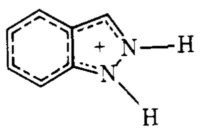

14

relative to the shifts of indazole **11** in the same solvent (acetic acid). The 34.2-ppm difference in the shifts of N1 and N2 of **14** is close to 35 ppm, the difference between the N1 shift of **12** and the N2 shift of **13**. One interpretation of this is that 35 ppm corresponds to an intrinsic shift difference resulting from the difference in positions of the nitrogens relative to the benzene ring, and there is a more or less equal positive charge on the two nitrogens of 14.

Partial protonation of indazole in acetic acid containing an equivalent of trifluoroacetic acid reduces the shift difference between N1 and N2 to 83.5 ppm. From this, the extent of protonation in this solvent can be estimated to be near 38%, which is nearly half the value calculated for the more basic *N*-methylpyrazole **2** under the same conditions.

Experimental Section

The ^{15}N NMR spectra were obtained using a Bruker WH-180 spectrometer operating at 18.25 MHz. The conditions for signal accumulation and solvent purification have been described elsewhere.[2] Commercial samples of the pyrazoles were used without further purification.

Registry No.—**2**, 930-36-9; **4**, 288-13-1; **5**, 1453-58-3; **6**, 67-51-6; **11**, 271-44-3; **11**·HCl, 63725-55-3.

References and Notes

(1) Supported by the National Science Foundation and by the Public Health Service, Research Grant No. GM-11072 from the Division of General Medical Sciences.

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^{15}N Nuclear Magnetic Resonance of Organophosphorus Compounds. Ring Size and Aziridine Methylation Effects on ^{15}N Shifts and ^{15}N–^{31}P Nuclear Spin Couplings in Heterocyclic Phosphoramidates

George A. Gray,*[1a] Gerald W. Buchanan,[1b] and Frederick G. Morin[1b]

NMR Applications Laboratory, Varian Instrument Division, Palo Alto, California 94303, and the Department of Chemistry, Carleton University, Ottawa, Canada, K1S 5B6

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Natural abundance ^{15}N NMR studies have been carried out on a series of cyclic phosphoramidates, including several methylated three-membered ring versions. The three-membered ring aziridine phosphoramidate was observed to have a substantial shielding (34 ppm) with respect to larger ring systems. Large β-substituent effects on the ^{15}N shift were noted along with changes in directly bonded ^{15}N–^{31}P couplings from 9.3 Hz in the nonsubstituted three-membered ring compound to ≤ 1 Hz in the fully substituted 2,2,3,3-tetramethylphosphoramidate. This directly bonded coupling experiences a large increase in going to the larger ring system, reflecting the change from a pyramidal-like (sp^3) nitrogen in the three-membered ring to trigonal (sp^2) in the larger ring compounds and the acyclic (diethylamino)dimethylphosphoramidate, where the observed coupling is 42.2 Hz.

Modern pulsed Fourier transform NMR spectrometers have provided instrumental access to the NMR spectroscopy of increasingly less sensitive nuclei such as ^{15}N (0.36% natural abundance). We have been interested in the systematic study of organosphosphorus compounds using NMR, taking advantage of the doubling of the spectral information via the spin couplings of ^{31}P to such nuclei as ^{13}C, ^{15}N, and ^{17}O. ^{15}N studies in general over the last few years have been more frequent and have concentrated on information obtained through measurements of the ^{15}N chemical shift.[2-4] In this work we analyze, in part, a particular class of organophosphorus compounds containing nitrogen—the aziridine phosphoramidates. There is much interest in the transferability of the substituent effect methodology for ^{13}C analysis to those of ^{15}N. In this class of compounds we were able to systematically test the reliability of such a method and as well explore the sensitivity of directly bonded ^{15}N–^{31}P couplings to those changes in the molecular framework.

