Conformational study of six-membered phostones. *cis*- and *trans*[1]-3-(Methoxycarbonyl)-2-methoxy-2-oxo-1,2-oxaphosphorinane[2]

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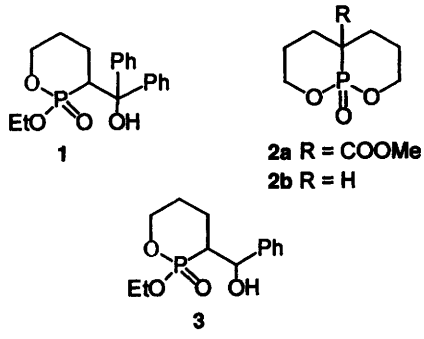
The conformations of *cis*- and *trans*-3-(methoxycarbonyl)-2-methoxy-2-oxo-1,2-oxaphosphorinane have been investigated by variable temperature ^{31}P, ^{1}H and $^{1}H\{^{31}P\}$ NMR spectroscopy and semiempirical calculations. An X-ray diffraction study of the *trans* isomer has also been performed. The ^{31}P NMR spectra of both isomers did not change with temperature over the range of 183–333 K. The temperature dependence of the C(3)–H spectral pattern in the *cis* isomer suggested an important change in the conformer distribution with temperature. For the *trans* isomer, no changes were detected. The crystal structure of *trans*-3-(methoxycarbonyl)-2-methoxy-2-oxo-1,2-oxaphosphorinane was solved by direct methods and refined to $R = 0.046$. The space group is $P2_1/n$, $a = 8.644(1)$, $b = 7.432(1)$, $c = 15.718(2)$ Å, $\beta = 105.38(1)°$. The molecule in the asymmetric unit adopted a chair conformation with equatorial phosphoryl and methoxycarbonyl groups. The conformation in the crystal agreed well with the calculated global energy minimum conformation.

In this paper we describe the synthesis and conformational study of the *cis* and *trans* isomers of 3-(methoxycarbonyl)-2-methoxy-2-oxo-1,2-oxaphosphorinane (**7a** and **7b**, respectively). Variable temperature ^{1}H and ^{31}P NMR analysis and semiempirical calculations on both isomers, as well as an X-ray study of **7b** were used to probe the conformations. The methoxycarbonyl substituent in the 3-position of the ring greatly simplified the ^{1}H NMR spectra of both isomers and made it possible to investigate the conformation of **7** in solution.

The research was prompted by our continuing interest in the synthesis and conformational studies of variably substituted phostone ring systems. Recently, cyclic phosphonates as analogues of naturally occurring carbohydrates with a phosphorus atom replacing the anomeric carbon have received a lot of attention in the literature.[3] Likewise, the extensive reports on the stereochemistry and conformational behaviour of various six-membered, phosphorus heterocycles[4] (both in the solid state and in solution) provided a basis for comparison relative to the phostones described here.

Most structural studies of 1,2-oxaphosphorinane derivatives reveal a chair conformation.[5] Also, we have recently reported[6] that both the *cis* and *trans* isomer of the 3-(diphenylhydroxymethyl)-2-ethoxy-2-oxo-1,2-oxaphosphorinane (**1**) possess chair conformations in the solid state. In a related study, we found that 6-(methoxycarbonyl)-2,10-dioxa-2-oxo-1-phosphabicyclo[4.4.0]decane (**2a**) has both rings in chair conformations,[7] as did the parent heterocycle 2,10-dioxa-1-oxo-1-phosphabicyclo[4.4.0]decane (**2b**).[8] Moreover, 1,3,2-dioxaphosphorinanes and 1,3,2-oxazaphosphorinanes adopt chair conformations.[9,10] However, there are several examples of related molecules with boat and twist-boat conformation.[10]

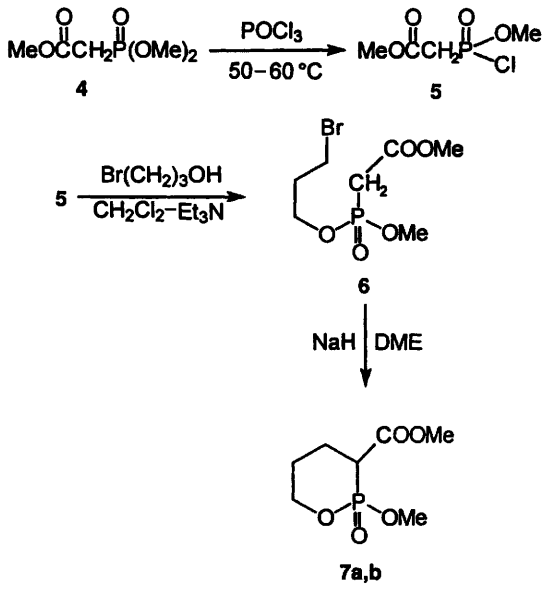
It is known that methyl cyclohexanoate in solution assumes a chair conformation with the substituent in an equatorial position. In contrast, the methoxy group in methoxycyclohexane occupies an axial position. This axial preference of an alkoxy group is enhanced by stereoelectronic effects[11] in heterocyclic systems with a suitably placed oxygen atom in the ring. Similar stereoelectronic effects were identified in 1,3,2-dioxaphosphorinanes[11,14] bearing an alkoxy group on phosphorus. The concept of an anomeric effect was used to explain the axial disposition of both the *tert*-butyl and methoxy groups found by X-ray crystallography in 4-*tert*-butyl-2-methoxy-2-oxo-1,3,2-dioxaphosphorinane.[12] However, X-ray studies revealed both *cis*- and *trans*-**1** possess a chair conformation with the diphenylhydroxymethyl group in an equatorial position. Likewise, both the ethoxy and the phenylhydroxymethyl substituents in the crystal structure of *cis*-3-(phenylhydroxymethyl)-2-ethoxy-2-oxo-1,2-oxaphosphorinane (**3**)[13] are equatorial. Of particular interest to us was the extent to which the expected anomeric effect would influence the conformational equilibrium of the title compound, **7a**, in solution.



