equiv in refluxing ethanol). This reaction did not yield tetrahydropyridine **21** but rather pyrrolidine **23**,[4,16] which arises from intramolecular Mannich cyclization[12] of allylsilane iminium ion **22**.



21 **20** **22** **23**

Related cyclizations to form unsaturated azabicyclics, which utilize acyliminium ion initiators,[17] are illustrated in eq 1. Imides



(1)

24 **25**, n = 1, R = H; **26**, n = 2, R = H; **27**, n = 1, R = Br; **28**, R = CH(OH)CH2CH2CH3; **29**, R = C(=O)CH2CH2CH3

24[4] were readily prepared by Mitsunobu[18] coupling of succinimide and glutarimide with the appropriate vinylsilane alcohol.[5] Reduction ($NaBH_4$, MeOH, 0 °C)[17,19] of **24** (R = H, *n* = 1 or 2) to the hydroxy lactam, followed by cyclization at 25 °C in trifluoroacetic acid afforded indolizidine **25**[4] and quinolizidine **26**[4], in 92% and 91% yields, respectively. The *Elaeocarpus* alkaloids, elaeokanine B (**28**) and A (**29**),[20,21] could be easily assembled using this chemistry. Thus, reduction[19] of **24** (R = Br) and cyclization of the resulting hydroxy lactam in refluxing trifluoroacetic acid provided the bromoindolizidine **27**[4] in 63% yield. This reaction constitutes the first report of the use of a 1-substituted vinylsilane terminator and, importantly, yields directly an alkene product regioselectively functionalized for subsequent transformations. Hydride reduction ($LiAlH_4$) of **27** followed by bromine-lithium exchange (*sec*-BuLi, -78 °C, THF) and reaction of the derived alkenyllithium with butanal gave elaeokanine B (**28**)[20,21] as a 1:1 mixture of alcohol diastereomers in 58% overall yield from **27**. Oxidation of **28** as described by Weinreb[21] provided elaeokanine A (**29**), which showed spectral properties identical with those of natural material.[20,21]

Acknowledgment. Financial support from the National Institutes of Health (Grant GM-30859 and NRSA-GM-08155 to G.P.M.) and the Camille and Henry Dreyfus Foundation (teacher-scholar award to L.E.O.) is gratefully acknowledged. We particularly thank Professor S. Weinreb for providing comparison spectra of racemic elaeokanines A and B. NMR and mass spectra were determined with spectrometers purchased with the assistance of NSF Departmental Instrumentation Grants.

Supplementary Material Available: Copies of the 250-MHz ^1H NMR spectra for new compounds **6-13**, **23**, and **25-29** (12 pages). Ordering information is given on any current masthead page.

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Solvent and Intramolecular Proton Dipolar Relaxation of the Three Phosphates of ATP: A Heteronuclear 2D NOE Study

Chin Yu and George C. Levy*

N.I.H. Biotechnology Research Resource for Multi-Nuclei NMR and Data Processing Department of Chemistry, Syracuse University Syracuse, New York 13210

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The nuclear Overhauser effect (NOE) arises from changes in nuclear spin populations resulting from dipolar relaxation in the presence of double irradiation.[1] Because it is related to $(r_{AB})^{-6}$, where r_{AB} is the distance between two dipolar coupled spins, A and B, nuclear Overhauser effects can provide valuable molecular structure information for solutions of organic and biological molecules. Due to their inverse dependence on the sixth power of r_{AB}, most reports of NOE arise from intramolecular relaxation. However intermolecular effects have been noted.[2-6]

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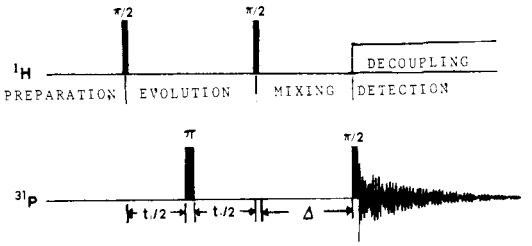

Figure 1. Pulse sequence for the $^{31}P\{^1H\}$ heteronuclear 2D NOE (HOESY) experiment.

Ernst et al.[7-10] developed a homonuclear 2D experiment to observe NOE phenomena, which is able to resolve many individual spin NOE effects with a single instrument setting.[11] Jacobson[12] used this technique to observe homonuclear ^{31}P–^{31}P dipolar interactions in the ATP molecule. In this communication, we propose a heteronuclear 2D experiment[13] (HOESY) to elucidate dipolar interactions between phosphorus and intramolecular and intermolecular protons.

