JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 11, 149–154 (1998)

Ab initio calculations on P—C bond cleavage in phosphoranyl radicals: implications for the biodegradation of organophosphonate derivatives

Myong Lim and Christopher J. Cramer*

Department of Chemistry and Supercomputer Institute, University of Minnesota, 207 Pleasant St, SE, Minneapolis, Minnesota, 55455-0431, USA

Received 1 July 1997; revised 4 August 1997; accepted 7 August 1997

ABSTRACT: Barrier heights for P—C bond homolysis in *P*-hydroxy-*P*-methyl-*P*,*P*-dioxophosphoranyl and *P*,*P*,*P*-trihydroxy-*P*-methylphosphoranyl were calculated using well correlated levels of electronic structure theory. The best estimate for the difference in barriers between the two indicates that homolysis is more facile for *P*,*P*,*P*-trihydroxy-*P*-methylphosphoranyl by roughly 9 kcal mol^{-1}. This result suggests that bacterial pathways leading to P—C bond cleavage in organophosphonate derivatives will preferentially proceed via initial one-electron reduction of substrates rather than oxidation. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: P—C bond cleavage; phosphoranyl radicals; organophosphonate biodegradation; *ab initio* calculations

INTRODUCTION

Organophosphonate derivatives, which find use as agricultural chemicals and chemical warfare agents, can exhibit high neurotoxicity; they typically act as acetylcholinesterase inhibitors.[1] Current technology for the detoxification of these compounds focuses primarily on the hydrolysis of phosphorus–heteroatom bonds, either with hydroxide ion or with another nucleophile that ultimately exchanges with hydroxide in water.[2–20] Sometimes, however, this hydrolysis does not proceed to afford exclusively less toxic products, as in the case of the nerve agent VX.[17] An alternative approach to detoxification is 'hydrolysis' of the P—C bond [i.e. converting the phosphonate derivative into a (less toxic) phosphate derivative]. Although the P—C bond in organophosphonates is not labile under acidic or basic conditions, it has been observed that *Escherichia coli* can grow under conditions where organophosphonates serve as the sole source of phosphorus,[21–24] implying that the organism enzymatically cleaves the P—C bond. Similar P—C bond-cleaving activity has been observed for *Pseudomonas fluorescens* even under non-phosphate-starvation conditions.[25] Based on the observation of organic products derived from the radical of the organic ligand (e.g. alkyl dimers, alkenes), this P—C lyase activity presumably derives from a one-electron oxidation or reduction of the phosphonate derivative followed by P—C bond homolysis (see Figure 1).[21–24]

Phosphorus-containing radicals with four substituents on phosphorus are known as phosphoranyl radicals.[26] These inorganic species are typically metastable and many examples have been characterized by electron spin resonance.[27–39] Phosphoranyl radicals can be produced in biological systems upon radiation damage of the phosphate backbone of cellular genetic material,[26,40] and they have seen extensive theoretical study aimed at understanding their electronic structures and overall geometries as a function of substituents.[37,41–57]

An interesting question with respect to biological P—C lyase activity has to do with the intrinsic P—C bond strengths in the phosphoranyl radicals derived from either one-electron oxidation or reduction of a given substrate. As they are chemically distinct species, one might expect there to be a non-trivial difference. Also, since the organism presumably has no means of lowering the intrinsic barrier to bond homolysis, if there is a naturally more labile species, one might expect the enzymatic system to evolve so as to produce it exclusively. In this work, we calculated the gas-phase barriers to P—C bond homolysis for *P*-hydroxy-*P*-methyl-*P*,*P*-dioxophosphoranyl and *P*,*P*,*P*-trihydroxy-*P*-methylphosphoranyl; these two molecules are produced, respectively, by oxidation or reduction of methanephosphonic acid followed by neutralization of charge by deprotonation or protonation (Figure 1). We expect this comparison to be a reasonable

**Correspondence to:* C. J. Cramer, Department of Chemistry and Supercomputer Institute, University of Minnesota, 207 Pleasant St, SE, Minneapolis, Minnesota, 55455-0431, USA. E-mail: cramerchem.umn.edu
Contract/grant sponsor: United States Army Research Office.
Contract/grant sponsor: Alfred P. Sloan Foundation.

