and about 15 ml of liquid hydrogen fluoride was stirred for 30 min at 0°. The hydrogen fluoride was evaporated with a stream of nitrogen at 0° (*ca.* 10 min). The residue was dried *in vacuo* over NaOH and then stirred with 10 ml of trifluoroacetic acid for 15 min. The polymer support was filtered off and rinsed with two 5-ml portions of trifluoroacetic acid. The filtrate was evaporated *in vacuo*, and the resulting oily residue was taken up in a mixture of 10 ml of 0.2 *N* acetic acid and 10 ml of ether. The ether layer was discarded and the aqueous phase was washed again with a 5-ml portion of ether, and lyophilized to give crude peptide I. Amino acid analysis of an acid hydrolysate gave $His_{1.92}Arg_{0.96}Glu_{0.99}Ala_{2.70}Leu_{2.00}$. Chromatography on CM-cellulose gave 80 mg of peptide I.

For further purification partition chromatography on Sephadex G-25 was employed. A 1.92 × 63 cm column was equilibrated with the solvent system 1-butanol–ethanol–0.2 *N* aqueous NH_4OH containing 0.04% acetic acid (4:1:5). The column was thoroughly equilibrated with organic phase (330 ml) before carrying out chromatography. The material from carboxymethylcellulose chromatography was subjected to partition chromatography in two batches with collection of 5.55 ml fractions. Only one peak was detected in each case by the Folin–Lowry method[26] with R_f 0.33 (Figure 2). Isolation of the two batches gave 78 mg of I (63% yield based on starting resin): tlc (BPAW) R_f 0.40; $[\alpha]^{24}D$ −56° (*c* 1, 1 *N* acetic acid); $[\alpha]^{24}D$ −57° (*c* 0.33, 10% acetic acid). For analysis a sample was dried at 100° for 6.5 hr *in vacuo* over P_2O_5.

Anal. Calcd for $C_{38}H_{63}N_{13}O_{11}\cdot 3H_2O$ (928.09): C, 49.2; H, 7.49; N, 22.6. Found: C, 49.3; H, 7.19; N, 23.0.

Paper electrophoresis in pyridine acetate buffer (pH 3.7, 400 V, 4 hr) and in collidine acetate buffer (pH 6.9, 400 V, 4 hr) showed single ninhydrin and Pauly positive spots with mobilities of R_f 0.94 and 0.55, respectively, relative to lysine. Amino acid analyses of an acid hydrolysate and a leucine aminopeptidase digest (pH 8, 24 hr, 37°) gave $His_{1.97}Arg_{1.02}Glu_{1.01}Ala_{0.95}Leu_{2.00}$ and $His_{2.02}Arg_{0.91}Gln_{0.74}Ala_{0.94}Leu_{2.00}$, respectively.

B. From Bpoc-alanyl-Im-Boc-histidyl-N^G-nitroarginylleucyl-Im-Boc-histidylglutaminylleucyl Resin. A portion of the above dried heptapeptide resin (485 mg) was treated with 0.5 ml of anisole and 10 ml of hydrogen fluoride for 30 min at 0°. After evaporation of the hydrogen fluoride at 0° and thorough drying, the resin was stirred for 15 min with 10 ml of trifluoroacetic acid. The mixture was filtered and the filtrate was evaporated to a residue which was distributed between 10 ml of 0.1 *N* acetic acid and 10 ml of ether. The aqueous layer was washed with 5 ml of ether, and lyophilized to a residue which was purified by carboxymethylcellulose chromatography as above to give 55 mg of peptide. Rechromatography gave 47 mg (54% yield based on starting Boc-leucyl resin) of I: $[\alpha]^{24}D$ −56° (*c* 0.3, 10% acetic acid). Paper electrophoresis in pyridine acetate buffer (pH 3.7, 400 V, 4 hr) showed one ninhydrin positive, Pauly positive spot at R_f 0.93 (with respect to lysine). Paper electrophoresis in collidine acetate buffer (pH 6.9, 400 V, 4 hr) showed one ninhydrin positive, Pauly positive spot at R_f 0.51. Amino acid analyses of an acid hydrolysate and a leucine aminopeptidase digest gave $Leu_{2.00}His_{2.02}Arg_{1.03}Glu_{1.04}Ala_{0.95}$ and $Leu_{2.00}His_{2.04}Arg_{1.02}Gln_{0.80}Ala_{0.97}$, respectively.