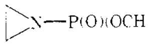
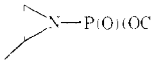
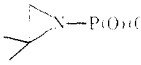
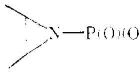
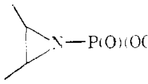
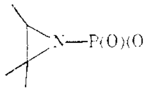
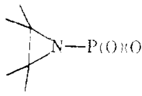
Experimental Section

^{15}N spectra were obtained on ~50% solutions in C_6D_6 in 10-mm tubes using a Varian XL-100 WG12/S124 FT NMR spectrometer at 10.138 MHz or FT-80A at 8.059 MHz. Typical conditions were 2500 Hz spectral width, 1–4 s acquisition time, 12–25° pulses, no pulse delay, and 35000–53000 transients. ^{15}N resonance frequencies were directly measured for each compound and compared with the frequency of CH_3NO_2 in a 90% solution in C_6D_6 in a separate experiment for purposes of chemical shift referencing. For the 8.059-MHz studies, 0.05 M Cr(AcAc)$_3$ was used to shorten the long ^{15}N T_1's.

^{13}C spectra were obtained on a Varian FT-80A at 20.0 MHz using ~30% solutions (C_6D_6) in 10-mm tubes. Typical conditions were 2000 Hz spectral width, 2–4 s acquisition times, 45 ° pulses, no pulse delay, collecting 100–200 transients, and transforming without exponential weighting.

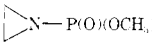
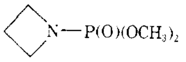
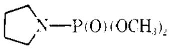
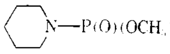
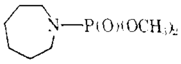
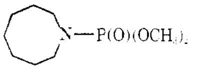
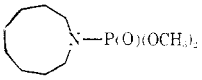
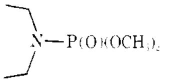
Materials. All compounds were prepared by reaction between trimethyl phosphite and the appropriate 2-iodoalkyl azide, according to the published procedure.[5] The iodo azides were synthesized via the method of Fowler et al.[6] For the aziridine phosphoramidates the boiling points are: 1, bp 79–80 °C (3.0 mm) [lit.[7] bp 107 °C (15 mm)];

Table I. ^{15}N Chemical Shifts and ^{15}N–^{31}P Nuclear Spin Coupling Constants[a]

compd	compd no.	registry no.	$\delta_{^{15}N}$	J_{PN}, Hz
	1	469-47-6	−367.4	9.3
	2	58503-35-8	−352.2	10.0
	3	58503-31-4	−340.9	4.4
	4	30271-50-2	−338.4	4.3
	5	27278-92-8	−338.1	10.6
	6	27356-56-5	−327.2	5.0
	7	58503-32-5	−320.6	≤1

[a] ^{15}N shifts are relative to CH_3NO_2 and are accurate to ±0.1 ppm. Negative shift implies greater shielding. Couplings are accurate to ±0.5 Hz.

Table II. ^{15}N Chemical Shifts and ^{15}N–^{31}P Nuclear Spin Coupling Constants[a]

compd	compd no.	registry no.	$\delta_{^{15}N}$	J_{PN}, Hz
	1		−367.4	9.3
	8	3550-92-3	−346.2	20.9
	9	24058-95-5	−334.4	41.2
	10	597-24-0	−333.7	39.1
	11	69502-67-6	−333.6	42.7
	12	69502-68-7	−337.0	41.8
	13	69502-69-8	−335.4	37.6
	14	65659-19-0	−330.6	42.2

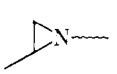
[a] ^{15}N shifts are relative to CH_3NO_2 and are accurate to ±0.1 ppm. Negative shift implies greater shielding. Couplings are accurate to ±0.5 Hz.

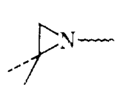
2, bp 69–71 °C (1.0 mm) [lit.[8] bp 56–62 °C (0.1 mm)]; **3**, bp 71–73 °C (1.0 mm) [lit.[8] bp 56–62 °C (0.1 mm)]; **4**, bp 70–73 °C (1.0 mm) [lit.[6] bp 54–58 °C (0.1 mm)]; **5**, bp 88–90 °C (2.0 mm) [lit.[6] bp 53–60 °C (0.1 mm)]; **6**, bp 84–86 °C (1.0 mm) [lit.[6] bp 59–63 °C (0.1 mm)]; and **7**, bp 82–88 °C (2.0 mm) [lit.[8] bp 70 °C (0.1 mm)].

