a variety of non-transition-metal oxides[16] can effect the heterolytic cleavage of molecular hydrogen and in some instances even serve as efficient hydrogenation catalysts.[16,17] If further follows that such considerations are most probably responsible for the ready hydrogenolysis of both main groups[21] as well as certain transition-metal–carbon σ bonds.[22-24]

Finally, although there can be no doubt of the unique role of d electrons in the activation of molecular hydrogen by many homogeneous and heterogeneous transition-metal catalysts,[17,18] the results and conclusions presented here suggest that attempts to associate patterns in metal–hydrogen reactivity solely through correlations in isoelectronic structure may be oversimplied since such reactivity clearly involves other factors as well.

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(16) Cf.: Satterfield, C. F. "Heterogeneous Catalysis in Practice"; McGraw-Hill: New York, 1980; pp 295–301. Thomas, C. L. "Catalytic Processes and Proven Catalysts"; Academic Press: New York, 1970.

(17) So-called "oxidation addition" of hydrogen to various transition-metal complexes[18]

$$L_nM + H_2 \rightarrow L_nM(H)_2$$

represents another pathway for hydrogen activation. Although the kinetics of this process have been examined in some detail, there remains some ambiguity concerning their significance in terms of the detailed mechanism of these addition processes.[19] We suspect that the unusually low isotope effect ($k_H/k_D = 1.22$)[19] associated with the addition of hydrogen to $IrCl(CO)(Ph_3P)_2$ may also be a consequence of the cyclic three-center transition-state geometry of the purported activated complex. Studies aimed at clarifying this point are in progress.

(18) Cf.: James, B. R. "Homogeneous Hydrogenation"; Wiley: New York, 1973.

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(23) We are currently examining several reactions in an attempt to establish this possibility.

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Midinfrared Vibrational Circular Dichroism Studies of Cyclophosphamide and Its Congeners

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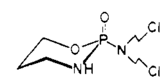
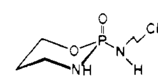
Vibrational circular dichroism (VCD) is the measurement of the difference in absorption of left and right circularly polarized infrared light by vibrational transitions of chiral molecules.[1] Several studies have noted correlation of the sign of the VCD (or that of its Raman analogue) for certain diagnostic bands with molecular configuration[2] or conformation[3] in solution. The availability of a large number of resolved bands that are often characteristic of localized parts of a molecule gives VCD the potential of offering new insights into the stereochemistry of a variety of different molecular systems.

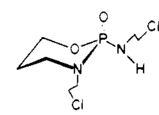
We report here preliminary VCD results for four organophosphorus compounds: 2-[bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorine 2-oxide (cyclophosphamide, I); 2-((2-chloroethyl)amino)-3-(2-chloroethyl)tetrahydro-2*H*-oxazaphosphorine 2-oxide (ifosphamide, II); 2-((2-chloroethyl)amino)tetrahydro-2*H*-1,3,2-oxazaphosphorine 2-oxide (III); 2-amino-3-(2-chloroethyl)-tetrahydro-2*H*-1,3,2-oxazaphosphorine 2-oxide (IV). Racemic forms of compounds I and II are clinically useful anticancer drugs while compounds III and IV are metabolites of II.[4] The stereospecific synthesis and assignment of the absolute configurations of I–III have been published.[5,6] Absolute configuration of IV was assigned by means of stereochemical correlation. Thus it was of interest to utilize compounds I–IV as models for studies of the applicability of VCD to organophosphorus structure.



