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ISOMERIC DIADAMANTYLPHOSPHINIC ACID CHLORIDES

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Abstract - The syntheses of isomeric diadamantylphosphinic acid chlorides are reported. By high-field two-dimensional NMR spectroscopy all proton and carbon-13 signals were identified and assigned unequivocally. Diastereotopism effects and the conformational behaviour of these compounds are discussed.

Adamantane derivatives have been used by us for a series of spectroscopic investigations[1] since they are excellent model compounds due to their unique skeletal geometry and rigidity. Although the literature describes many adamantanes bearing carbon-, nitrogen-, oxygen- and halogen-substituents[1,2], little is known about phosphorylated derivatives[3,4] which may be pharmacologically active. Recently, we started a synthetic[5] and spectroscopic[6] investigation of such compounds; our results on diadamantyl phosphinic acid chlorides are reported here.

RESULTS AND DISCUSSION

Syntheses

We found that the most suitable method for the synthesis of phosphorylated adamantanes is the Friedel-Crafts alkylation of phosphorus trichloride which was reported first by Stetter and Last[3]. Using 1-bromoadamantane only monoalkylation occurred giving 1-adamantyl phosphonic acid derivatives[3,5,6]; with 2-bromoadamantane (1) the reaction afforded surprising products. In no instance 2-adamantylphosphonic halides could be isolated. The results are gathered in the reaction scheme and can be rationalized as follows:

Reaction Scheme:

$$\underset{\mathbf{1}}{\text{2-AdBr}} \xrightarrow[2)\ H_2O]{1)\ PBr_3/AlBr_3} \underset{\mathbf{2}}{\text{1-AdP(O)Br}_2}$$

$$\mathbf{1} \xrightarrow[2)\ H_2O]{1)\ PCl_3/AlBr_3} \underset{\mathbf{3}}{\text{(2-Ad)}_2\text{P(O)Cl}} + \underset{\mathbf{4}}{\text{(2-Ad)}_2\text{P(O)Br}} + \underset{\mathbf{5}}{\text{(1-Ad)(2-Ad)P(O)Cl}}$$

Ad ≡ Adamantyl

Two different types of reactions can take place:

(**a**) Phosphorylation of the carbonium ion produced intermediately:

$$\mathbf{1} \xrightarrow{PX_3/AlBr_3} [\text{2-Ad}^+] \longrightarrow \text{2-AdPX}_3^+\ AlBr_4^-\ (\mathbf{6})$$

(**b**) Rearrangement of the secondary to the tertiary carbonium ion:

$$[\text{2-Ad}^+ \longrightarrow \text{1-Ad}^+]$$

This reaction has been investigated extensively by other authors[7] and probably proceeds intermolecularly and/or via a complex skeletal isomerization[7].

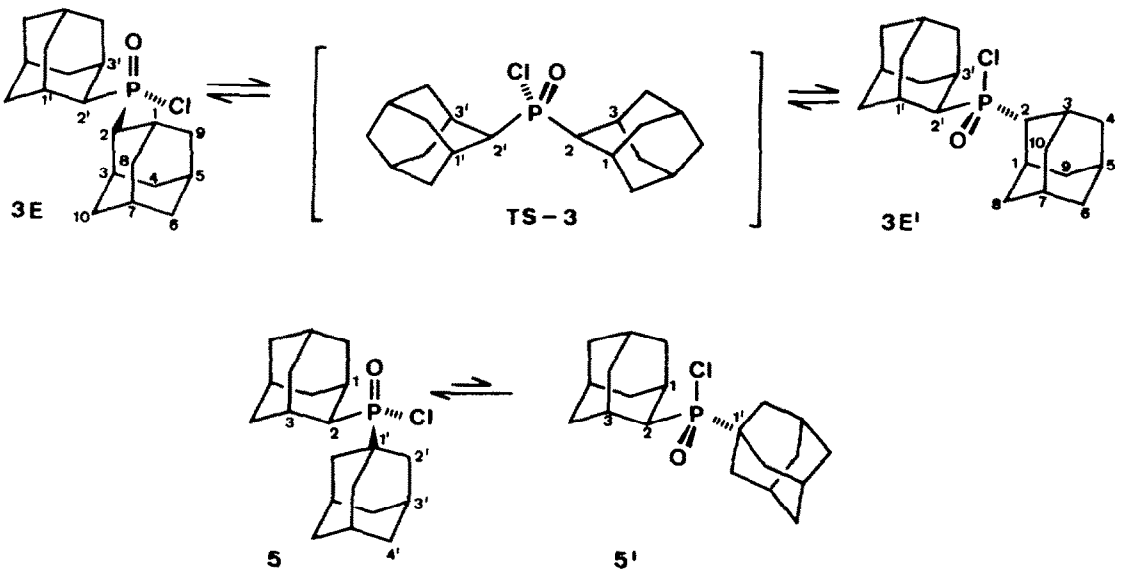
The products of the phosphorylation of **1** strongly depend on the relative rates of these two competing reaction steps (**a**) and (**b**):
If (**b**) is faster than (**a**) [**1** + $PBr_3/AlBr_3$] the phosphonium salt 1-$AdPBr_3^+$ $AlBr_4^-$ (**7**) is formed which cannot undergo further alkylation to form e.g. di-1-adamantylphosphinic halides[3,5], probably due to steric hindrance. Thus, **2** is obtained.
If (**a**) is faster than (**b**) [**1** + $PCl_3/AlBr_3$] the primary salt **6** is produced which, however, is not so hindered as **7** so that it is capable of undergoing a second alkylation. This can occur either with another 2-Ad^+ to give **3** and - with additional halogen exchange - **4** (**3** and **4** could not be separated) or with another 1-Ad^+ affording **5**.