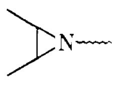
Results and Discussion

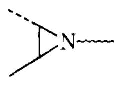
The ^{15}N chemical shifts and ^{15}N–^{31}P nuclear spin coupling constants are presented in Tables I and II. As reported earlier,[2–4] ^{15}N shifts have been analyzed in terms of substituent parameters. Shift data for primary alkylamines[2] led to substituent shift parameters of $\alpha = 8.7$, $\beta = 18.2$, and $\gamma = 2.7$ ppm, while data for secondary alkylamines were interpreted[4] through a regression analysis in terms of $\beta = 14.3$ and $\gamma = -2.1$ ppm.

The data for **1–7** allow substituent parameter sets to be formulated in a straightforward manner in terms of two to four parameters:


β


G


V_c


V_t

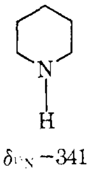
Taking **1** as the base compound there are six other independent shift measurements, allowing prediction of two to four shifts. Compounds **2**, **3**, and **4** were used to determine a two-parameter set β and G. Using this basis set ^{15}N shifts (relative to **1**) were calculated and are tabulated in Table III. Similarly, shifts for **2**, **3**, and **4** were used for the three-parameter basis set, and shifts for **2–5** were used for the four parameter basis set. The result for β can be compared with the 14.3 β from the work of Warren and Roberts.[4] In all of the parameter sets β is 15.3 ppm, somewhat higher than their 14.3 ppm value. The two-parameter set β and G is able to qualitatively place the shifts for **4–6** to within 1 ppm but both this and the three-parameter set have difficulty predicting the shift of **7**. Only with the introduction of V_t does the shift analysis correctly predict the shift of **7**. It is not clear, however, that the ability to analyze implies the importance of the interaction symbolized by V_t. Other more subtle effects may be present and not considered in this elementary analysis. As previously noted in ^{13}C substituent analyses, progressive replacement of β hydrogens with methyls must be rationalized either by different β's for each methyl or by introducing factors such as G. In these analyses G is fairly large in effect and not easily explained (if separate β's are permitted three-, four-, and five-parameter analysis of the data for **1–7** now show G dropping to −2.4 ppm, when $\beta_1 = 15.3$ and $\beta_2 = 13.7$ ppm).

Table III. Substituent Shift Analysis

		analysis (error)		
basis set	prediction[a]	b	c	d
2, 3	4	30.6 (1.6)		
	5	30.6 (1.2)		
	6	42.0 (1.6)		
	7	53.3 (6.4)		
2, 3, 4	5		30.6 (1.6)	
	6		40.8 (0.4)	
	7		50.9 (4.0)	
2, 3, 4, 5	6			39.2 (−1.2)
	7			47.7 (0.8)

[a] ^{15}N shift of **1** taken as zero. [b] Two parameters: $\beta = 15.3$; $G = -4.0$. [c] Three parameters: $\beta = 15.3$; $G = -4.0$; $V_c = -1.2$. [d] Four parameters: $\beta = 15.3$; $G = -4.0$; $V_c = -1.2$; $V_t = -1.6$

There is a generalized shielding experienced by the nitrogen in **1–7** relative to larger ring size compounds. For example, the previously reported six-membered rings **15** and **16** have ^{15}N shifts[4] considerably deshielded from **1**. The effect of substitution of a phosphoramidate group for a proton on an ^{15}N shift has not previously been determined (the ^{13}C analogue[9] shows a 13.2 ppm *deshielding* upon this substitution). The similarity of shifts in **15** and **16** points out a clear difference between ^{15}N shifts and ^{13}C shifts when such a substitution would lead to