C. From Boc-alanylhistidyl-N^G-nitroarginylleucylhistidylglutaminylleucyl Resin. A sample (767 mg) of Boc-alanylhistidyl-N^G-nitroarginylleucylhistidylglutaminylleucyl resin was treated with liquid HF in exactly the same manner as described in part A. Isolation of the crude cleavage product in the same way gave 164 mg of solids. Amino acid analysis of an acid hydrolysate of this material gave $Orn_{0.16}His_{1.84}Arg_{0.63}Glu_{1.04}Ala_{2.88}Leu_{2.00}$. Chromatography on CM-cellulose gave two major peaks as analyzed at 240 mμ. The faster moving peak (fraction A) gave 27.6 mg after lyophilization; the slower moving peak (fraction B) gave 44.1 mg after lyophilization.

Fraction A was subjected to partition chromatography under conditions identical with those described above. A major peak with R_f 0.33 was detected along with a substantial peak with R_f 0.25 (Figure 3). Isolation of materials corresponding to these peaks gave 15.5 and 9.2 mg, respectively. In like manner fraction B was chromatographed to give a major peak with R_f 0.33 and a smaller peak with R_f 0.27. The yields in this case were 36.7 and 5.2 mg, respectively.

The materials represented by the major peak with R_f 0.33 were pooled and rechromatographed in exactly the same manner to give one peak with the same R_f. Recovery of peptide I was 43.8 mg (41% yield based on starting resin): tlc (BPAW) R_f 0.40; $[\alpha]^{24}D$ −55° (*c* 0.32, 10% acetic acid). Paper electrophoresis performed under conditions identical with those described in part A gave exactly the same results. Amino acid analyses of an acid hydrolysate and a leucine aminopeptidase digest gave $His_{1.97}Arg_{0.99}Glu_{0.93}Ala_{0.97}Leu_{2.00}$ and $His_{2.21}Arg_{0.97}Gln_{0.77}Ala_{1.02}Leu_{2.00}$, respectively.

Materials represented by the minor peak with low R_f value (Figure 3) were combined along with the same material obtained after HF cleavage from a second batch of protected peptide resin (506-mg run) and rechromatographed on the partition column. An unsymmetrical peak with R_f 0.27 was obtained and isolation gave 20.1 mg. Amino acid analysis of an acid hydrolysate showed a peak running 4.8 min before the histidine peak. Authentic samples of ornithine and lysine ran 4.8 and 4.0 min, respectively, ahead of histidine. Paper electrophoresis (collidine acetate buffer of pH 6.9, 400 V, 6.5 hr) of the acid hydrolysate gave a ninhydrin spot with color and mobility identical with an authentic sample of ornithine, while authentic samples of lysine and arginine had mobilities of R_f 0.90 and 0.80, respectively, relative to ornithine.

Acknowledgments. We thank Mr. W. F. Hain for skilled technical assistance. This work was supported in part by the American Cancer Society, the Allen Foundation, and the Geffen Foundation.

(26) O. H. Lowry, N. J. Rosebrough, A. L. Farr, and R. J. Randall, *J. Biol. Chem.*, **193**, 265 (1951).

Communications to the Editor

Effect of Ligand Electronegativity on the Inversion Barriers of Arsines[1]

Sir:

We have recently shown[2] that, by analogy with the planarity or near planarity at nitrogen in silylamines,[3] the barrier to pyramidal inversion at phosphorus is markedly lowered by the incorporation of silyl substituents. We now report the operation of a similar effect when arsenic is the inversion center. The inversion barrier in isopropylphenyltrimethylsilylarsine (**2a**) (Table I) represents a decrease of *ca.* 18 kcal/mol relative to ethylmethylphenylarsine (**1a**). Moreover, the trend in barrier heights within the arsine series **1a–4a** (Table I) exactly parallels the trend previously observed[4] in the analogous phosphines **1b–4b** (Table I). Hence, the predominant influence upon pyramidal stability in these systems appears to be the atomic electronegativity[5] of the

(1) This work was supported by the National Science Foundation (GP-30257).

(2) R. D. Baechler and K. Mislow, *J. Amer. Chem. Soc.*, **92**, 4758 (1970).

(3) C. Glidewell, D. W. H. Rankin, A. G. Robiette, and G. M. Sheldrick, *J. Mol. Struct.*, **6**, 231 (1970), and references cited therein.