 CCC 0894–3230/98/020149–06 $17.50

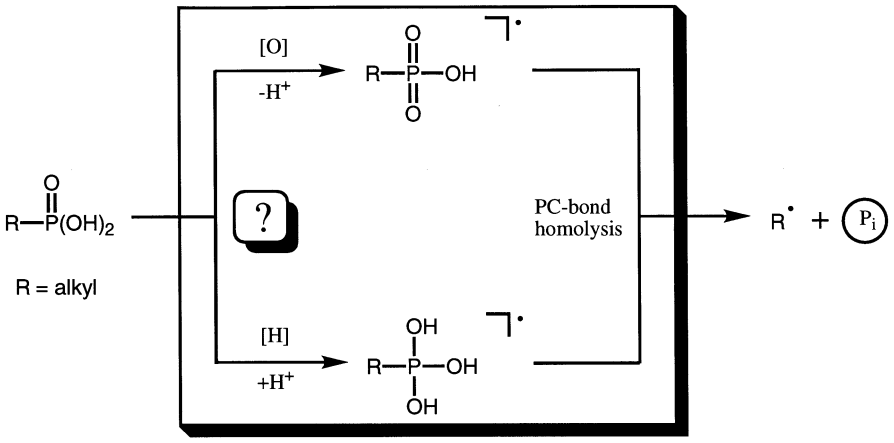

Figure 1. Possible pathways for biodegradation of organophosphonate derivatives, shown here for an alkylphosphonic acid. The products of biodegradation include inorganic phosphate and organic materials derived from the alkyl radical

model for the biological system since medium effects on the non-polar homolytic process are expected to be small. One caveat, however, is that the biological P—C lyase activity may precede the hydrolysis of any heteroatomic substituents on phosphorus, in which case charge neutralization of a phosphoranyl radical cation by proton elimination might not be possible. Moreover, the pK_a values of the phosphoranyl radicals studied here are not known, and it is conceivable that they are charged in neutral aqueous solution. However, one would not necessarily expect the P—C bond strengths to be significantly different in the corresponding conjugate acids and bases of these molecules, and we emphasize that the intent of this study is to gain a *qualitative* insight into the likelihood of biological P—C bond cleavage proceeding preferentially by either an oxidative or reductive path, not to provide quantitative differences for any particular substrate.

COMPUTATIONAL METHODS

The geometries of all species were fully optimized at the unrestricted Hartree–Fock, second-order perturbation theory (MP2), and density functional levels of theory employing the correlation-consistent polarized valence-double-ζ basis set (cc-pVDZ) of Dunning.[58,59] Density functional calculations employed the local exchange and correlation functionals of Slater[60] and of Vosko *et al.*,[61] respectively. All transition states were verified as having a single imaginary frequency and calculations of intrinsic reaction coordinates (IRC) were carried out at lower