ATP (adenosine triphosphate) plays an essential role in the metabolism of living organisms. However analysis of ^{31}P relaxation in the ATP molecule is not trivial due to the following factors: (a) ^{31}P relaxation for the three non-proton-bearing phosphorus nuclei may occur via a mix of mechanisms including dipolar, chemical shift anisotropy (CSA), spin rotation (SR), and dipolar–paramagnetic, in cases where metal ions having unpaired spins are bound to the molecule; (b) the interplay of these relaxation mechanisms is complex, depending on the magnetic field of the instrument, solvent, concentration, sample purity, etc.; (c) other complications are possible including spin diffusion in the ^{31}P manifold and cross relaxation terms associated with CSA and proton and phosphorus dipolar relaxation.[14,15] Furthermore, the $^{31}P\{^1H\}$ dipolar relaxation contributions in ATP can be difficult to assign, since no proton is directly bonded to the phosphorus atoms. This latter point is particularly true at the high magnetic fields most useful to biological NMR, where dipolar relaxation of ATP is largely displaced by chemical shift anisotropy. For example, Brauer and Sykes[15] reported that at 162.0 MHz, CSA accounts for 85%, 82%, and 78% of the total rate of spin–lattice relaxation of the α-, β-, and γ-phosphate resonances in ATP bounded to nitrated G-actin.

The pulse sequence for heteronuclear 2D NOE (HOESY) experiments is shown in Figure 1. In principle, this is similar to the homonuclear 2D NOE experiment, except that the 180° (^{31}P) pulse removes scalar interactions between ^1H and ^{31}P, so that only cross relaxation through dipole–dipole (^1H–^{31}P) interactions leads to exchange of magnetization between ^1H and ^{31}P during the mixing period Δ. The interval Δ is kept fixed, and the signal is recorded as a function of f_2 right after a 90° observe pulse. By using the general 2D principle, data sets (FIDs) were created, with constant t_2 (acquisition time) while linearly increasing t_1 (evolution time). A two-dimensional Fourier transformation of the data matrix then produces the desired frequency domain spectrum.[16]

ATP was purchased from Sigma. The 0.5 M solutions were prepared in 15% D_2O phosphate buffer (pH 5.2) and 100% D_2O buffer (by repeated lyophilization) with treatment of Chelex 100

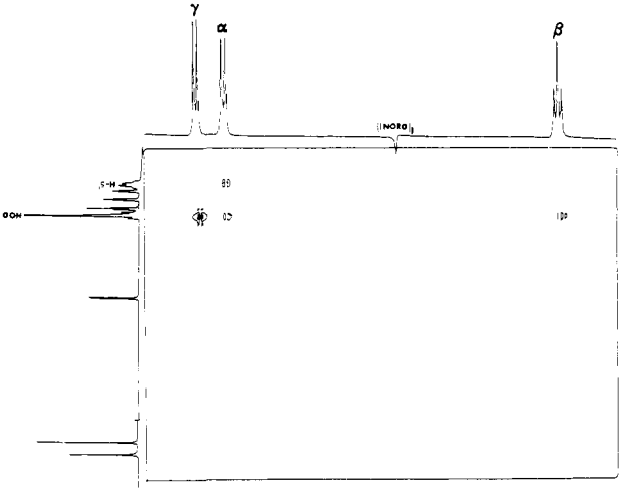

Figure 2. Contour plot of HOESY experiment for 0.5 M ATP in phosphate buffer (85% H_2O/15% D_2O). Spectral acquisition parameters: 0.222-s acquisition time, 2300-Hz sweep width in the f_2(^{31}P) dimension, and 0.5-s mixing time; 64 spectra (64 scans each) were accumulated with t_1 incremented to provide the equivalent of a 1950-Hz sweep width in the f_1 dimension. Zero filling was executed once (to 128) along the f_1 dimension to give better digital resolution. Conventional ^{31}P and ^1H (in 100% D_2O) 1D spectra are shown along the f_2 and f_1 dimensions, respectively. Inorganic phosphate is folded in f_2 and labeled as $(inorg)_f$.