NMR Spectra and Conformational Analysis

The conformational behaviour of **3** is characterized by the rotation around the two C-P bonds. If it is assumed that the molecule prefers staggered conformations three possibilities for each C-P bond are conceivable, i.e. one has to take into account 3 × 3 = 9 conformations. Among these, however, only two, **3E** and **3E'** (Fig. 1), exist in which strong repulsive interactions between the adamantane moieties are absent. Both are enantiomers which easily interconvert via a symmetric transition state **TS-3** so that their populations are exactly equal. In **5** the two adamantane residues are different. The rotation mode of the C^2-P bond is similar to that in **3** whereas the $C^{1'}$-P bond lies in the local C_3-axis of this adamantyl group. Thus, all conformations produced by a rotation around the $C^{1'}$-P bond are identical so that one has to consider only three different rotamers. Again one of them can be ruled out because it would require a penetration of the two adamantane moieties; the remaining conformations **5** and **5'** are depicted in Fig. 1. As can easily be seen, however,

5 and 5' are not enantiomers so that they cannot be of equal energy (see below). Of course, 5 is chiral and we obtained a racemate by the synthesis, but there is no way for the interconversion of the 5-enantiomers without breaking σ bonds.

Fig. 1: Conceivable Conformations of 3 and 5

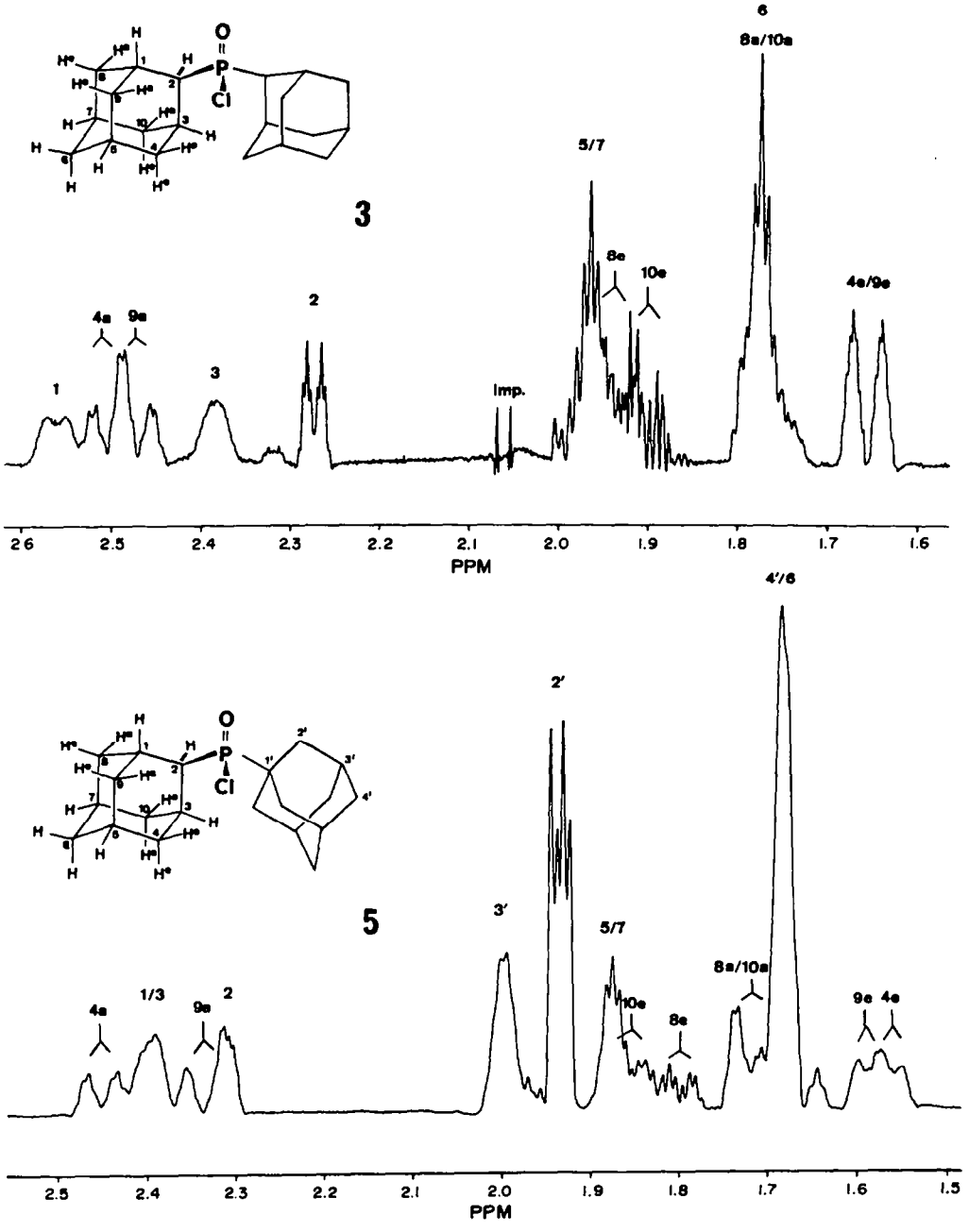


