

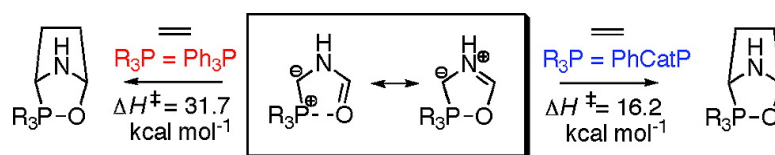
Communication

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 Electronic Characterization of “Montre#alones”**

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## Cyclic 1,3-Dipoles or Acyclic Phosphonium Ylides? Electronic Characterization of “Montréalones”

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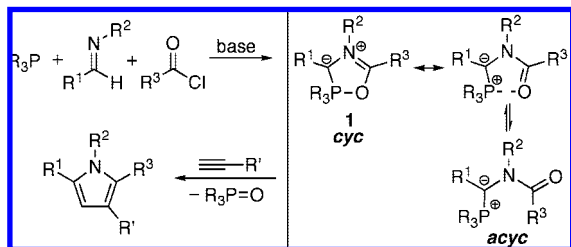
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A recently reported one-pot synthesis of pyrroles from phosphine, imine, and acid chloride precursors (Scheme 1) involves intermediates **1**, which undergo cycloaddition reaction with loss of  $R_3P=O$ .<sup>1</sup>

Intermediates **1** were designed to behave as cyclic 1,3-dipoles, related to Sydnone<sup>2,3</sup> and Münchnone,<sup>4</sup> but can alternatively be formulated as phosphonium ylides. Phosphonium ions are known to cyclize to phosphoranes when  $\gamma$ -alkoxide groups are present,<sup>5</sup> and similar interactions involving  $\gamma$ -keto groups have also been invoked<sup>6</sup> to explain the catalysis of certain aldol reactions by phosphines. Accordingly, **1** may potentially exist in either a cyclic form “*cyc-1*” or an acyclic form “*acyc-1*”. Because the efficiencies of cycloadditions between **1** and  $CH_2=C(Cl)CN$  depended markedly on the electronic and steric environment at phosphorus, their reactivity was postulated to be a function of the extent of *cyc-1* in the *cyc-acyc* equilibrium. Best results were obtained with a PPh(catechyl) unit. However, beyond the suggestions posed by spectroscopic and synthetic evidence, the structural features of **1** have not been determined. To characterize these potentially versatile reagents, we therefore provide a computational study of the nature of the reactive species and their cycloaddition reactions.

### Scheme 1



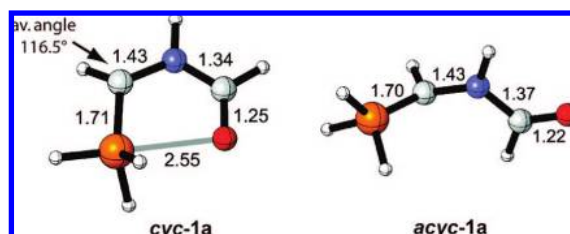
Calculations with a variety of methods using Gaussian 03<sup>7</sup> and NWChem 5.0<sup>8</sup> revealed that the structural features of the parent compound *cyc-1a* ( $R^1, R^2, R^3 = H$ ) are relatively insensitive to the theoretical method used for geometrical optimization (Table 1). Consistency was seen over a range of theoretical levels including B3LYP, M06-2X, MP2, and QCISD, with various basis sets. In most cases the  $P\cdots O$  distance fell within the relatively narrow range 2.51–2.57 Å.

In keeping with experiment, cyclic and acyclic isomers were both identified as local minima for **1a**. Geometries of *cyc-1a* and the lowest-energy conformer of *acyc-1a*, at the B3LYP/6-31+G(d) level, are shown in Figure 1. The energy difference between *cyc-1a* and *acyc-1a* is essentially invariant across the methods studied, the enthalpy difference being approximately 2–3 kcal mol<sup>-1</sup> in favor of the cyclic form.<sup>9</sup>