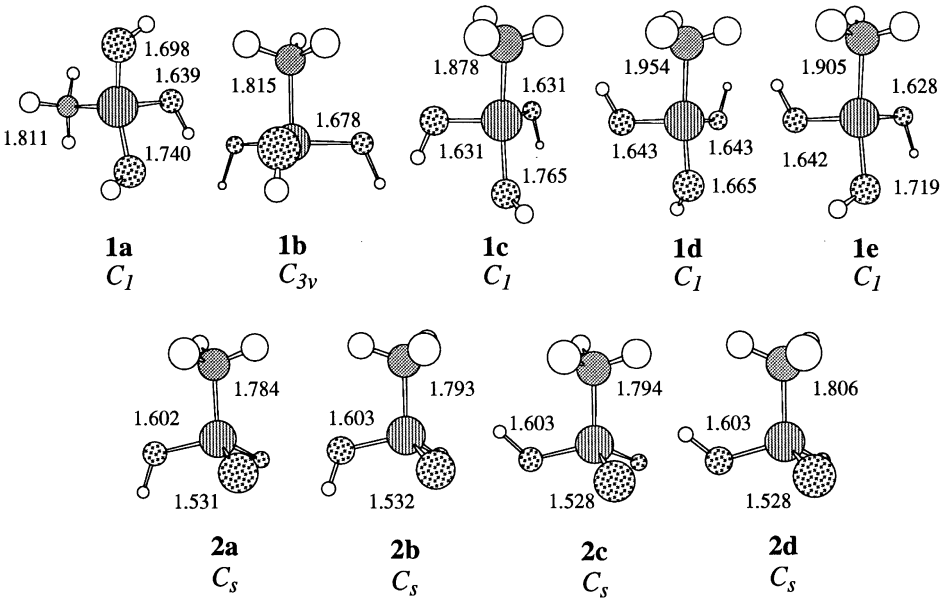

Figure 2. Stationary points for **1** and **2** as calculated at the UHF/cc-pVDZ level of theory; heavy atom bond lengths (Å) are indicated

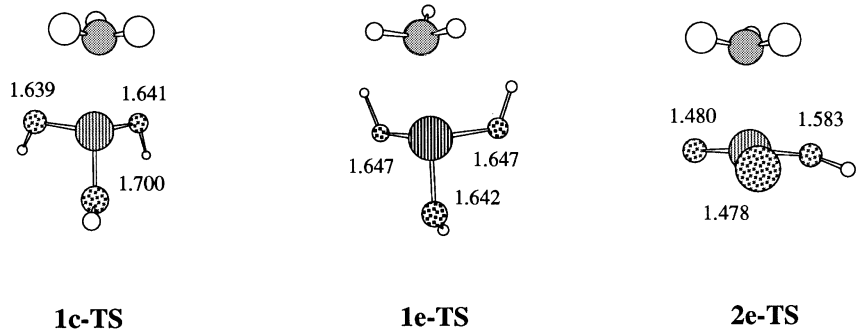

Figure 3. Transition state structures for P—C bond homolysis in **1** and **2** as calculated at the UHF/cc-pVDZ level of theory; heavy atom bond lengths (Å) are indicated (see text for P—C bond lengths)

levels of theory to determine what two minima were connected by different transition state structures. Single-point energy calculations were carried out with the cc-pVDZ basis set at the configuration interaction level including all single and double substitutions (CISD) and complete up to fourth order in perturbation theory (MP4). Computations employed the Gaussian94 suite of electronic structure programs.[62]

P,*P*,*P*-Trihydroxy-*P*-methylphosphoranyl (**1**) exhibits $<S^2>$ values between 0.75 and 0.80 for all stationary points. However, symmetric stationary points of *P*-hydroxy-*P*-methyl-*P*,*P*-dioxophosphoranyl (**2**) are characterized by larger spin contaminations (typically about 0.82) and Hartree–Fock doublet instability. As discussed in more detail below, various methods of accounting for electron correlation alleviate this instability to some extent, and density functional 'wavefunctions' do not exhibit any instability (the tendency of DFT to provide wavefunctions free from spin contamination has been noted elsewhere,[63–65] and is correlated with freedom from doublet instability).

RESULTS AND DISCUSSION

Figure 2 depicts the structures of different stationary points for **1** and **2**, and Figure 3 depicts the transition state structures for homolysis of the P—C bond in these species. Radical **1** is a standard phosphoranyl radical insofar as it adopts trigonal bipyramidal (TBP) minima where the unpaired electron is viewed as occupying one ligand position in the TBP. However, even though the unpaired electron is usually observed by ESR to localize in an equatorial position, there *is* a local minimum (**1b**) which localizes the electron axially. Such structures have occasionally been assigned from interpretation of phosphoranyl radical ESR spectra,[35] and have found previous computational support—in this instance the 'apicophobicity' of the unpaired electron is overcome by favorable hyperconjugative interactions between the equatorial hydroxyl groups as described previously for closely related systems (e.g. trihydroxyphosphoranyl).[51,55] Four TBP minima all exhibiting equatorial localization of the unpaired electron are also found, and these minima differ either by the axial/equatorial substitution pattern of the ligands—**1a** has the methyl group equatorial whereas **1c, 1d** and **1e** place it axial—or as hydroxyl group rotamers amongst the latter three. The hydrogen bonding and hyperconjugative interactions that control the hydroxyl group orientations have been extensively discussed for other hydroxy-substituted phosphoranyl radicals,[48,51,52,55] and we find similar results here; in particular, the greater apicophilicity of hydroxyl compared with methyl[66] is offset by favorable hyperconjugative interactions between two equatorial hydroxyl groups, making the energies of the lowest energy conformers, **1a** and **1c**, very similar at all levels of theory. Relative energies for all five structures as calculated at different levels of theory are given in Table 1. There is generally good agreement between UHF, MP2 and DFT for the relative energies of all species except **1b**. We have noted elsewhere the tendency for correlation effects to preferentially stabilize TBPs with axially localized unpaired electrons,[52,55] but have noted that this effect is overestimated at the MP2 level,[52] suggesting that the DFT and UHF results are probably reasonably accurate.