In 3 the phosphorus atom represents a centre of prochirality. Thus, the atom pairs C^1/C^3, C^4/C^9 and C^8/C^{10} as well as corresponding hydrogen pairs are diastereotopic and thus anisochronic. These chemical shift differences can be of remarkable size as shown in the 400 MHz ^1H NMR spectrum of 3 (Fig. 2) and Table 1. Corresponding atoms in the two adamantyl groups of 3 (e.g. C^1 and $C^{1'}$) are enantiotopic and therefore principally isochronous.

Since the ^1H-^1H, ^1H-^{13}C and ^{13}C-^{13}C connectivities can be extracted from two-dimensional (2D) NMR spectra (see next section), only the assignment of one pair of diastereotopic nuclei has to be made by an independent method. For this one can make use of an observation reported several times in the literature: If a C-H bond is parallel to a P=O group the hydrogen is significantly deshielded, i.e. its ^1H signal is shifted downfield[8]. That is the case only for C^1-H^1 in 3E (and $C^{1'}$-$H^{1'}$ in 3E') as shown in Fig. 3. Therefore, we assume that the signal of H^1 in 3 is at lower field (δ=2.56) than that of H^3 (δ=2.39). It is interesting to note that the sequence of the C^1 and C^3 chemical shifts is reversed (C-3: δ=29.7; C-1: δ=29.1); and also the corresponding $^3J(^1H,^{31}P)$ and $^2J(^{13}C,^{31}P)$ values vary significantly pairwise (Table 1).

The sequence of the ^{13}C chemical shifts and the diverging $^2J(^{13}C,^{31}P)$ values were used for the assignment of the diastereotopic atom pairs in 5. Here, however, H^1 and H^3 are practically isochronous. This may be explained by a prevalence of rotamer 5 (Fig. 1) so that the time-averaged orientation of the C^1-H^1 and C^3-H^3 bonds with respect to the P=O group is similar. Such a preponderance is reasonable since the oxygen atom is much smaller than the chlorine and the P=O bond much shorter than the P-Cl bond. Thus, the steric perturbance in 5 is expected to be smaller than in 5'.