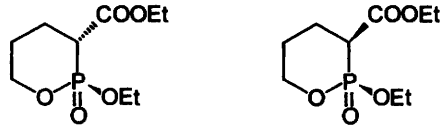
Results and discussion

Synthetic strategy

The synthesis of 3-(methoxycarbonyl)-2-methoxy-2-oxo-1,2-oxaphosphorinane (**7**) is summarized in Scheme 1.[13] The starting dialkylphosphonate **4** was converted into the corresponding monochloride **5** with trichlorooxophosphorus at 50 °C.[14] Subsequently, **5** reacted with 3-bromopropanol in methylene chloride in the presence of triethylamine, to produce the bromoesters **6**. Cyclization of the latter under basic conditions afforded, *via* intramolecular alkylation of the corresponding ylid, the desired heterocycle as a mixture of



Scheme 1



8a: *cis* **8b**: *trans*

isomers **7a** and **7b**, in almost equal amounts. The same reaction sequence was followed for the synthesis of *cis*- and *trans*-3-(ethoxycarbonyl)-2-ethoxy-2-oxo-1,2-oxaphosphorinane(**8a,b**).

X-Ray study

Upon standing, the *trans* isomer **7b** crystallized from the oily mixture of isomers. The X-ray crystal study revealed no unusual features of the molecular structure. Fig. 1 presents an ORTEP diagram of the molecule. As expected for the *trans* isomer (*vide supra*), the molecule adopted a chair conformation, with both methoxycarbonyl and phosphoryl groups in equatorial positions. The structural parameters (bond length and angles) at the phosphorus were very close to those measured in *trans*-**1**.[6]

NMR studies

The ^{1}H NMR spectra of both **7a** and **8a** revealed that substantial changes occurred in solution upon variation of the temperature. A similar temperature variation was also seen in the spectra of *cis* isomers of **1** and **3**. This temperature dependence was not observed for the *trans* isomers **7b** and **8b**. Owing to the absence of complications introduced by the methylene fragments in the ethoxy groups, the spectra of **7** were much more suitable for analysis and therefore selected for further studies. Two sets of ^{1}H NMR data were collected on a sample of **7a**, over the temperature range 213–293 K, with and without simultaneous phosphorus irradiation (the proton numbering is given in Fig. 2). The values of the chemical shifts and the proton–proton coupling constants for all protons were extracted from the ^{31}P-decoupled spectra; these parameters were iteratively refined by computer simulation.[15] In the final steps of the refinement the linewidth was 0.8–1.0 Hz; the lines were assumed to be symmetric and purely Lorentzian. Assignment of the multiplets of the methylene groups was rather straightforward and based on the value of the chemical shifts. It was, however, much more challenging to assign the specific diastereotopic proton of a methylene unit to a given multiplet. The assignments presented here led to the best root mean square (rms) values for both

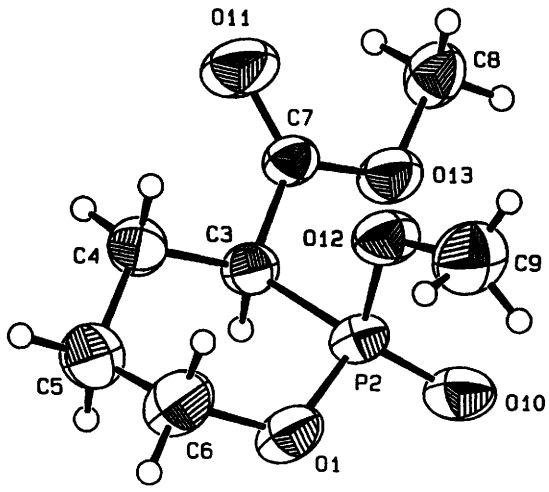
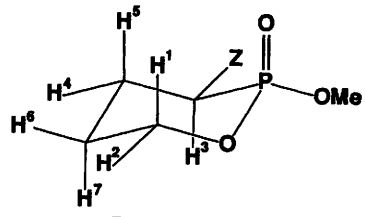