Radical **2**, in contrast to **1**, is roughly tetrahedral in geometry (Figure 2). Experimental evidence supports this geometry in other *P*,*P*-dioxophosphoranyl radicals.[53] In this instance, two C_s minima are found, both having a staggered arrangment about the P—C bond, with **2a**

Table 1. Relative energies (kcal mol^{-1}) for stationary points of **1** at UHF, MP2 and DFT levels

	Relative energy		
Structure	UHF/cc-pVDZ	MP2/cc-pVDZ	SVWN/cc-pVDZ
1a	0.0	−0.2	0.3
1b	6.5	2.4	4.2
1c	0.0	0.0	0.0
1d	8.9	9.6	9.9
1e	3.0	3.3	3.9

Table 2. Relative energies (kcal mol^{-1}) for stationary points of **2** at UHF, MP2 and DFT levels

	Relative energy		
Structure	UHF/cc-pVDZ	MP2/cc-pVDZ	SVWN/cc-pVDZ
2a	0.0	0.0	0.0
2b[a]	1.4	1.5	1.1
2c	5.7	5.8	5.1
2d[a]	7.6	8.0	7.0

[a] Transition state structure for P—C bond rotation.

being lower in energy than **2c** by virtue of having the P—O hydroxyl torsion *anti* to the P—C bond instead of eclipsing it. The rotational transition state structures **2b** and **2d** are each about 2 kcal mol^{-1} (1 kcal = 4.184 KJ) higher in energy than their corresponding minima, with some slight variation depending on the level of theory. Relative energies for these species as calculated at different levels of theory are given in Table 2. Frequency calculations for minima **2a** and **2c**, however, show extremely large imaginary frequencies (of the order of 20 000*i*). Such a non-physical result is often diagnostic of so-called Hartree–Fock doublet instability—a phenomenon where the UHF wavefunction is unstable to breaking symmetry. Such symmetry breaking is an artifact introduced by the degree to which symmetry breaking can provide electron correlation energy not otherwise captured at the UHF level of theory. Indeed, we find that if we permit structure **2a** to break electronic state symmetry, the energy of the system decreases by about 14 kcal mol^{-1} at the UHF level of theory. We have found a number of other dioxophosphoranyl radical wavefunctions that suffer from doublet instability,[53,67] so this behavior is not unusual. Calculations at the UMP2 level of theory almost completely remove the instability—the energy lowering on symmetry breaking is reduced to 0.4 kcal mol^{-1}—and DFT calculations with the SVWN functional do not exhibit any instability, a phenomenon presumably associated with the well known tendency for DFT wavefunctions to be resistant to spin contamination[63–65] (a problem occasionally found for UHF theory, where the wavefunctions are contaminated with character from higher spin states). Interestingly, in spite of the UHF doublet instability, when C_s symmetry is enforced, the relative energies of structures **2a–2d** agree reasonably well across all three levels of theory, lending some confidence in these values.