**Table 1.** Geometrical and Energetic Features of *cyc-1a*

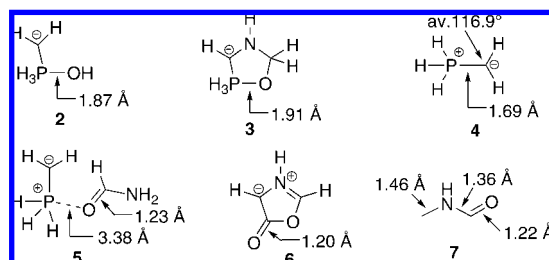
level of theory	$P\cdots O$ (Å)	$\angle OPC$ (°)	$\angle POC$ (°)	av. $\angle$ at $C_p$ (°) <sup>a</sup>	$\Delta H_{cyc-acyc}$ <sup>b</sup> (kcal/mol)
B3LYP/6-31G(d)	2.52	78.1	99.5	116.3	-2.8
B3LYP/6-31+G(d)	2.55	77.5	99.3	116.5	-1.8
B3LYP/6-311+G(2df,p)	2.51	77.2	100.3	118.0	-3.1
B3LYP/cc-pVTZ	2.51	77.6	99.9	117.0	-2.7
M06-2X/6-31+G(d)	2.54	77.8	99.1	116.4	-1.7
MP2/6-31+G(d)	2.53	78.4	99.2	115.8	-2.1
QCISD/6-31G(d)	2.57	78.4	97.8	115.1	-2.1

<sup>a</sup> Average angle at ylidic carbon. <sup>b</sup>  $\Delta H$  at 298.15 K.



**Figure 1.** Geometries of cyclic and open-chain isomers of **1a** at the B3LYP/6-31+G(d) level.

**Chart 1.** B3LYP/6-31+G(d) Features of Model Compounds

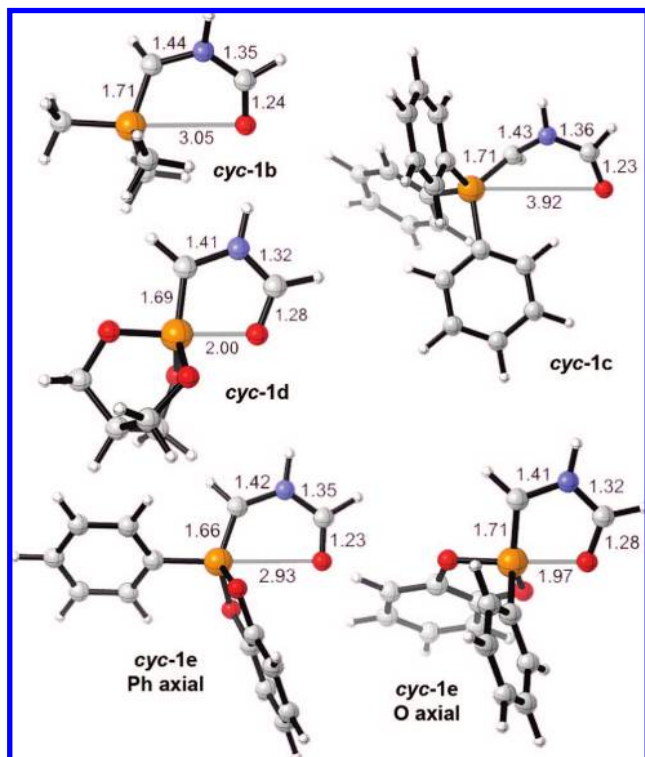


The  $P\cdots O$  interaction in *cyc-1a* is relatively weak. Comparison with the model compounds **2** and **3** (Chart 1) indicates that the  $P\cdots O$  interaction in *cyc-1a* is too long to be considered a normal covalent bond. Although the  $P\cdots O$  distance is considerably shorter than that in a complex of **4** with formamide (via O) (**5**) (viz. 3.38 Å), the shortened  $P\cdots O$  interaction provides small enthalpic benefit.  $\Delta H$  for formation of **5** from its components is  $-2.7$  kcal mol<sup>-1</sup>.

The  $P\cdots O$  interaction leads to a distorted trigonal bipyramidal geometry at phosphorus: the average of the three equatorial bond angles in *cyc-1a* is 116.1°. In contrast to the more traditional 1,3-dipole, Münchnone **6** (which is planar), *cyc-1a* is nonplanar with an average angle at  $C_p$  of 116.5°. The bond lengths and bond angles in the PCNCO framework of *cyc-1a* are quite similar to those of *acyc-1a*, except for the amide C–N bond lengths, which are 1.34 and 1.37 Å, respectively, and the C–O bond lengths, which are 1.25 and 1.22 Å. The amide unit in *cyc-1a* possesses greater C=N

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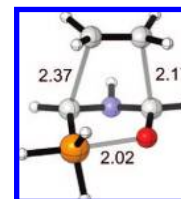
**Figure 2.** Geometries of substituted derivatives **1b–1e**.

character than does the simple amide **7**, the result of favorable interaction of the negative charge on O with the phosphonium group. In addition, the P–C bond length in **1a** is almost identical to that in ylide **4**. Therefore, species **1a** is best regarded as an acylamino-phosphonium ylide, the cyclic conformer of which is stabilized by a weak P $\cdots$ O interaction.