Fig. 1 ORTEP diagram of **7b**



7a Z = COOMe

Fig. 2 Proton numbering used in the NMR studies

Table 1 ^{1}H NMR chemical shift in **7a** at various temperatures refined by MLDC 8 spectra simulations

	δ						
T/°C	H1	H2	H3	H4	H5	H6	H7
−60	4.291	4.226	2.985	2.182	2.112	1.871	1.724
−40	4.301	4.228	2.983	2.192	2.134	1.886	1.728
−20	4.312	4.232	2.983	2.201	2.155	1.904	1.731
1	4.326	4.237	2.984	2.212	2.178	1.931	1.738
19	4.337	4.240	2.984	2.220	2.199	1.935	1.744

Table 2 Proton–phosphorus coupling constants in **7a** at various temperatures

	J_{PH}/Hz				
T/°C	H1	H2	H3	H4	H5
−60	6.42	18.92	−23.45	27.02	10.8
−40	6.27	18.49	−23.33	26.60	11.1
−20	6.53	17.83	−23.28	26.36	11.58
1	6.76	17.68	−23.23	26.26	11.67
19	6.90	17.29	−23.18	26.29	12.10

chemical shifts and coupling constants; these also minimized the correlation between spectral parameters. The final values of chemical shifts and coupling constants are collected in Tables 1–3 together with their estimated errors. Table 2 gives the values of P–H couplings, which were taken directly from the spectra and then verified/refined by MLDC8[15] simulations (X-approximation). The same procedure was then repeated for **7b**.

A two-step analysis, based on the recently published[16] comprehensive approach to the conformational analysis of six-membered rings in solution, was then applied to the data. In the first step, only the hydrocarbon portion of the phostone ring was considered. This part is conformationally characterized by a set of torsional angles φ_3, φ_4 and φ_5(see Fig. 3 for definition).

The ring was assumed to be engaged in a fast, two-state

Table 3 H–H vicinal coupling constants at various temperatures, refined by simulation of spectra with MLDC8 (**7a**)

	J_{HH}/Hz									
T/°C	H6–H1	H7–H1	H6–H2	H7–H2	H3–H4	H3–H5	H4–H6	H4–H7	H5–H6	H5–H7
−60	2.54	10.88	3.71	4.11	4.60	11.20	3.65	3.58	3.58	11.79
−40	2.66	10.71	3.95	4.00	4.80	11.01	5.65	3.37	3.34	11.73
−20	2.62	10.66	4.13	4.00	4.94	10.72	4.79	3.74	3.49	11.47
1	2.79	10.48	4.19	4.08	5.03	10.55	5.70	3.63	3.49	11.47
19	2.80	10.34	4.36	4.13	5.25	10.29	4.16	4.05	4.35	11.04

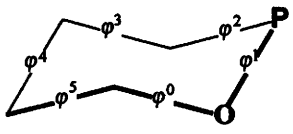


Fig. 3 Labelling of the endocyclic torsional angles

conformational equilibrium [equilibrium (1)] where primed

$$(\varphi_3, \varphi_4, \varphi_5) \rightleftharpoons (\varphi_3', \varphi_4', \varphi_5') \quad (1)$$

and non-primed φ values belong to a conformer participating in the equilibrium. In this model the experimental proton–proton coupling constants J_{exp} represent the averaged values which are related to the coupling constants of the individual conformers and their relative population in equilibrium [eqn. (2)] where J

$$J_{exp} = \alpha J + (1 - \alpha)J' \quad (2)$$

and J' represent the individual coupling constants for a single conformer, and α is the mole fraction of the first conformer. The population averaging used in this model instead of time averaging, is justified by the assumption of fast interconversion of the conformers.

It was also assumed that the individual conformers do not change over the temperature range used in this study and that only the ratio of conformers varied. This assumption leads to a function implemented to calculate the coupling constants [eqn. (3)] where α_i represents a mole fraction of the first conformer at

$$J_{HH} = f(\varphi_3, \varphi_4, \varphi_5, \alpha_i, \varphi_3', \varphi_4', \varphi_5'), i = 1\text{–}5 \quad (3)$$

the ith temperature, and φ_3, φ_4, φ_5, φ_3', φ_4', φ_5' describe the conformers participating in the equilibrium.

All the parameters in eqn. (3) had to be determined from the experimental coupling values (J_{exp}). This task was accomplished by an iterative minimization procedure, with a minimized function defined in eqn. (4).

$$F = \Sigma(J_{exp} - J_{HH})^2 \quad (4)$$

In eqn. (4), J_{HH} represents a coupling constant calculated from eqn. (3), with the summation being extended over the entire set of coupling constants. The goodness of fit was judged from the residual F values. The optimization was stopped when the F value, after two consecutive cycles of minimization did not change by more than a preset value (usually 10^{-5} Hz). In each step of the minimization, the values of J_{HH} were computed using the generalized Karplus equation.[17] Parameters $P1$–$P6$[18] of the Karplus equation were taken directly from ref. 17. Values of the relative electronegativities[18,19] for the phosphorus and oxygen were used to make the necessary modifications.