Fig. 2: 400 MHz ^{1}H NMR Spectra of the Diadamantylphosphinic Acid Chlorides 3 and 5[a]



[a] The indices a and e indicate axial and equatorial positions of the hydrogen atoms with respect to the cyclohexane subunit bearing the phosphorus atom.

Table 1: NMR Data of the Diadamantylphosphinic Acid Halides 2-4[a]

	3				4		5			
	^1H		^{13}C		^{13}C[b]		^1H		^{13}C	
C/H	δ	J(HP)	δ	J(CP)	δ	J(CP)	δ	J(HP)	δ	J(CP)
1	2.56	7.9	29.1	5.4	30.3	5.1	2.39	-[c]	29.5	5.6
2	2.28	6.6	51.1	65.8	53.6	57.5	2.31	-[c]	45.6	60.3
3	2.39	~5	29.7	1.9	30.5	1.9	2.39		30.6	
4a	2.51		32.8				2.45		32.7[d]	
4e	1.66						1.56			
5	1.97		27.0				1.87		26.7	
6	1.78[e]		37.1				1.68[e]		36.8	
7	1.97		27.6	1.9	27.3		1.87		27.3	1-3[f]
8a	1.78		39.6	14.3			1.72		39.0	15.9
8e	1.94						1.80			
9a	2.47		32.6				2.34		32.7[d]	
9e	1.66						1.59			
10a	1.78		39.4	15.9			1.72		39.2	13.6
10e	1.91						1.85			
1'	-		-		-		-		42.4	68.6
2'	-		-		-		1.93/ 1.92	5.5/ 5.5	35.2	1.9
3'	-		-		-		2.00		27.2	11.0
4'	-		-		-		1.68/ 1.68		36.0	

[a] Chemical shifts (δ) relative to internal TMS; coupling constants (in Hz, accuracy ± 0.3 Hz) are reported only if clearly detectable, i.e. if $J(^1H, ^{31}P) > 3$ Hz and $J(^{13}C, ^{31}P) > 1$ Hz; solvent: $CDCl_3$.

[b] Reported only if different from the corresponding signals of 3.

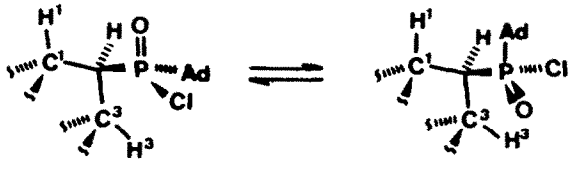
[c] Could not be identified due to signal overlap.

[d] The signals of C^4 and C^9 are anisochronous but the difference of the chemical shifts is < 0.05 ppm; the low-field signal corresponds to C^9.

[e] The two H^6 atoms are diastereotopic but isochronous.

[f] Due to signal overlap the coupling constant can only be estimated from the C-H correlated 2D-NMR spectrum.

Fig. 3: Orientation of H^1, H^3, C^1 and C^3 with Respect to the Oxygen and Chlorine Atoms in the Two Rotamers 3E and 3E'



3E 3E'

^{1}H and ^{13}C Signal Assignment

The assignment of the ^{1}H and ^{13}C NMR signals is based on the extensive use of high-field (9.2 Tesla) two-dimensional correlated NMR techniques[9]. The correlation- or cross-peaks in these spectra indicate scalar couplings between NMR-active nuclei in the molecule[9]. In the homonuclear case both dimensions represent ^{1}H chemical shifts (COSY45 experiment)[9] whereas the heteronuclear experiment (^{13}C-^{1}H correlation) affords spectra with ^{1}H chemical shifts in one dimension and ^{13}C chemical shifts in the other[9]. In the COSY45 experiment even small ^{1}H-^{1}H couplings (e.g. $^{4}J(^{1}H,^{1}H)$ in W orientation) can be detected; the signals in the normal ^{13}C-^{1}H correlated 2D NMR spectra indicate only one-bond ^{13}C-^{1}H couplings between directly bonded carbon and hydrogen atoms. By the combination of both techniques most of the ^{1}H and ^{13}C signals in the spectra of 3 and 5 could be identified unequivocally.