1, $\delta_{^{15}N}$ −341.6

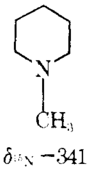
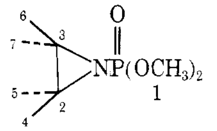

16, $\delta_{^{15}N}$ −341.3

Table IV. ^{13}C Chemical Shifts and ^{13}C–^{31}P Nuclear Spin Coupling Constants[a]



1

	J_{CP}, Hz						
	OCH_3	C-2	C-3	C-4	C-5	C-6	C-7
1	6.3	6.8					
2	6.4	6.3	7.2	5.2			
3	6.5	7.2	7.1	5.0	5.0		
4	6.6	6.9	6.9	5.1			5.1
5	6.4	6.9	6.9	5.4		5.4	
6	6.4	7.8	7.3	4.8	5.4	3.6	
7	6.5	7.4	7.4	4.4	4.4	4.4	4.4
	δ_C						
	OCH_3	C-2	C-3	C-4	C-5	C-6	C-7
1	53.83	24.05					
2	53.68	32.15	31.59	17.85			
3	53.27	40.37	38.53	23.14	23.14		
4	53.39	40.94	40.94	16.38			16.38
5	53.64	36.59	36.59	12.79		12.79	
6	53.15	44.57	44.04	20.67	22.36	14.00	
7	53.00	47.41	47.41	20.98	20.98	20.98	20.98

[a] Shifts in ppm relative to internal Me_4Si. Couplings accurate to ±0.2 Hz.

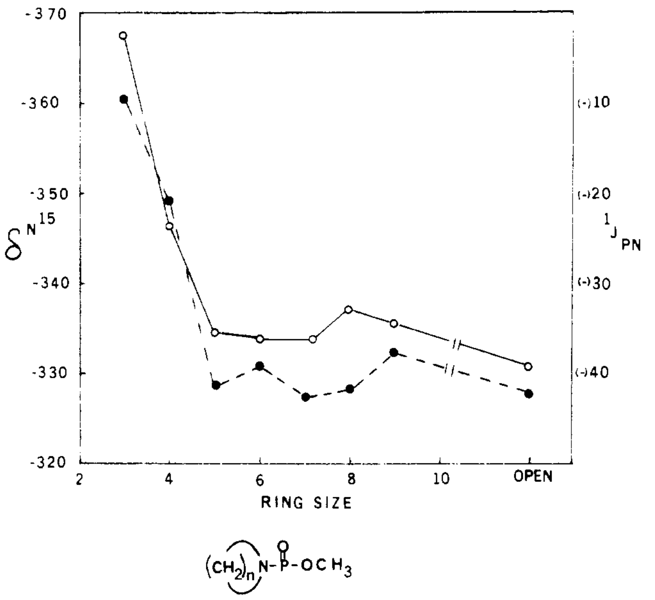


Figure 1. Ring size dependence of ^{15}N chemical shift and ^{15}N–^{31}P nuclear spin couplings. Open circles refer to chemical shifts and closed circles refer to couplings.

substantial deshielding, so that the shifts of a six-membered ring analogue of **1** cannot be accurately predicted, a priori. To accurately determine the dependence on ring size, the ^{15}N shifts of **8–14** were determined. The 33.7-ppm shielding observed for **10** → **1** is indeed very sizable and in the same direction as in ^{13}C and ^{1}H NMR shifts for cyclohexyl → cyclopropyl systems. In this case replacement of a proton by a phosphoramidate results in a 7.9-ppm deshielding of the ^{15}N shift.

The ^{13}C data in Table IV were taken to explore the conformational nature of the aziridine ring. Species **3**, **4**, **5**, and **7** give methyl shifts and couplings which point out that on the NMR time scale there is rapid rotation of the phosphoramidate group. In **6** the single methyl C-6 serves to destroy the degeneracy through chemical nonequivalence. The identical shifts and couplings of the geminal methyls in **3** indicate that the phosphoramidate group is rotating fast enough to average out the two methyl environments.