For the purpose of the calculations, the CH_2 groups were considered rigid and assumed to possess C_{2v} symmetry with a projected H–C–H angle of 118°.[20] The CH fragment was modelled as a methylene group with one proton substituted. These assumptions lead to the following relations between the endocyclic torsional angle φ and the torsional angles ϑ between the vicinal protons present at the torsion centre [eqns. (5)–(7)] (see Fig. 4 for the proton labelling).

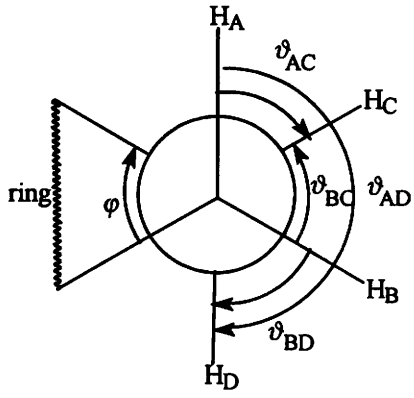


Fig. 4 Relation between endocyclic and interproton torsional angles illustrated by the Newman projection of a torsion centre. Arrows indicate the positive sign of the angle.

$$\vartheta_{BC} = \varphi - 118° \quad (5)$$

$$\vartheta_{AC} = \varphi = \vartheta_{BD} \quad (6)$$

$$\vartheta_{AD} = \varphi + 118° \quad (7)$$

In the second step of the analysis, the remaining torsional angles φ_0–φ_2 (and φ_0'–φ_2' for the other conformer present in equilibrium) were calculated. For this purpose, the truncated Fourier formalism (TF)[16] was employed. The torsional angles φ_j, j = 0–5 of a six-membered ring were assumed to fulfil eqn. (8), therefore defining three parameters: two puckering

$$\varphi_j = \Phi_2 \cos(P_2 + 4\pi j/6) + \Phi_3 \cos(\pi j) \quad (8)$$

parameters Φ_2 and Φ_3 and one pseudorotational parameter P_2.[21] To assure the consistency of the conventional signs of the torsional angles with the signs emerging from eqn. (8) and to assure the distinction between enantiomers, Φ_2 in eqn. (8) was set to be greater than or equal to 0. In an iterative procedure, the parameters Φ_2, Φ_3 and P_2 were adjusted to reproduce the three torsional angles which were established in the first stage of the analysis. As a result, the remaining endocyclic torsional angles φ_0, φ_1 and φ_2 were calculated for each conformer participating in the equilibrium. To verify the applicability of the TF concept in the analysis of cyclic phostones, the procedure described above was used to predict the corresponding torsional angles in **1** and **3**, which were known from previous X-ray studies. The calculated angles φ_0, φ_1 and φ_2 did not differ from the experimental more than 2°.

The aforementioned analysis showed that both conformations participating in the equilibrium of the *cis* isomer are most likely chair forms, with the form featuring equatorial P–methoxy and –methoxycarbonyl groups predominating. On the basis of the temperature dependence of the calculated equilibrium constant [eqn. (9)] and the relation $\Delta G° = -RT$

$$K_i = \alpha_i/(1 - \alpha_i), i = 1\text{–}5 \quad (9)$$

ln K, the free energy difference ('A value') between these two chair forms was estimated for the *cis* isomer to be 0.85

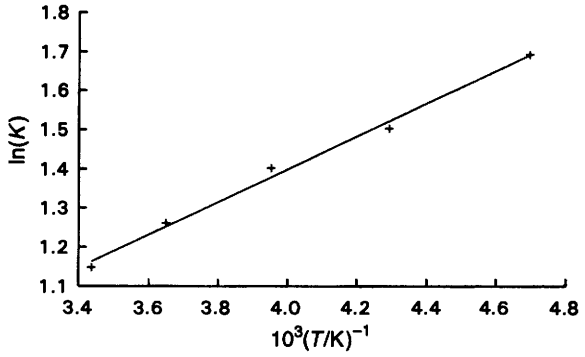


Fig. 5 Plot of ln K_i as a function of $1/T$, *cis* isomer of **7**

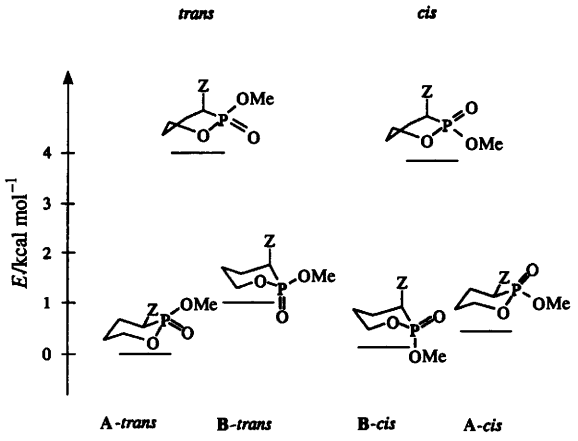


Fig. 6 PM3 calculated energies of *cis* and *trans* isomers of **7**

± 0.12 kcal mol^{-1}. Fig. 5 presents the plot of the logarithm of the equilibrium constant K_i at various temperatures *versus* $1/T$. The estimated $\Delta G°$ value is smaller than the *A* value published for (methoxycarbonyl)cyclohexane,[22] therefore indicating the axial preference of the alkoxy group bonded to phosphorus (or equatorial preference of the phosphoryl group).