For the P—C bond homolysis reaction, two transition states were located at the Hartree–Fock level connecting minima of **1** to separated methyl radical and phosphorous acid (the latter presumably readily oxidized to phosphoric acid under biological conditions). When the IRCs for these structures are followed, they correspond directly to lengthening of the P—C bond in **1c** (2.299 Å) and **1e** (2.251 Å) and are hence referred to as **1c-TS** and **1e-TS**. The IRC for **1c-TS** is shown in Figure 4. Both of these cases, then, represent the loss of an apical ligand from the phosphorus TBP; this situation is typically preferred over

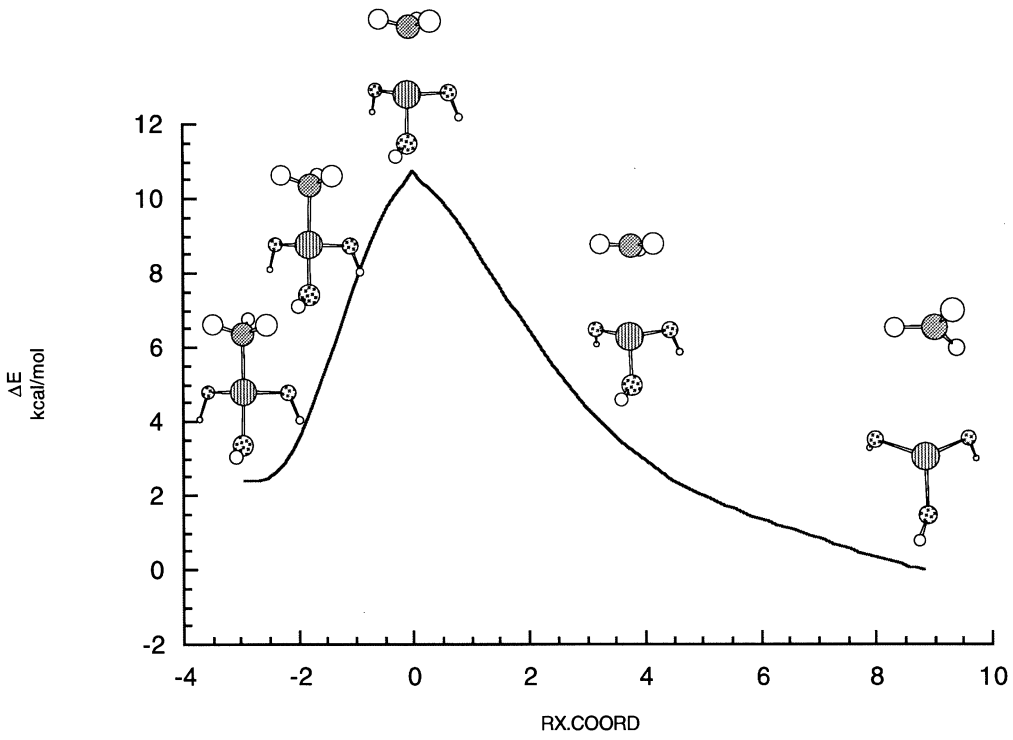

Figure 4. Intrinsic reaction coordinate (in mass scaled internal coordinates) for transition state structure **1c-TS**

Table 3. Barrier heights (kcal mol^{-1}) for P—C bond homolysis[a]

Structure	Barrier height	
	CISD/cc-pVDZ	MP4/cc-pVDZ
1c-TS[b]	10.6	11.0
1e-TS[b]	14.0	14.1
2-TS[c]	18.8	15.9
$CH_3^{\bullet} + HPO_3$[d]	20.0	20.3

[a] Calculated for HF/cc-pVDZ geometries.
[b] Barrier heights relative to **1c**.
[c] Barrier heights relative to **2a**.
[d] Separated products relative to **2a**.

equatorial loss.[68] When one lengthens the P—C bond in **1a**, the molecule undergoes a pseudorotation to a **1e**-like structure (with a barrier of 3.5 kcal mol^{-1} at the MP2/cc-pVDZ level), and bond homolysis can then proceed directly through **1e-TS** (or, or course, **1e** can convert into **1c** by hydroxyl rotation and homolyze via the lower energy **1c-TS** structure). Similarly, if one stretches the P—C bond in **1b**, one induces pseudorotation to **1a** with a barrier of 2.3 kcal mol^{-1}) rather than proceeding to homolysis, and **1a** can go on to react as just described. Finally, if one stretches the P—C bond in **1d**, it too ultimately connects to **1e-TS**, suggesting that the IRC path down from this transition state structure may bifurcate to both **1d** and **1e**. Such bifurcations have been described by Windus and Gordon[69] for isoelectronic siliconate anions.