(4) R. D. Baechler and K. Mislow, *J. Amer. Chem. Soc.*, **93**, 773 (1971).

(5) A. L. Allred, *J. Inorg. Nucl. Chem.*, 17, 215 (1961).

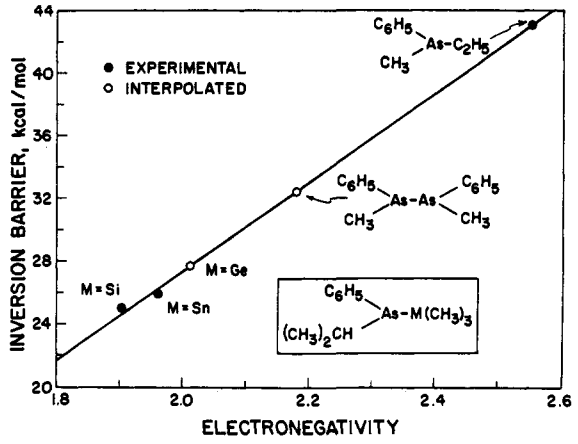

Figure 1. Pyramidal inversion barriers *vs.* electronegativity.

adjacent heteroatom. If a linear correlation is assumed to exist between this parameter and barrier height,[6] a barrier of 28 kcal/mol may be estimated by interpolation (Figure 1) for the germylarsine **3a**, consistent with the experimentally determined lower limit (Table I). As with the phosphines, there is no need to invoke (p–d)π conjugation as a source for the observed barrier lowering in **2a** and **4a**.

Table I. Barriers to Pyramidal Inversion in Arsines and Phosphines

Compd[a]	Structure	Inversion barrier,[b] $\Delta G^{\ddagger}_T$, kcal/mol (T, °C) M = As	M = P
1a–b	$(C_6H_5)(CH_3)MR$	43.1 (218)[c]	33.3 (130)[d]
2a–b	$(C_6H_5)(CH(CH_3)_2)$-$MSi(CH_3)_3$	25.1 (181)	18.9 (62)[e]
3a–b	$(C_6H_5)(CH(CH_3)_2)$-$MGe(CH_3)_3$	>27 (200)[f]	21.4 (109)[e]
4a–b	$(C_6H_5)(CH(CH_3)_2)$-$MSn(CH_3)_3$	25.9 (191)	19.3 (72)[e]
5a–b	$(C_6H_5)M(SiH(CH_3)_2)_2$	17.7 (49)	12.2 (−42)

[a] In these compound numbers **a** refers to the arsine and **b** to the phosphine. [b] No solvent or concentration dependence was observed for the reported barriers. [c] Based on $\Delta G^{\ddagger}$ of racemization (42.4 kcal/mol) reported by G. H. Senkler, Jr., and K. Mislow, *J. Amer. Chem. Soc.*, **94**, 291 (1972); R = CH_2CH_3. [d] Based on $\Delta G^{\ddagger}$ of racemization (32.7 kcal/mol) reported by R. D. Baechler and K. Mislow, *ibid.*, **92**, 3090 (1970); R = $C(CH_3)_3$. [e] See ref 4. [f] This value is a lower limit to the barrier and is based on the absence of any detectable line broadening in the high-temperature spectrum.

Lambert, *et al.*,[7] in a study of the thermal stereomutation of 1,2-dimethyl-1,2-diphenyldiarsine (**6**), reported an activation energy (E_a) of 27 ± 1 kcal/mol,[8] which was attributed to pyramidal inversion at arsenic. However, the inversion barrier for **6** which may be estimated from Figure 1 (32 kcal/mol)[9] is substantially higher than the reported value;[7,8] moreover, the apparently greater pyramidal stability of the germylarsine **3a** relative to the diarsine **6** is unexpected from a consideration of factors which have been postulated to influence barrier heights (*e.g.*, ligand electronegativity, lone-pair repulsion, or (4p–4d)π conjugation).[7,11] In this connection, we have noted that the nmr spectrum of **6** in biphenyl exhibits an apparent concentration dependence at 176°, in the region of coalescence; this finding casts a modicum of doubt on the claim that the observed rate process corresponds to unimolecular pyramidal inversion.[7,12]