The ^{15}N–^{31}P couplings are sensitive to neighboring structural differences. In view of the rapid nitrogen inversion in similarly substituted aziridines at room temperature[10] and the above demonstrated rapid rotation of the phosphoramidate group, these structural differences must create different average electronic environments for the N–P bond, which result in variations in the observed ^{15}N–^{31}P coupling. The mechanism or mechanisms of this coupling are not well-known even though earlier calculations[11] using the Finite Perturbation method demonstrated that the Fermi contact contribution could account for the observed ^{15}N–^{31}P couplings in $[(CH_3)_2N]_3P$, $[(CH_3)_2N]_3PS$, and $[(CH_3)_2N]_3PO$. The ^{15}N–^{31}P coupling in $[(CH_3)_2N]_3PO$ is −26.9 ± 0.1 Hz (−21.0 calcd)[11] where the nitrogen was assumed to have a conformation intermediate between trigonal and pyramidal. Pure trigonal geometry gave a calculated ^{15}N–^{31}P coupling of −39 while pure pyramidal gave −12. In **1** through **7** substituents on both N and P are changed, as well as geometry, so any detailed explanation of the coupling is hazardous. In addition, other coupling mechanisms, such as dipolar or orbital, may contribute on the order of a few hertz and be sensitive to structural differences.

A significant change in the ^{15}N–^{31}P coupling is observed in going to the larger rings. The coupling becomes increasingly (assumedly) negative as the C–N–C bond angle opens up, pointing out the high sensitivity of the ^{15}N–^{31}P coupling to the nitrogen hybridization. Note that these values are much closer to the value calculated[11] for the trigonal form of $[(CH_3)_2N]_3PO$, although substituent effects here may obscure any detailed comparison. Ignoring, for the moment, any differences in substituent effects, the large differences in the ^{15}N–^{31}P couplings for **1–7** and **8–14** may lie in a substantially higher pyramidal character for **1–7**. The results may be interpreted as representing an increase in the s character of the exocyclic nitrogen bonding hybrid orbital at the expense of the endocyclic bonding hybrid orbitals, a situation similar to that for carbon in the cyclopropyl ring as demonstrated by increased $^1J_{CH}$, $^1J_{CC}$, and ^{13}C chemical shielding.

Figure 1 illustrates the dependence on ring size of the ^{15}N shifts and one-bond N-P couplings. The shift dependence is strikingly similar to that noted for carbocyclic systems[12] except that the four-membered ring is intermediate between the three and higher membered ring systems here. In both carbocyclic systems[12] and in these nitrogen analogues, the six- or seven-membered ring has the lowest shielding. The ^{15}N shifts and N-P couplings have a very similar ring size dependence. As discussed above, N-P couplings are sensitive to the geometry at the nitrogen, i.e., large and negative in the trigonal geometry. These data seem to indicate substantially complete trigonal character at the five-membered ring stage.

Acknowledgment. G.W.B. thanks the National Research Council of Canada for financial aid.

Registry No.—Trimethyl phosphite, 121-45-9; 1-azido-2-iodoethane, 42059-3-3; 2-azido-1-iodopropane, 69500-70-1; 2-azido-1-iodo-2-methylpropane, 16484-01-8; 2-azido-3-iodobutane, 69502-71-2; 2-azido-3-iodo-2-methylbutane, 25022-26-8; 2-azido-3-iodo-2,3-dimethylbutane, 58503-58-5.