When this model was applied to the study of the *trans* isomer, the calculations resulted in erratic and unrealistic conformations participating in the equilibrium. Therefore, the model was modified and the chair–chair equilibrium was *a priori* assumed. The torsional parameters φ_3', φ_4', φ_5' of the less abundant isomer (which are much less well defined due to the low mole fraction of this conformer in the equilibrium) were not optimized, but restricted to parameters that were devised from the molecular calculations (*vide infra*). The conformation of the more abundant form calculated as a result of the analysis described above corresponded very well to the X-ray structure of the *trans* form.

PM3 calculations

For each of the isomers, the geometry was optimized for the two chair conformers which are related by a ring inversion process. These initial geometry optimizations were done without any restraints. Comparison of the calculated total energies revealed that the most stable of all stereoisomers is the *trans* isomer in the same form that is present in the crystal structure, with equatorially disposed methoxycarbonyl and phosphoryl groups (**A**-*trans* form, see Fig. 6). The 'inverted' chair conformation (**B**-*trans*) was calculated to be 1.00 kcal mol^{-1}† higher in energy. The most stable conformer of the *cis* isomer was found to be a chair conformation, with an axial methoxycarbonyl group and equatorial phosphoryl (**B**-*cis* form, see Fig. 6); the total energy difference of the two chair forms was found to be only 0.22 kcal mol^{-1}. The **A**-*trans* form was calculated to be only 0.12 kcal mol^{-1} below the total energy of the **B**-*cis* form. For the *trans* isomer, these findings are generally in agreement with the experimental results, concluding the **A**-*trans* form as the lowest energy conformation. For the *cis* isomer, the calculations favour the structure with axial methoxycarbonyl and equatorial phosphoryl groups; however, the energy difference between this structure and an 'inverted' one was very small. Experimentally, an equilibrium between forms **A**-*cis* and **B**-*cis* is found, with the **A**-*cis* form predominating. The amount of the latter seems to increase at lower temperatures.

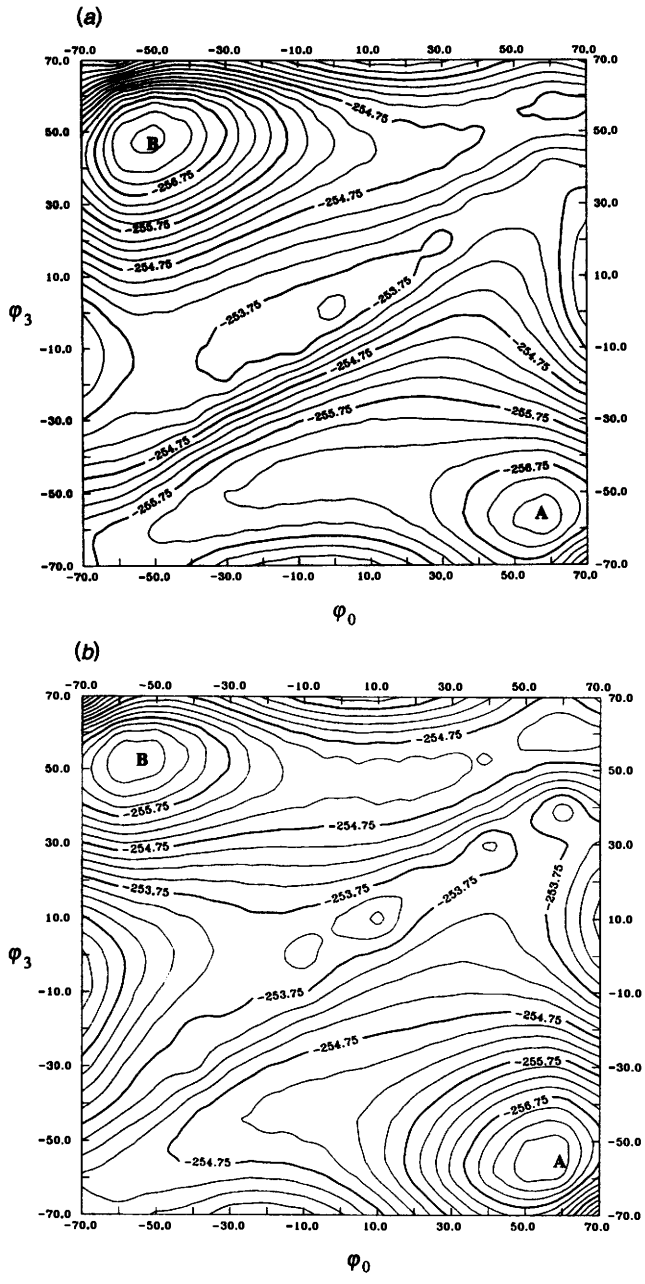


Fig. 7 (*a*) Calculated energy map for **7a**. Positions of the **A**-*cis* and **B**-*cis* forms are marked on the map. (*b*) Calculated energy map for **7b**. Positions of the **A**-*trans* and **B**-*trans* forms are marked on the map.