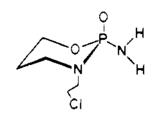
(−)-S-I



(+)-S-III



(+)-R-II



(+)-R-IV

Our focus is on those vibrations that contain significant contributions from the P–O and P=O bonds. We have found what appears to be a "VCD marker mode" for the absolute stereochemistry about phosphorus. Such a correlation is not possible with optical rotation[5] and ORD CD studies[7]. In addition, this is one of the first reports of VCD in the 1000-cm^{-1} (10 μm) region.[8,9]

The optical isomers of the compounds I–IV, were prepared by our previously published methods.[5a,6] Optical rotations obtained were as follows: (+)-(*R*)-I, $[\alpha]^{25}{}_D$ +2.3° (c 3, CH_3OH); (−)-(*S*)-I, $[\alpha]^{25}{}_D$ −2.3° (c 3, CH_3OH); (+)-(*R*)-II, $[\alpha]^{25}{}_D$ +44.0° (c 2, CH_3OH); (−)-(*S*)-II, $[\alpha]^{25}{}_D$ −39.0° (c 4, CH_3OH); (−)-(*R*)-III, $[\alpha]^{25}{}_D$ −15.1° (c 3, CH_3OH); (+)-(*S*)-III, $[\alpha]^{25}{}_D$ + 15.1° (c 3, CH_3OH); (+)-(*R*)-IV, $[\alpha]^{25}{}_D$ +16.1° (c 3, CH_3OH), (−)-(*S*)-IV, $[\alpha]^{25}{}_D$ −18.0° (c 3, CH_3OH).

VCD and absorption spectra were obtained on the UICC spectrometer.[1a] Extentions to our optical configuration[10] along with spectra of a variety of other molecules in the 10-μm region are detailed elsewhere.[9] Spectra were run on solution samples placed in a demountable cell having two NaCl windows separated by Teflon spacers. Solvents used included CS_2, CH_2Cl_2, and CH_3CN. The noise level of spectra run on samples in CH_3CN

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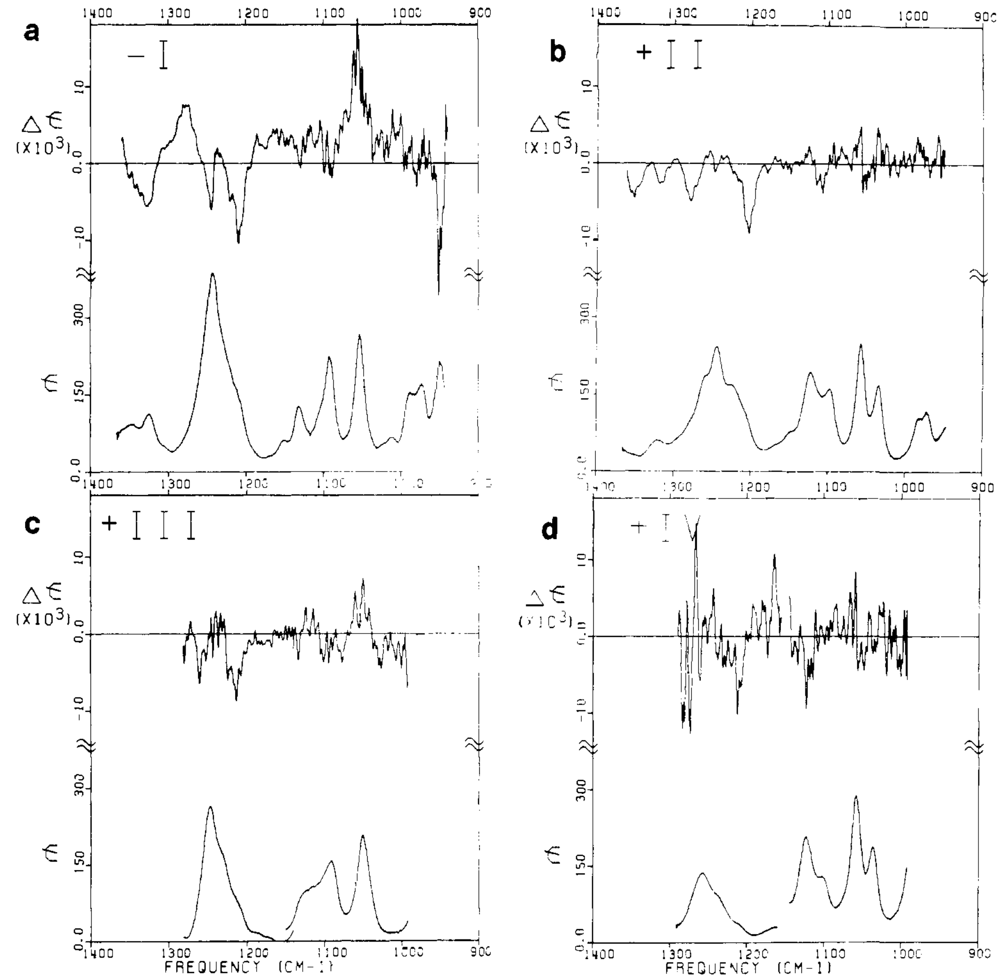