(Bio Rad Laboratories). Data were acquired at 145.8 MHz on Bruker WM-360 WB spectrometer (equipped with a Aspect-2000 computer) in a 10-mm broad-band probe. The 90° pulse width for ^1H was carefully calibrated with the method described by Bax[17] to be 124 μs. In order to separate the positive and negative modulation frequencies (hence quadrature detection in f_1) and suppress the unwanted axial peaks,[18] four-step phase cycling was used, and it was further expanded to 16 cycles by incrementing the phases of all proton and phosphorus pulses, as well as receiver, by 90° each time to cancel out the image along $f_1 = 0$ axis. Since quad detection operated on f_1, the proton transmitter frequencies were set to the center of the ^1H chemical shift region of interest to minimize the required acquisition frequency and amount of data storage space, as well as to optimize decoupling.[19]

In order to maximize the efficiency of the experimental time with respect to sensitivity, the preparation period D1 was set to be 1.3 times the mean proton T_1[20] (those having dipolar interactions with phosphorus). Because cross relaxation between phosphorus and protons occurred during the mixing period, Δ was set to be of the order of T_1 of these protons.[9] Shifted sinebell[21] and Lorentzian digital filtering functions were applied in f_1 and f_2 dimensions, respectively.

Figure 2 shows the contour plot of the HOESY experiment on 0.5 M ATP (15% D_2O). The normal one-dimensional ^{31}P and ^1H spectra are also shown, along their respective chemical-shift axes. All the cross peaks in Figure 2 originate from heteronuclear dipolar interactions. All three phosphates in ATP show intense cross peaks with the H_2O (HOD) signal. This means there are strong dipolar interactions between solvent protons and the phosphorus nuclei. The terminal (γ) phosphorus, apparently most accessible to the water, has the strongest cross peak and hence intermolecular dipolar interactions. The α phosphorus shows reduced intermolecular dipolar interactions and also intramolecular dipolar interactions with the sugar 5′-hydrogens. The β phosphorus shows only low-level dipolar interaction with solvent protons.

Figure 3 shows the contour plot of a similar HOESY experiment for 0.5 M ATP in 100% D_2O buffer. In this instance, all

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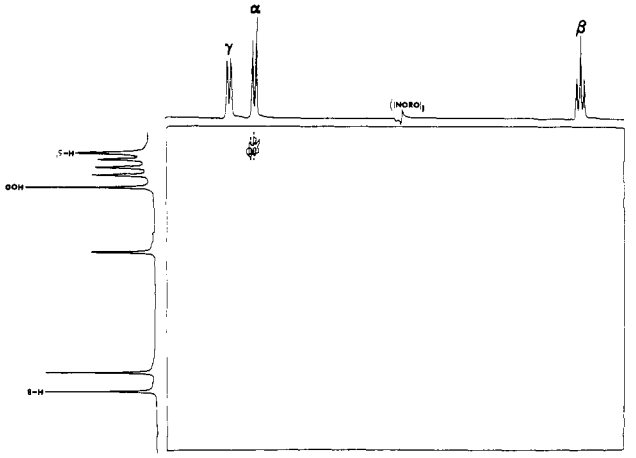

Figure 3. Contour Plot of the HOESY experient for 0.5 M ATP in phosphate buffer (100% D_2O, repeated lyophilizations). Acquisition parameters, same as figure 2.

the cross peaks between phosphorus and protons in the solvent disappear (there is no significant concentration of water protons remaining). Cross peaks arising from H-5′ sugar and H-8 base protons to α-phosphorus and from H-5′ to β-phosphorus are easily observed.

The heteronuclear 2D NOE experiment presented here provides information to analyse the dipolar relaxation behavior of the nonprotonated phosphorus atoms in ATP. This HOESY experiment should prove useful for evaluation of molecular conformation and also for studies of solvent–solute interactions. The observed nucleus is of course not restricted to phosphorus, and this technique is expected to have significant potential in studies of peptides (^{15}N, ^{13}C), metalloenzymes (M), and metabolic studies (^{31}P, ^{13}C).

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Registry No. Phosphate, 14265-44-2; phosphorus, 7723-14-0; hydrogen ion, 12408-02-5; adenosine triphosphate, 56-65-5.