An attempt was made to evaluate the stability of the flexible non-chair forms of both *cis* and *trans* isomers. For this purpose, a series of calculations was performed in which the torsional angles φ_0 and φ_3 were independently varied over the range of $-70°$ to $+70°$. For every pair of torsional angles, a PM3 optimization of the rest of the structure was made until the energy converged within a 0.01 kcal mol^{-1} range. The angles φ_0 and φ_3 were kept constant by using an 800 kcal mol^{-1} restraint. The results are presented in Fig. 7(*a*,*b*) in the form of energy

† 1 cal = 4.184 J.

maps drawn as a function of the torsional angles φ_0 and φ_3. The conformations of both *cis* and *trans* highest energy transition forms are presented in Fig. 6.

Conclusions

The *trans* isomer of 3-(methoxycarbonyl)-2-methoxy-2-oxo-1,2-oxaphosphorinane is in a chair conformation in the crystal, as confirmed by the X-ray study. There were no unusual structural features in the molecule. In particular, the bond lengths and valence angles around the phosphorus are similar to those found in other phostones. The molecular structure of the *cis* isomer is not available from crystallographic investigations and was evaluated from the ^{1}H NMR measurements. These results indicate a fast equilibrium between two chair forms. The form featuring an equatorial methoxycarbonyl group and an axial phosphoryl predominates at room temperature in CH_2Cl_2 solution. The estimated A value for this isomer was 0.85 ± 12 kcal mol^{-1}, which indicates a significant amount of the 'inverted' chair form present in solution; this value was based on the variable temperature measurements. Similar measurements for the *trans* form did not allow a legitimate evaluation of this parameter. The molecular calculations performed at the PM3 level, despite their qualitative character, are in accordance with the findings for the *trans* isomer. The energy maps obtained from the calculations predict a larger energy difference between the two chair forms in the *trans* isomer than in the *cis* isomer, which is confirmed experimentally. These maps also enable prediction of the low inversion energy barrier between the chair forms. This is partially confirmed by experiment, since no line broadening or splitting was detected in the ^{31}P NMR spectra at 183 K for either isomer. Also, the PM3 calculations indicate the accessibility of energetically close non-chair conformations, which may contribute significantly to the average structure of each isomer in solution at room and higher temperatures.

Experimental

Crystal data

$C_7H_{13}O_5P$, M = 208.15, monoclinic, a = 8.644(1), b = 7.432(1), c = 15.718(2) Å, β = 105.38(1)°, V = 973.7 Å^3 (by least-squares fit from 25 reflections $9 < \theta < 18°$, λ = 0.710 73 Å), space group $P2_1/n$ (No. 14), Z = 4, D_c = 1.42 g cm^{-3}. Colourless plates obtained from diethyl ether solution; crystal dimensions 0.20 × 0.30 × 0.60 mm. μ(Mo-Kα) = 2.6 cm^{-1}.

Data collection and processing

Enraf-Nonius CAD4 diffractometer, graphite crystal monochromator: $\omega/2\theta$ mode with ω scan width = 0.8 + 0.580 tan θ, Mo-Kα radiation; 1149 reflections measured, $\theta \leqslant 25°$, $-8 \leqslant h \leqslant 7$, $-7 \leqslant k \leqslant 0$, $0 \leqslant l \leqslant 15$, 1090 unique reflections, 880 observed [$I > 3\sigma(I)$ criterion]. Three control reflections were checked every 120 min; 1.46% decay of intensity was found over the data collection period; linear decay correction applied. Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC).‡

Structure analysis and refinement

Direct methods, full-matrix least squares refinement for all non-hydrogen atoms, hydrogen atoms located from the difference map. The weighting scheme: unit weight. Final R = 0.046; R_w = 0.051. The data were collected on the Enraf-Nonius CAD4 Diffractometer and transferred to an 80486/66 Compaq PC. The structure was solved using Personal-SDP software.[23] Scattering factors were taken from International Tables for X-ray Crystallography.[24]

‡ For details of the CCDC deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/20.