The barrier heights corresponding to **1c-TS** and **1e-TS** at highly correlated levels of theory are provided in Table 3. The lower energy barrier **1c-TS** is about 11 kcal mol^{-1} above the lowest energy precursor **1c**, while the other is 14 kcal mol^{-1} above **1c**. We note that these homolyses are isogyric processes [i.e. the total number of unpaired electrons (one) is conserved] and as such single-configuration levels of theory are expected to provide adequate reference wavefunctions for the calculation of barrier heights. The corresponding transition state structures located at the MP2 level show some lengthening of the P—C bond (2.479 and 2.406 Å in **1c-TS** and **1e-TS**, respectively), but are otherwise similar. Corresponding DFT transition state structures, on the other hand, showed very long P—C bond lengths (in excess of 2.8 Å). We have noted elsewhere[56] that DFT appears to be unreliable for predicting the structures of certain phosphoranyl radicals (for instance, many modern functionals predict the known radical PCl_4 to be unstable to dissociation into PCl_3 and $Cl^{\bullet}$!) and this flaw appears to extend here to the location of bond homolysis transition states. As a result, we do not consider DFT to be a reliable level of theory for the prediction of homolytic barriers in these species.

The location of a transition state structure for the P—C bond homolysis in **2** proves to be considerably more problematic than for **1**. This difficulty arises because of the Hartree–Fock doublet instability. Since the products of homolysis lack the C_s symmetry plane present in the reactants, the reaction coordinate *must* break symmetry at some point and, since this potentially gives rise to a discontinuity in the wavefunction because of doublet instability, it is hard to assign a saddle point with confidence. Table 3 reports the barrier height calculated at well correlated levels of theory for a UHF structure having a P—C bond length of 2.183 Å and characterized by exactly one imaginary frequency (it is unfortunately impractical to search the reaction coordinate using the correlated levels, which probably suffer much less from any instability). The energy of this species relative to **2a** is between 16 and 19 kcal mol^{-1} higher, depending on level of theory (the 3 kcal mol^{-1} spread is a manifestation of some remaining spin contamination—when spin contamination is projected out of the MP4 wavefunctions, that barrier is 17 kcal mol^{-1}). Given the uncertainty in position of this transition state structure, 17 kcal mol^{-1} should be regarded as only a lower bound to the barrier height (which is the local maximum on the reaction coordinate). To provide additional information, we calculated the relative energy of the infinitely separated products methyl radical and metaphosphoric acid [the latter presumably hydrating to phosphoric acid in a biosystem (and converting to an equilibrium mixture of phosphate anions at neutral pH)]. These products are 20 kcal mol^{-1} above the reactant. It is thus possible that the UHF transition state structure is an artifact of spin contamination and the homolysis is barrierless out to this asymptote.

Hence we calculate the intrinsic barrier to P—C bond homolysis to be roughly 9 kcal mol^{-1} higher for *P*-hydroxy-*P*-methyl-*P*,*P*-dioxophosphoranyl than for *P*,*P*,*P*-trihydroxy-*P*-methylphosphoranyl. Given this substantial difference, it seems reasonable to assume that biological P—C lyase activity will be initiated by one-electron reduction of organophosphonate derivates. Of course, the biological systems are considerably more complex, and it is conceivable that other factors might significantly influence the gas-phase results discussed here. However, to the extent that bond homolysis is a non-polar process, medium effects are expected to be minimal and, given the large difference in barrier heights calculated, it seems likely that the qualitative ordering of barrier heights will be maintained *in vivo*.

Acknowledgments

We are grateful for high-performance vector and parallel computing resources made available by the Minnesota Supercomputer Institute and the University of Minnesota-IBM Shared Research Project, respectively. This work was supported by funding from the United

States Army Research Office and the Alfred P. Sloan Foundation.