So for example the H^{4e}/H^{9e} signals of 3 were differentiated from those of the respective geminal H^{4a}/H^{9a}, because the 4e/9e-hydrogen atoms are in W arrangement relative to H^{2} (Fig. 2) and therefore showed an intense cross-peak whereas there were no such signals for H^{4a}/H^{9a}. Moreover, it was easy to distinguish the H^{4a} from the H^{9a} signal since each gave only one cross-peak with one vicinal bridgehead-hydrogen: H^{1} ~ H^{9a} and H^{3} ~ H^{4a}. Analogously, the H^{8e} and H^{10e} signals had cross-peaks identifying couplings with the same H^{1} and H^{3}. Thus, only the differentiation of H^{8a}/H^{10a} versus H^{8e}/H^{10e} had to be made. Since there were clear cross-peaks for the high-field H^{8}/H^{10} signal group ($\delta = 1.78$) with those of H^{4a}/H^{9a} but not for the low-field group ($\delta = 1.94$ and 1.91) we attributed the signals at $\delta = 1.78$ to H^{8a}/H^{10a} since these and H^{4a}/H^{9a} are in W arrangements pairwise (Fig. 2).

The only NMR signals of 3 which could not be assigned by the methods described above are those of C^{5} and C^{7} because the H^{5} and H^{7} signals are isochronous. In this case we took into consideration that only one of the carbon signals ($\delta = 27.6$) is split by a 1.9 Hz ^{13}C-^{31}P coupling. This is analogous to the corresponding signals of 5 where we proved that the split signal corresponds to C-7 (see below).

For the unequivocal signal assignment of 5 further 2D NMR experiments in addition to the COSY45 and normal ^{13}C-^{1}H correlated spectra were carried out. First, again the assessment for one signal pair of diastereotopic nuclei had to be made. In analogy to 3 this was done with C^{1} and C^{3} based on their chemical shift sequence and the fact that one of them (C^{1}) shows a 5-6 Hz ^{13}C-^{31}P coupling splitting. Since H^{1} and H^{3} are isochronous the connectivities of the other ^{1}H signals could not be determined. Therefore, we recorded a two-dimensional double-quantum ^{13}C NMR spectrum (2D-INADEQUATE)[9]. By this technique connectivities between directly bonded ^{13}C nuclei can be obtained so that it was easy to identify C^{4} (connected to C^{3}) and C^{9} (connected to C^{1}) and analogously C^{8} versus C^{10} and C^{5} versus C^{7}. After this, the unequivocal assignment of all hydrogen atoms was routine. These arguments were confirmed by a ^{13}C-^{1}H correlated 2D NMR spectrum with the multipulse parameters optimized to smaller ^{13}C-^{1}H coupling constants. In this spectrum there are peaks indicating not only directly attached hydrogens but also those two or even three bonds apart [$^{2}J(^{13}C,^{1}H$; $^{3}J(^{13}C,^{1}H)$ if the torsional angle is ca 180°]. Thus, the results from all these experiments are redundant and allow a safe identification of all signals.

As mentioned above the only assumption based on empirical grounds is the assignment of the diastereotopic H^1 and H^3 in **3**. Finally, it should be noted that only few signals of the bromide **4** could be identified safely (Table 1); the others are apparently overlapped by corresponding signals of **3**.

EXPERIMENTAL

The NMR spectra were recorded in $CDCl_3$ solutions with TMS as internal standard using Bruker WP-80 (80 MHz ^1H), WM-250 (250 MHz ^1H, 62.9 MHz ^{13}C) and AM-400 (400 MHz ^1H, 100.6 MHz ^{13}C) spectrometers. For the multipulse experiments Bruker software - occasionally modified - was used. The IR spectra were measured on a Bruker IFS-45 and the mass spectra on Varian CH-5 and CH-7 spectrometers.
The synthesis of 1-adamantylphosphinic bromide (**2**) is described elsewhere[5].

Reaction of 1 with $PCl_3/AlBr_3$

3.6 g **1** (16.8 mmol), 6.6 g anhydrous $AlBr_3$ (25 mmol) and 35 ml PCl_3 were refluxed for five hours under vigorous stirring. After cooling the solid material was washed with 15 ml benzene, suspended in 350 ml CCl_4 and hydrolyzed under cooling. The organic layer was separated, washed with water, dried over anhydrous $CaCl_2$ and evaporated. The residue was subjected to silicagel column chromatography using petrol ether containing 1% acetone as eluent.
The first fraction (0.42 g) was a solid material consisting of **3** with ca 10% **4** which could not be separated.
MS (m/e): 396/398 (6/6)(M^+ of **4**), 352/354 (89/32)(M^+ of **3**), 135 (100)(Ad^+), 93 (22), 79 (26), 67 (24), 55(9), 41(13).
The second fraction (0.98 g) was pure **5** as colourless crystals, m.p. 185-187°C. IR (KBr): 2910, 2855, 1214 (P=O), 536 (P-Cl) cm^{-1}. MS (m/e): 352/354 (11/3)(M^+), 135 (100)(Ad^+), 93 (8), 79 (10), 67 (5), 55 (3), 41 (4).