PM3 Calculations

The calculations were performed using the PM3[25] method implemented by a HyperChem 4.0 package.[26]

Syntheses

Unless noted, all reactions were carried out in flame-dried glassware under a nitrogen atmosphere. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a GE OMEGA 300 NMR spectrometer. $CDCl_3$ was used as the solvent in all cases unless stated otherwise. Chemical shifts for the ^{1}H and ^{13}C NMR spectra were reported in ppm referenced to TMS and to 85% H_3PO_4 for ^{31}P NMR spectra. Coupling constants, J, are given in Hz. GC–MS data were obtained on a Hewlett-Packard 5890A Gas Chromatograph-5970 Series Mass Selective Detector: capillary column DB-1, 0.25 mm id × 30 m; inj. temp. 260 °C; det. temp. 265 °C; init. temp. 70 °C for 4 min then 10 °C min^{-1}; final temp. 250 °C. All chemicals were purchased from Aldrich Chemical Co. and used without further purification. Elemental analyses were performed by Midwest Microlab of Indianapolis, IN.

Methyl (methoxycarbonylmethyl)phosphonochloridate (5). A mixture of methyl (methoxycarbonylmethyl)methoxyphosphonate (11.6 g, 0.064 mol) and $POCl_3$ (12.7 g, 0.083 mol) was heated in an oil bath maintained at 50–55 °C for 18 h. The reaction progress was monitored by ^{31}P NMR spectroscopy. The product was purified by fractional distillation, bp 89–90 °C/0.7 mmHg. This afforded 4.51 g (38%) of pure **5** as a clear oil. $\delta_H(CDCl_3)$ 3.94 (d, 3 H, J_{PH} 13.4), 3.79 (s, 3 H) and 3.37 (d, 2 H, J_{PH} 21.2). $\delta_P(CDCl_3)$ 30.5.

Methyl (3-bromopropanoxy)(methoxycarbonylmethyl)phosphonate (6). To a solution of 3-bromopropanol (4.20 g, 30.0 mmol) and Et_3N (4.2 ml, 30 mmol) in 50 ml of CH_2Cl_2 cooled to 0 °C in an ice bath, the phosphonochloridate **5** (4.5 g, 24.0 mmol) was added dropwise with a syringe over 20 min. After 5 h at 0 °C the reaction mixture was allowed to warm up to room temperature and 100 ml of 5% aq. HCl was added. The layers were separated and the aqueous layer was extracted with 4 × 20 ml CH_2Cl_2. The combined organic layer was dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by column chromatography (SiO_2, EtOAc, R_f 0.32) gave 4.2 g (61%) of pure **6** as a clear oil. $\delta_C(CDCl_3)$ 165.95 (J_{PC} 6.1), 64.16 (J_{PC} 6.1), 53.19 (J_{PC} 6.1), 52.64 (s), 33.42 (J_{PC} 135.5) and 33.15 (J_{PC} 6.1), 28.76 (s); $\delta_H(CDCl_3)$ 4.20–4.32 (m, 2 H), 3.82 (d, 3 H, J_{PH} 11.2), 3.75 (s, 3 H), 3.51 (t, 2 H, J_{HH} 6.4), 3.01 (d, 2 H, J_{PH} 21.5) and 2.21 (quintet, 2 H, J_{HH} 6.1); $\delta_P(CDCl_3)$, 22.4; *m/z* 259 (80) and 257 (76, M$^+$ − MeO), 209 (886, M$^+$ − Br), 169 (566), 137 (913), 109 (427), 79 (245) and 41 (1000) (calcd. for $C_7H_{14}O_5PBr$: C, 29.09; H, 4.88. Found: C, 29.43; H, 5.08%).

The same procedure was used to prepare ethyl (3-bromopropanoxy)(ethoxycarbonylmethyl)phosphonate (clear oil): $\delta_C(CDCl_3)$ 165.62 (J_{PC} 6.1), 63.89 (J_{PC} 6.1), 62.94 (J_{PC} 6.1), 61.64 (s), 34.11 (J_{PC} 146.5), 33.26 (J_{PC} 6.1), 28.94 (s), 16.31 (J_{PC} 6.1 and 14.07 (s); $\delta_H(CDCl_3)$ 4.05–4.40 (m, 4 H), 4.20 (q, 2 H, J_{HH} 7.1), 3.51 (t, 2 H, J_{HH} 6.4), 2.98 (d, 2 H, J_{PH} 21.2), 2.21 (quintet, 2 H, J_{HH} 6.0), 1.35 (t, 3 H, J_{HH} 7.1), 1.32 (t, 3 H, J_{HH} 7.2); $\delta_P(CDCl_3)$, 21.2; *m/z* 319 (9) and 317 (5) M$^+$, 291 (28), 291 (28), 273 (77), 271 (73), 237 (604, M$^+$ − Br), 197, 163, 123 (767), 81, 41 (1000) (calcd. for $C_9H_{18}O_5PBr$: C, 34.09; H, 5.72. Found: C, 34.33; H, 5.83%).

3-(Methoxycarbonyl)-2-methoxy-2-oxo-1,2-oxaphosphorinane (7). A solution of **6** (3.58 g, 12.4 mmol) in anhydrous 1,2-dimethoxyethane (DME) (100 ml) was cooled to 0 °C in an ice bath, and 0.40 g of NaH (80% dispersion in mineral oil, 13.3 mmol) was added in one portion while the reaction mixture was

vigorously stirred. An immediate reaction was observed as hydrogen was evolved from the mixture. The mixture was stirred at 0 °C for 5 h. The solvent was removed *in vacuo* at room temperature and 50 ml of 5% aq. HCl was added to the residue. The mixture was extracted with 5 × 25 ml CH_2Cl_2.