REFERENCES

1. H. P. Benschop, L. P. A. de Jong. *Acc. Chem. Res.* **21,** 368 (1988).
2. A. H. Aharoni, R. D. O'Brien. *Biochemistry* **7,** 1538 (1968).
3. J. Epstein, J. J. Callahan and V. E. Bauer. *Phosphorus* **4,** 157 (1974).
4. J. H. Fendler and E. J. Fendler. *Catalysis in Micellar and Micromolecular Systems,* p. 150. Academic Press, New York (1975).
5. E. Buncel, H. Wilson and B. Chuaqui. *J. Am. Chem. Soc.* **104,** 4896 (1982).
6. C. A. Bunton, L.-H. Gan and G. Savelli. *J. Phys. Chem.* **87,** 5491 (1983).
7. C. A. Bunton, M. M. Mhala, J. R. Moffatt, D. Monarres and G. Savelli. *J. Org. Chem.* **49,** 426 (1984).
8. R. A. Moss, S. Swarup, T. F. Hendrickson and Y. Z. Hui. *Tetrahedron Lett.* **25,** 4079 (1984).
9. B. A. Burnside, B. L. Knier, R. A. Mackay, H. D. Durst and F. R. Longo. *J. Phys. Chem.* **92,** 4505 (1988).
10. R. A. Moss, D. Bolikal, H. D. Durst and J. W. Hovanec. *Tetrahedron Lett.* **29,** 2433 (1988).
11. R. A. Moss, Y.-C. Chung, H. D. Durst and J. W. Hovanec. *J. Chem. Soc., Perkin Trans. 1* 1350 (1989).
12. P. S. Hammond, J. S. Forster, C. N. Lieske and H. D. Durst. *J. Am. Chem. Soc.* **111,** 7860 (1989).
13. K. E. DeBruin, C. W. Tang, D. M. Johnson and R. L. Wilde. *J. Am. Chem. Soc.* **111,** 5871 (1989).
14. C. A. Bunton, M. M. Mhala and J. R. Moffatt. *J. Phys. Org. Chem.* **3,** 390 (1990).
15. Y.-C. Yang, L. L. Szafraniec, W. T. Beaudry and D. K. Rohrbaugh. *J. Am. Chem. Soc.* **112,** 6621 (1990).
16. C. A. Panetta, S. M. Garlick, H. D. Durst, F. R. Longo and J. R. Ward. *J. Org. Chem.* **55,** 5202 (1990).
17. Y. C. Yang, J. A. Baker and J. R. Ward. *Chem. Rev.* **92,** 1729 (1992).
18. Y.-C. Yang, L. L. Szafraniec, W. T. Beaudry and C. A. Bunton. *J. Org. Chem.* **58,** 6964 (1993).
19. R. A. Moss and H. Zhang. *J. Am. Chem. Soc.* **116,** 4471 (1994).
20. D. R. Leslie and S. Pantelidis. *Aust. J. Chem.* **47,** 545 (1994).
21. M. L. Cordeiro, D. L. Pompliano and J. W. Frost. *J. Am. Chem. Soc.* **108,** 332 (1986).
22. L. Z. Avila, S. H. Loo and J. W. Frost. *J. Am. Chem. Soc.* **109,** 6758 (1987).
23. S. H. Loo, N. K. Peters and J. W. Frost. *Biochem. Biophys. Res. Commun.* **148,** 148 (1987).
24. J. W. Frost, S. Loo, M. L. Cordeiro and D. Li. *J. Am. Chem. Soc.* **109,** 2166 (1987).
25. G. McMullan and J. P. Quinn. *J. Bacteriol.* **176,** 320 (1994).
26. W. G. Bentrude. *Acc. Chem. Res.* **15,** 117 (1982).
27. G. F. Kokoszka and F. E. Brinckman. *J. Am. Chem. Soc.* **92,** 1199 (1970).
28. P. J. Krusic, W. Mahler and J. K. Kochi. *J. Am. Chem. Soc.* **94,** 6033 (1972).
29. A. J. Colussi, J. R. Morton and K. F. Preston. *J. Phys. Chem.* **79,** 1855 (1975).
30. T. Berclaz, M. Geoffroy and E. A. C. Lucken. *Chem. Phys. Lett.* **36,** 677 (1975).
31. P. Schipper, E. H. J. M. Jansen and H. M. Buck. *Top. Phosphorus Chem.* **9,** 407 (1977).