The inversion barriers for bis(dimethylsilyl)phenylarsine (**5a**) and its phosphorus analog **5b** (Table I) demonstrate that attachment of a second silicon atom to the inversion center induces an additional and substantial reduction in barrier magnitude. The barriers for **5a** and **5b** represent the lowest values yet reported for pyramidal inversion at arsenic and phosphorus.[13] By assuming a proportional reduction in barrier magnitude of 42% per silyl group, based on the barriers for **1a** and **2a**, the inversion barrier for **5a** may be estimated at 14.6 kcal/mol,[15] significantly below that observed (Table I). This discrepancy has its origin in the circumstance, previously discussed,[16] that the "proportionality method"[17] is a linear free-energy relationship which assumes an intercept (I) of zero; however, the linear correlation[16] of barriers for corresponding silyl- and alkylarsines, defined by the barriers for (**1a**,**2a**) and (**2a**,**5a**), yields I = 7.4 kcal/mol. Hence, the value predicted from this linear correlation for trisilylarsine (14.7 kcal/mol) differs substantially from that predicted by the proportionality method (8.5 kcal/mol). Similarly, the corresponding correlation for phosphines (I = 3.4 kcal/mol) predicts a barrier of 9.1 kcal/mol for trisilylphosphine.

Arsines **2a–4a** were synthesized by the reaction of isopropylphenylarsine[18] with sodium dispersion in refluxing dioxane, followed (for **2a**, **3a**, and **4a**, respectively) by trimethylsilyl chloride, trimethylgermyl bromide, and trimethylstannyl chloride. The disilyl compounds, **5a** and **5b**, were synthesized by reaction of dimethylchlorosilane with dilithiophenylarside[21] and phosphide,[22] respectively. The pmr spectra of **2a–5a**

(6) The existence of such a correlation has been demonstrated[4] for a series of heteroatomically substituted phosphines.

(7) J. B. Lambert, G. F. Jackson, III, and D. C. Mueller, *J. Amer. Chem. Soc.*, 90, 6401 (1968); J. B. Lambert and G. F. Jackson, III, *ibid.*, 90, 1350 (1968).

(8) From reported[7] kinetic data, this value corresponds to $\Delta G^{\ddagger}_{173}$ = 24.5 kcal/mol.

(9) This value, based on an electronegativity of 2.18 for arsenic,[5] is in satisfactory agreement with the barrier calculated for **6**, E_{inv} = 32.0 kcal/mol, using a specially parameterized CNDO/2 scheme.[10]

(10) A. Rauk, J. D. Andose, and K. Mislow, unpublished work.

(11) For reviews, see A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem., Int. Ed. Engl.*, 9, 400 (1970), and J. B. Lambert, *Top. Stereochem.*, 6, 19 (1971).

(12) The report[7] that there is "no observable effect" of concentration on the reaction rates at 131 and 142° is of questionable significance, since these temperatures are at least 30° below coalescence, where nmr line shapes are quite insensitive to the rates of site exchange.

(13) A report[14] that the cyclic disilylarsine, $((CH_3)_2SiAsCH_3)_4$, displays an nmr coalescence at *ca.* 130°, attributable to rapid inversion at arsenic, is supported by our results.

(14) E. W. Abel and J. P. Crow, *J. Organometal. Chem.*, 17, 337 (1969).

(15) A similar treatment has been used to estimate barriers in amines: H. Kessler and D. Leibfritz, *Tetrahedron Lett.*, 4289, 4293, 4297 (1970).

(16) J. Stackhouse, R. D. Baechler, and K. Mislow, *ibid.*, 3441 (1971).

(17) The proportionality method is defined as follows: the effect of substituents on barrier magnitudes for compounds possessing the same inversion center is estimated by assuming that replacement of a substituent X by a substituent Y produces the same fractional increase (or decrease) in the inversion barrier, regardless of the nature of the remaining ligands.

(18) Prepared from phenylarsine[19] by reaction of the monosodium phenylarside[20] in liquid ammonia with isopropyl bromide.

(19) C. S. Palmer and R. Adams, *J. Amer. Chem. Soc.*, **44**, 1356 (1922).

(20) F. G. Mann and B. B. Smith, *J. Chem. Soc.*, 4544 (1952).

(21) Prepared from phenylarsine[19] by treatment with *n*-butyllithium in tetrahydrofuran.

(22) P. R. Bloomfield and K. Parvin, *Chem. Ind. (London)*, 541 (1959).