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(1) (a) Varian Instrument Division, Palo Alto, Calif. 94303. (b) Carleton University, Department of Chemistry, Ottawa, Canada, K1S 5B6.
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Role of the Central Thiol in Determining Rates of the Thiol-Disulfide Interchange Reaction

Rolf Freter, Eric R. Pohl, Janet M. Wilson, and D. J. Hupe*

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109

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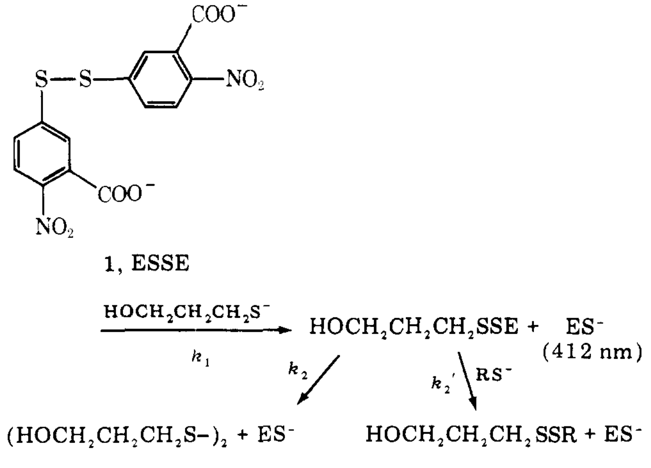
Ellman's reagent, 5,5′-dithiobis(2-nitrobenzoic acid) (1, ESSE) in dilute aqueous solution, reacts with excess 3-mercaptopropanol to form $HOCH_2CH_2CH_2SSE$ followed by a slower second reaction giving the symmetrical disulfide and a second mole of ES^-. In this study, we report the rates of reaction of a variety of aliphatic and aromatic thiol anions with $HOCH_2CH_2CH_2SSE$ which were measured by rapidly mixing the thiol with the mixed disulfide immediately after it was formed. The Brønsted type plot for this reaction shows a β_{nuc} of about 0.58 for either aromatic or aliphatic thiol anions. The aromatic thiol anions were more reactive for their basicity by a factor of about 6 than aliphatic thiols. Exactly the same behavior has been observed for ESSE and $HOCH_2CH_2CH_2SSE$, indicating that the cause of the split structure reactivity correlation cannot be a favorable aryl-aryl interaction between attacking and central thiols. The previously proposed explanation based on hard-soft acid-base theory is therefore supported. Inductively withdrawing groups on the central thiol increase the rate with $\beta_{CT} \approx -0.3$. The rates of reaction with ES as the central thiol are slower than predicted by extrapolation of data for aliphatic central thiols, probably because of the effect of the negative charge on ES.

It has been shown previously[1,2] that Ellman's reagent,[3] 5,5′-dithiobis(2-nitrobenzoic acid) (1, ESSE), reacts in aqueous solution with thiols in a biphasic manner. When RS^- is a highly basic alkyl thiol anion, the first step is much faster than the second ($k_1/k_2 \simeq 50$) and this difference decreases as the basicity of attacking thiol decreases. By adding, for example, excess mercaptopropanol to 1, a solution of the mixed disulfide $HOCH_2CH_2CH_2SSE$ is generated in a few seconds and this is then more slowly converted to the symmetrical disulfide yielding a second mole of ES^-.

Scheme I



The rates of attack (k_1) on ESSE by aryl and alkyl thiol anions were fit by separate correlation lines, each with a slope, β_{nuc}, of 0.5. The rates for the aromatic thiol anions were faster by a factor of about 6 than correspondingly basic alkyl thiol anions.[1] Two explanations seemed possible for this behavior. The greater reactivity of aryl thiol anions could have arisen because of a favorable aryl-aryl interaction between the attacking and central thiols in the transition state since such small hydrophobic enhancements are precedented.[1,4-6] Alternatively, this split β_{nuc} plot may have reflected the fact that aromatic thiol anions are softer than correspondingly basic aliphatic thiol anions. With hard electrophiles, a single correlation line is found for aromatic and aliphatic thiol anions[7,8] whereas with suitably soft electrophiles aryl thiol anions react much more rapidly even though they are much less basic than the aliphatic thiol anions with which they are compared.[9,10]

In this study we present measurements of the rates of reaction of a series of aliphatic and aromatic thiol anions with the mixed disulfide of mercaptopropanol and ESH. These data should demonstrate whether an aryl central thiol is re-

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