Figure 1. VCD and absorption spectra in the P═O and P–O stretching regions for the compounds studied: (a) (−)-(*S*)-I; (b) (+)-(*R*)-II; (c) (+)-(*S*)-III; (d) (+)-(*R*)-IV. Spectra a and b were run in CS_2. For c and d, 1250- and 1050-cm^{-1} regions were run in separate solutions (CH_3CN and C_2Cl_4, respectively). Path length and concentration were adjusted to give A_{max} <0.5, and all plots are averages of two or more 10-s time constant scans.

and CH_2Cl_2 is much higher than in CS_2 due to interferring solvent bands. Flat VCD base lines were obtained by measuring the VCD of both enantiomers and plotting half of the difference. This procedure enhances signal-to-noise ratio (S/N) over that obtained by using a racemic mixture as base line. Since only small amounts of samples were available, there may be error in the concentrations, but this affects ε and Δε equally.

Each of the four compounds studied has an intense IR absorption band at ~1250 cm^{-1}, which is typically assigned to the P═O stretching mode.[11] For all the molecules except I, this mode shows no significant VCD. Such a result parallels our findings for carbonyl stretches.[3] Single, unique stretching modes of high local symmetry often do not give large VCD, presumably because they do not significantly interact with other modes. However, as can be seen in Figure 1, each molecule has a VCD feature at ~1220 cm^{-1} that is negative in Δε for (−)-(*S*)-I, (+)-(*R*)-II, (+)-(*S*)-III, and (+)-(*R*)-IV. While these four enantiomers differ in terms of the sign of their optical rotation and in their formal *R,S* notation, they all have the same spatial arrangement of ligands surrounding the phosphorus atom. Thus among these four species, the 1220-cm^{-1} VCD is indicative of the phosphorous stereochemistry while the optical rotation is not.

Unfortunately, this band appears to be due to some mode other than the P═O stretch or due to some mode interacting with the P═O stretch. C–N stretching could occur in this region[11] but would normally be expected to shift with substitution. We see only a variation from 1225 to 1205 cm^{-1} with these four compounds. C–O stretching might also occur in this region if shifted up from its more usual frequency. At present a definite assignment cannot be made; the empirical correlation found here must be further tested on acyclic compounds to examine its limitations.

While the P═O band is probably characteristic of a highly symmetrical part of the molecule, the P–O stretching mode (in the six-member ring) should be more highly mixed and, hence, more responsive to its environment. These modes generally give rise to intense absorption between 987 and 1042 cm^{-1}.[12] In these molecules, the absorption spectra of II and IV show a pair of bands at ~1035 and ~1060 cm^{-1}, the higher energy one being more intense. Compounds I and III have a single intense band at about 1050 cm^{-1}. These latter both have positive VCD for the (−)-(*S*)-I and (+)-(*S*)-III enantiomers. Again the sign of this single P–O stretch VCD correlates to the phosphorous stereochemistry. Both the 1060- and 1035-cm^{-1} bands in (+)-(*R*)-II and (+)-(*R*)-IV also appear to give rise to positive signals, but the S/N is much worse than for I and III. Apparently, interaction between two modes reduces the P–O rotational strength. Comparison of the structures indicates that the "split" P–O stretch is characteristic of oxazaphosphorines that are substituted on the endocyclic nitrogen atom. The nature of this new perturbing mode is unclear at present. Again additional experiments are needed to confirm the utility of this "VCD marker" band for phosphorous stereochemistry.

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