Table II. 60-MHz Pmr Spectral Data[a]

Compd	$M(CH_3)_3$, δ	$CH_{3(a)}$, δ	$CH_{3(b)}$, δ	$\Delta\nu_{ab}$, Hz	$^3J_{HH(a)}$, Hz	$^3J_{HH(b)}$, Hz
2a[b]	0.11	1.21	1.18	1.8	6.8	6.7
3a[b]	0.24	1.20	1.17	1.9	6.8	6.7
4a[b,c]	0.15	1.22	1.20	1.5	6.9	6.7
5a[d]		0.34	0.29	3.2	3.9	3.9
5b[e]		0.34	0.24	6.0	3.7	3.7

[a] All compounds were purified by distillation at 60–80° (0.01–0.1 mm). [b] Data obtained at ambient temperature for *ca.* 30 vol % solutions in toluene-d_8 with tetramethylsilane as internal reference. Cited barriers (Table I) refer to neat samples, in which $\Delta\nu_{ab}$ = 3–4 Hz. [c] Sample decomposition accompanying the coalescence phenomenon was too slow to interfere significantly with the line-shape analysis. [d] Data obtained at −6° for a *ca.* 10 vol % solution in toluene-d_8 with *p*-dioxane as internal reference. [e] Data obtained at −81° for a *ca.* 15 vol % solution in CF_2Cl_2 with dimethyl ether as internal reference; $^3J_{PH(a)}$ = 6.3 Hz, $^3J_{PH(b)}$ = 4.3 Hz.

and **5b** provide satisfactory evidence for the assigned structures. The relevant data are included in Table II. Inversion barriers (Table I) were determined by total line-shape analysis of the temperature-dependent isopropyl methyl pmr resonances in **2a–4a** and dimethylsilyl methyl pmr resonances in **5a** and **5b**.

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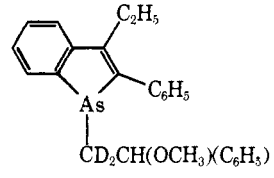
Pyramidal Inversion in Arsindoles. Evidence for Cyclic (4p–2p)π Conjugation[1]

Sir:

Prior work has shown that the barriers to pyramidal inversion in phosphole systems are significantly lowered through cyclic (3p–2p)π delocalization.[2] We now report our finding that the barrier to pyramidal inversion in arsindole **1**, $\Delta G^{\ddagger}_{151}$ = 35.2 kcal/mol, is appreciably



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lower than the barrier in a comparable acyclic arsine, ethylmethylphenylarsine ($\Delta G^{\ddagger}_{218}$ = 43.1 kcal/mol).[3] This result suggests that the electron pair on arsenic is involved in cyclic (4p–2p)π delocalization. The effect is maximal in the planar transition state, and in this sense the planar arsole system may be regarded as aromatic.[4]

The synthesis of **1** was achieved by the reaction of *d,l*-2-phenyl-2-methoxyethyl-*1*-d_2 bromide[5] with 1-lithio-2-phenyl-3-ethylarsindole[6] to yield a mixture of diastereomers (kugelrohr distilled, bp 160–175° (0.02 mm)) whose pmr spectrum featured absorptions at δ 6.9–7.8 (m, aromatic *H*), 4.16 (broadened s, C*H*(a)), 4.10 (broadened s, C*H*(b)), 2.93 (s, OCH_3(b)), 2.89 (s, OCH_3(a)), 2.62 (broadened q, $^3J_{HH}$ = 7.5 Hz, CH_2CH_3), 1.12 (broadened t, $^3J_{HH}$ = 7.5 Hz, CH_2CH_3). The diastereomers (*ca.* 50:50 mixture) were oxidized (H_2O_2 in acetone) to the respective arsindole 1-oxides. Diastereomeric enrichment by column chromatography (95:5 v/v benzene–ethanol on silica gel) afforded a 72:28 mixture of the oxides.[8] Stereospecific reduction (phenylsilane in benzene) yielded a 72:28 diastereomeric mixture of **1**.[8] Equilibration of this mixture at 151.1 ± 0.1° in a 20 vol% toluene-d_8 solution[9] yielded first-order rate constants[10] (k_1 = 6.1 × 10^{-6} sec^{-1}, k_{-1} = 5.9 × 10^{-6} sec^{-1}), whence an average $\Delta G^{\ddagger}$ was obtained by substitution into the Eyring equation.