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REFERENCES

1. H. Duddeck and M.R. Islam, Chem. Ber. **117**, 554 (1984) and references therein.
2. See e.g.: P.C. Fort, Jr.. Adamantane, Marcel Dekker, New York (1976).
3. H. Stetter and W.-D. Last, Chem. Ber. **102**. 3364 (1969).
4. R.I. Yurchenko, T.I. Klepa, M.I. Mishak and V.P. Tikhonov, Zh. Obshch. Khim. **50**, 2443 (1980), Chem. Abstr. **94**:139303k (1981); R.I. Yurchenko, T.I. Klepa, O.B. Bobrova, A.G. Yurchenko and A.M. Pinchuk, Zh. Obshch. Khim. **51**, 786 (1981), Chem. Abstr. **95**:133031u (1981); V.P. Kukhar, V.F. Gamaleya, A.E. Sorochinskii, A.M. Alexandrov and A.F. Pavlenko, Zh. Obshch. Khim. **50**, 2378 (1980), Chem. Abstr. **94**:175201j (1981); E.S. Shepeleva, P.I. Sanin, D.M. Oleinik and E.I. Bagrii, Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki, **49**, 235 (1972), Chem. Abstr. **77**: 74900e (1972); E.S. Shepeleva, P.I. Sanin, D.M. Oleinik, E.I. Bagrii and A.A. Polyakova, Dokl. Akad. Nauk SSSR **203**, 608 (1972), Chem. Abstr. **77**:101785e (1972); D.G. Gillespie and B.J. Walker, Tetrahedron Lett. 1673 (1977); R.A. Rossi, S.M. Palacios and A.N. Santiago, J. Org. Chem. **47**, 4654 (1982); L. Horner and W.D. Hohndorf, Phosphorus **6**, 71 (1976); H. Boehringer and H. Vogt, Arch. Pharm. (Weinheim) **310**, 894 (1977); E.S. Gubritskaya, Ya. Yu. Polis and N.S. Tishchishina, Zh. Obshch. Khim. **44**, 2105 (1974), Chem. Abstr. **81**:151629 (1974); L.A. Cates, M.B. Cramer and L. Williams, J. Med. Chem. **21**, 143 (1977); A.P. Khardin, O.I. Tuzhikov, and V.Yu. Lomakin, Zh. Obshch. Khim. **53**, 1429 (1983), Chem. Abstr. **99**:175898 v (1983).
5. H. Duddeck, M.H.A. Elgamal and A.G. Hanna, in preparation.
6. H. Duddeck and A.G. Hanna, Magn. Reson. Chem. **23**, 41 (1985); H. Duddeck and A.G. Hanna, Magn. Reson. Chem., in press.
7. Z. Majerski, P.v.R. Schleyer and A.P. Wolf, J. Am. Chem. Soc. **92**, 5731 (1970); P. Vogel, M. Saunders, W. Thielecke and P.v.R. Schleyer, Tetrahedron Lett. 1429 (1974) and references therein.
8. D.B. Cooper, J.M. Harrison and T.S. Inch, Tetrahedron Lett. 2697 (1974); S.E. Cremer, F.R. Farr, P.W. Kremer, H.-O. Wang, G.A. Gray and M.G. Newton, J. Chem. Soc., Chem. Commun. 374 (1975); L.D. Quin, The Heterocyclic Chemistry of Phosphorus, Wiley, New York (1981), p. 350-353.
9. A. Bax, Two-Dimensional NMR Spectroscopy in Liquids, Reidel, Dordrecht (1982); R. Benn and H. Günther, Angew. Chem. **95**, 381 (1983), Angew. Chem., Int. Ed. Engl. **22**, 390 (1983); A. Bax, in Topics in Carbon-13 NMR Spectroscopy, ed. G.C. Levy, Wiley, New York (1984), Vol. **4**, p. 199.