Selective Intramolecular [6 + 4] Cycloadditions of Aminodienylfulvenes

Tse-Chong Wu, Jiri Mareda, Y. N. Gupta, and K. N. Houk*

Department of Chemistry, University of Pittsburgh Pittsburgh, Pennsylvania 15260

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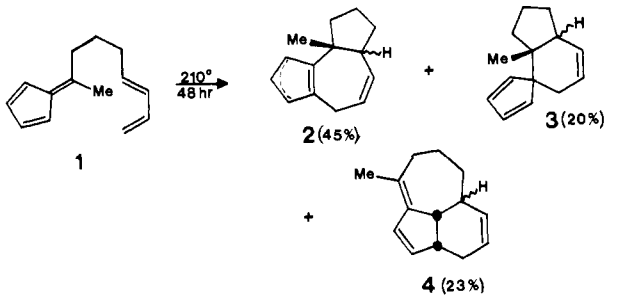
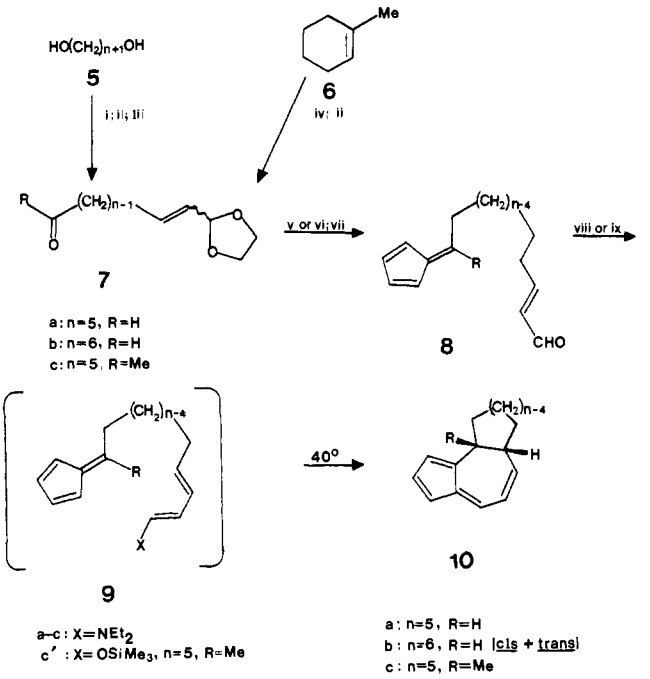
We recently reported several intramolecular [6 + 4] cycloadditions involving fulvenes as the 6π electron components and *o*-xylylenes as the 4π components.[1] We have now investigated similar reactions involving acyclic dienes as 4π electron components and have found that predictable substituent effects transform a despicably unselective reaction into a delightfully specific [6 + 4] cycloaddition.

The hydrocarbon dienylfulvene **1** was prepared in 74% yield by the reaction of sodium cyclopentadienide with 6,8-nonadien-2-one.[2] Thermolysis of a 1% solution of **1** in toluene at 210 °C for 48 h produces the complex mixture of thermally allowed cycloadducts shown in Scheme I. The different types of adducts were separated chromatographically, but the stereoisomers have not been separated.[3] The trimethylene connecting chain can be seen to promote the [6 + 4] and spiro-[4 + 2] cycloaddition modes, since the intermolecular reactions of alkyl-substituted dienes with fulvenes give only Diels–Alder adducts analogous to **4**.[4]

Scheme I. Intramolecular Cycloadditions of 6-Methyl-6-(4,6-heptadienyl)fulvene



Scheme II. Preparation and Cycloadditions of Fulvenes Linked to Electron-Rich Dienes[a]



[a] Reagents (yields): (i) PCC, CH_2Cl_2 (a, 62%; b, 41%); (ii) $Ph_3P^+CH_2CH(OCH_2CH_2O)\ Br^-$, *t*-BuOK, THF (a, 47%; b, 43%; c, 53%); (iii) PCC, CH_2Cl_2 (a, 81%; b, 72%); (iv) O_3, then KI, HOAc (30%); (v) C_5H_6, Et_2NH, MeOH (a, 50%; b, 72%); (vi) C_5H_6, KOH, THF, MeOH (c, 41%); (vii) 5% aqueous HCl, THF (a, 85%; b, 85%; c, 81%); (viii) Et_2NH, K_2CO_3, PhH, 5A molecular sieves (a, 55%; b, 46%; c, 54%);[14] (ix) Me_3SiCl, $ZnCl_2$, Et_3N (c).

Theoretical predictions and experimental studies[5] of intermolecular cycloadditions of dienes to fulvenes have shown that an electron donor at one terminal carbon of the diene provides sufficient nucleophilicity at the other diene terminus to promote

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(3) The product compositions were determined by NMR spectroscopy. The [6 + 4] adduct **2** is a mixture of cis and trans isomers and cyclopentadiene isomers,[1] while the [4 + 2] adducts are cis–trans mixtures. Details will be reported in a full paper.

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