An estimate for the barrier lowering effect in phosphindoles due to increased cyclic (3p–2p)π delocalization in the planar transition state relative to the pyramidal ground state has been placed at 11 kcal/mol.[2] Comparison of the barrier of **1** with that of ethylmethylphenylarsine[11] sets a lower limit[12] for the barrier lowering effect due to cyclic (4p–2p)π delocalization at 8 kcal/mol.

Substitution of silicon on phosphorus[13] and arsenic[14] markedly lowers barriers to pyramidal inversion at these centers. The silylarsindole **2** and its phosphorus analog **3** (Table I) provide the first examples of systems in which this effect and the effect due to cyclic (p–p)π delocalization are simultaneously operative.

The silylarsindole (**2**) (bp 115–120° (0.04 mm)) was obtained by reaction of 1-lithio-2-phenyl-3-ethylarsindole[6] with dimethylchlorosilane. The pmr spectrum featured absorptions at δ 6.7–7.9 (m, aromatic H), 4.18 (septet, $^3J_{HH}$ = 3.8 Hz, Si*H*), 2.75 (broadened q, $^3J_{HH}$ = 7.0 Hz, CH_2CH_3), 1.20 (t, $^3J_{HH}$ = 7.0 Hz, CH_2CH_3), −0.11 (d, $^3J_{HH}$ = 3.8 Hz, $SiCH_3$(a)), −0.18 (d, $^3J_{HH}$ = 3.8 Hz, $SiCH_3$(b)). Silylphosphindole (**3**) (bp 110–115° (0.05 mm)) was synthesized in a manner strictly analogous to that of **2**, and featured pmr absorptions at δ 7.05–7.75 (m, aromatic *H*), 3.95 (d septet, $^2J_{PH}$ = 25.0 Hz, $^3J_{HH}$ = 3.8 Hz, Si*H*), 2.84 (broadened q,

(1) This work was supported by the National Science Foundation (GP-30257).

(2) W. Egan, R. Tang, G. Zon, and K. Mislow, *J. Amer. Chem. Soc.*, 93, 6205 (1971).

(3) Based on $\Delta G^{\ddagger}$ of racemization (42.4 kcal/mol) reported by G. H. Senkler, Jr., and K. Mislow, *ibid.*, **94**, 291 (1972).

(4) (a) D. A. Brown (*J. Chem. Soc.*, 929 (1962)) has previously suggested, on the basis of HMO calculations, that arsole in the planar conformation gains considerable conjugation energy through involvement of the 4p orbital of arsenic. (b) Cyclic (4p–2p)π conjugation has also been invoked for arsabenzene (arsenin) by A. J. Ashe, III, *J. Amer. Chem. Soc.*, **93**, 3293 (1971).

(5) R. A. Lewis and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 7009 (1969).

(6) Synthesized by lithium cleavage of 1,2-diphenyl-3-ethylarsindole, which in turn was prepared by an extension of the cyclization reaction reported by Rausch and Klemann.[7]

(7) M. D. Rausch and L. P. Klemann, *J. Amer. Chem. Soc.*, 89, 5732 (1967).

(8) The diastereomeric ratios were determined from the methoxy proton nmr signals. For the oxides of **1** these signals appeared at δ 3.25 and 2.70.

(9) The sample was degassed and sealed in an nmr tube, placed in a constant temperature bath, and removed at periodic intervals. No decomposition was observed.

(10) Obtained from a least-squares treatment (correlation coefficient = 0.998) of ln $((R - K)/(1 + R))$ *vs.* *t* using 11 data points collected over *ca.* 2 half-lives. *R* is the ratio of the diastereomers at time *t*, and *K* is the equilibrium constant (*K* = 1.03).

(11) $\Delta G^{\ddagger}$ values are assumed to be temperature independent throughout since $\Delta S^{\ddagger}$ is typically near zero for simple inversion processes.

(12) By analogy with similar phosphorus compounds,[2] incorporation of arsenic into a five-membered ring may be assumed to raise the inversion barrier by 4–6 kcal/mol due to increased angle strain in the planar transition state.

(13) R. D. Baechler and K. Mislow, *J. Amer. Chem. Soc.*, **92**, 4758 (1970); R. D. Baechler and K. Mislow, *ibid.*, **93**, 773 (1971).

(14) R. D. Baechler, J. P. Casey, R. J. Cook, G. H. Senkler, Jr., and K. Mislow, *ibid.*, **94**, 2859 (1972).