Experimental results have suggested that the nature of the phosphorus substituents significantly influences the ability of **1** to undergo cycloaddition.<sup>1</sup> These influences were modeled by derivatives incorporating PMe<sub>3</sub>, PPh<sub>3</sub>, P(OCH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>CH, and PPh(catechyl) units (**1b–1e**). Geometries of the cyclic forms of these species are shown in Figure 2.

In the PMe<sub>3</sub> derivative **cyc-1b**, the P $\cdots$ O interaction is 0.5 Å longer than in **cyc-1a**. Electron donation from the Me groups is likely to contribute to this long P $\cdots$ O distance, but steric effects must also be considered since the two closest O $\cdots$ H contacts involving the PR<sub>3</sub> unit are 0.1–0.3 Å shorter than in **cyc-1a**. **Cyc-1b** is only 0.4 kcal mol<sup>-1</sup> more stable ( $\Delta H$ ) than the lowest-energy conformer of **acyc-1b**.

For the PPh<sub>3</sub> derivative **1c**, the P $\cdots$ O interaction is essentially nonexistent. The most “cyclic” isomer has a P $\cdots$ O distance of 3.92 Å and is now 1.0 kcal mol<sup>-1</sup> less stable than the lowest-energy acyclic geometry. Conversely, incorporation of electron-withdrawing P-substituents strengthens the P–O interaction. **Cyc-1d** has a P $\cdots$ O distance of 2.00 Å. The PPh(catechyl) derivative **cyc-1e** has two isomers differing in the stereochemistry at phosphorus; when the axial position of the phosphorus trigonal bipyramid is occupied by the Ph group, the P $\cdots$ O interaction is long (2.93 Å), but when one of the catechol oxygens occupies the axial position, the P $\cdots$ O interaction is much shorter (1.97 Å). The shorter P $\cdots$ O interactions in **cyc-1d** and O-axial **cyc-1e** are not, however, associated with any increase in stability. **Cyc-1d** is 1.5 kcal mol<sup>-1</sup> higher in energy than its acyclic form, while O-axial **cyc-1e** is 0.6 kcal mol<sup>-1</sup> higher



**Figure 3.** Transition state for cycloaddition of **cyc-1a** with ethylene.

in energy than the Ph-axial isomer and 2.6 kcal mol<sup>-1</sup> higher in energy than the most stable *acyclic* isomer.<sup>10</sup>

These data suggest that a large contribution of **cyc-1** to the **cyc-1**–**acyc-1** equilibrium is not, in itself, the factor responsible for cycloaddition efficiency. In order to probe this, the transition states for the cycloadditions of **1a**, **1c**, and **1e** with ethylene were computed. The parent **cyc-1a** (Figure 3) displays a concerted, moderately asynchronous transition structure ( $\Delta H^\ddagger = 22.8$  kcal mol<sup>-1</sup>), in which the bond to the carbonyl carbon is more developed (2.17 Å) than the bond to the ylidic carbon (2.37 Å). **Cyc-1c** and the Ph-axial and O-axial isomers of **cyc-1e** also display concerted asynchronous transition structures, with activation enthalpies of 31.7, 32.0, and 16.2 kcal mol<sup>-1</sup>, respectively. These barriers parallel the results of experiments using CH<sub>2</sub>=C(Cl)CN as the dipolarophile,<sup>1</sup> which indicated that a PPh<sub>3</sub> unit was ineffective in promoting cycloaddition (when R<sup>1</sup>, R<sup>3</sup> = Tol and R<sup>2</sup> = Bn), whereas PPh(catechyl) gave a 95% yield of the pyrrole in 30 min at 23 °C. The activation barriers follow the same trend as the energies to distort the dipoles to their TS geometries.<sup>11</sup> During cycloaddition, the dipole undergoes a contraction of the P–O distance, as well as the formation of two new C–C bonds. The barriers correlate with the change in P–O distance on going from reactant to TS. Cycloaddition is most facile when the P–O interaction is already well-developed in the substrate (e.g., O-axial **cyc-1e**).

A concerted mechanism is understood to operate in the reactions of Münchnones with alkynes.<sup>12</sup> However, for **1**, multistep mechanisms may occur, depending on electronic effects. These mechanisms and reaction regioselectivities are under investigation.

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**Supporting Information Available:** Total energies at various levels of theory for **cyc-1a** and **acyc-1a**; B3LYP/6-31+G(d) geometries for all species; and complete citations for refs 7 and 8. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- The free-energy difference is similar, being 1–2 kcal mol<sup>-1</sup> in most cases.
- X-ray data on derivatives of **1** show an *acyc* structure for PR<sub>3</sub> = PPh<sub>3</sub> and a *cyc* structure for PPh(catechyl) (Arndtsen and St. Cyr, unpublished data).
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