The combined organic layer was dried with Na_2SO_4 and the solvent was removed by evaporation. The crude product showed an approx. 50:50 mixture of isomers. Flash chromatography on silica gel (EtOAc, R_f 0.29) afforded 2.0 g (78%) of pure **7a,b** as a clear oil (the *trans* isomer **7b** crystallized from the mixture upon standing).

7a (*cis* isomer): Clear oil. $\delta_C(CDCl_3)$ 168.34 (J_{PC} 6.1), 69.45 (J_{PC} 6.1), 53.31 (J_{PC} 6.1), 52.48 (s), 41.71 (J_{PC} 120.9), 25.06 (J_{PC} 4.9) and 24.83 (J_{PC} 6.1); $\delta_H(CDCl_3)$ 4.27–4.40 (m, 1 H), 4.05–4.27 (m, 1 H), 3.80 (d, 3 H, J_{PH} 11.2), 3.72 (s, 3 H), 2.80–3.05 (m, 1 H), 2.10–2.35 (m, 2 H) and 1.55–2.00 (m, 2 H); $\delta_P(CDCl_3)$, 20.1.

7b (*trans* isomer): mp 79–82 °C (CH_2Cl_2–diethyl ether). $\delta_C(CDCl_3)$ 168.73 (J_{PC} 4.9), 70.30 (J_{PC} 7.3), 52.67 (s), 52.62 (J_{PC} 7.3), 42.56 (J_{PC} 123.3), 25.71 (J_{PC} 7.3), 25.42 (J_{PC} 6.1); $\delta_H(CDCl_3)$ 4.22–4.40 (m, 1 H), 4.07–4.22 (m, 1 H), 3.80 (d, 3 H, J_{PH} 10.7), 3.78 (s, 3 H), 3.04 (ddd, 1 H, J_{PH} 23.9, J_{HH} 12.2, J_{HH} 4.9), 2.00–2.40 (m, 2 H) and 1.75–1.90 (m, 2 H); $\delta_P(CDCl_3)$, 16.7 [calcd. for $C_7H_{13}O_5P$: C, 40.39; H, 6.30. Found (mix. isomers): C, 40.13; H, 6.30%].

The same procedure was used to synthesize the 3-(ethoxycarbonyl)-2-ethoxy-2-oxo-1,2-oxaphosphorinane **8a,b**.

8a (*cis* isomer): R_f = 0.36 (EtOAc). $\delta_C(CDCl_3)$ 168.07 (J_{PC} 4.9), 69.37 (J_{PC} 6.1), 63.23 (J_{PC} 6.1), 61.54 (s), 42.45 (J_{PC} 120.9), 25.34 (J_{PC} 6.1), 24.94 (J_{PC} 6.1), 16.42 (J_{PC} 6.1), 14.07 (s); $\delta_H(CDCl_3)$ 4.10–4.45 (m, 6 H), 2.83–3.05 (m, 1 H), 2.15–2.35 (m, 2 H), 1.85–2.00 (m, 1 H), 1.63–1.85 (m, 1 H), 1.36 (t, 3 H, J_{HH} 7.1), 1.28 (t, 3 H, J_{HH} 7.2); $\delta_P(CDCl_3)$ 19.2.

8b (*trans* isomer): R_f 0.28 (EtOAc). $\delta_C(CDCl_3)$ 168.29 (J_{PC} 6.1), 70.11 (J_{PC} 7.3), 62.47 (J_{PC} 7.3), 61.58 (s), 42.94 (J_{PC} 122.1), 25.63 (J_{PC} 7.3), 25.40 (J_{PC} 5.5), 16.39 (J_{PC} 5.5), 14.13 (s); $\delta_H(CDCl_3)$ 4.05–4.50 (m, 6 H), 3.01 (ddd, 1 H, J_{PH} 23.9, J_{HH} 11.9, J_{HH} 5.0), 2.03–2.37 (m, 2 H), 1.65–2.00 (m, 2 H), 1.32 (t, 3 H, J_{HH} 7.1), 1.29 (t, 3 H, J_{HH} 7.2); $\delta_P(CDCl_3)$ 15.7 [calcd. for $C_9H_{17}O_5P$: C, 45.76; H, 7.25. Found (mix. isomers): C, 45.10; H, 7.27%].

Acknowledgements

M. S. H. and M. U. H. are grateful to the KFUPM for providing research facilities and for funding the upgrading of the CAD4-SDP system in the Chemistry Department. M. K. T. is grateful to S. C. Johnson and Son for postdoctoral research support. We thank the Marquette University Commitee on Research for their financial aid.

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Paper 6/00407E
Received 18*th January* 1996
Accepted 21*st May* 1996