32. M. C. R. Symons and R. L. Petersen. *J. Chem. Soc., Faraday Trans. 2* **75,** 210 (1979).
33. R. S. Hay, B. P. Roberts, K. Singh and J. P. T. Wilkinson. *J. Chem. Soc., Perkin Trans. 2* 756 (1979).
34. J. R. Morton, K. F. Preston and S. J. Strach. *J. Magn. Reson.* **37,** 321 (1980).
35. J. H. H. Hamerlinck, P. Schipper and H. M. Buck. *J. Am. Chem. Soc.* **102,** 5679 (1980).
36. J. R. M. Giles and B. P. Roberts. *J. Chem. Soc., Perkin Trans. 2* 1211 (1981).
37. R. A. J. Janssen and H. M. Buck. *Chem. Phys. Lett.* **132,** 459 (1986).
38. O. M. Aagaard, R. A. J. Janssen and H. M. Buck. *Recl. Trav. Chim. Pays-Bas* **108,** 262 (1989).
39. O. M. Aagaard, B. F. M. de Waal, M. J. T. F. Cabbolet and R. A. J. Janssen. *J. Phys. Chem.* **96,** 614 (1992).
40. O. M. Aagaard, R. A. J. Janssen, B. F. M. de Waal and H. M. Buck. *J. Am. Chem. Soc.* **112,** 938 (1990).
41. T. Gillbro and F. Williams. *J. Am. Chem. Soc.* **96,** 5032 (1974).
42. J. M. Howell and J. F. Olsen. *J. Am. Chem. Soc.* **98,** 7119 (1976).
43. B. P. Roberts. *Tetrahedron Lett.* **24,** 3377 (1983).
44. R. A. J. Janssen and H. M. Buck. *J. Mol. Struct. (Theochem)* **110,** 139 (1984).
45. R. A. J. Janssen, G. J. Visser and H. M. Buck. *J. Am. Chem. Soc.* **106,** 3429 (1984).
46. D. Gonbeau, M.-F. Guimon, J. Ollivier and G. Pfister-Guillouzo. *J. Am. Chem. Soc.* **108,** 4760 (1986).
47. A. Demolliens, O. Eisenstein, P. C. Hiberty, J. M. Lefour, G. Ohanessian, S. S. Shaik and F. Volatron. *J. Am. Chem. Soc.* **111,** 5623 (1989).
48. C. J. Cramer. *J. Am. Chem. Soc.* **112,** 7965 (1990).
49. C. J. Cramer. *J. Am. Chem. Soc.* **113,** 2439 (1991).
50. C. J. Cramer. *Chem. Phys. Lett.* **202,** 297 (1993).
51. C. J. Cramer and S. M. Gustafson. *J. Am. Chem. Soc.* **115,** 9315 (1993).
52. C. J. Cramer and S. M. Gustafson. *J. Am. Chem. Soc.* **116,** 723 (1994).
53. C. J. Cramer and M. H. Lim. *J. Phys. Chem.* **98,** 5024 (1994).
54. M. Guerra. *Chem. Phys. Lett.* **237,** 61 (1995).
55. S. M. Gustafson and C. J. Cramer. *J. Phys. Chem.* **99,** 2267 (1995).
56. M. H. Lim, S. E. Worthington, F. J. Dulles and C. J. Cramer. in *Density-Functional Methods in Chemistry*, edited by B. B. Laird, R. B. Ross and T. Ziegler, p. 402. American Chemical Society, Washington, DC (1996).
57. M. T. Nguyen, S. Creve, L. G. Vanquickenborne, *J. Phys. Chem. A* **101,** 3174 (1997).
58. T. H. Dunning. *J. Chem. Phys.* **90,** 1007 (1989).
59. D. E. Woon and T. H. Dunning. *J. Chem. Phys.* **98,** 1358 (1993).
60. J. C. Slater. *Phys. Rev.* **81,** 385 (1951).
61. S. H. Vosko, L. Wilks and M. Nussair. *Can. J. Phys.* **58,** 1200 (1980).
62. M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople. *Gaussian 94, Revision D.1*. Gaussian Pittsburgh, PA (1995).
63. J. Baker, A. Scheiner and J. Andzelm. *Chem. Phys. Lett.* **216,** 380 (1993).
64. C. W. Murray, N. C. Handy and R. D. Amos. *J. Chem. Phys.* **98,** 7145 (1993).
65. C. J. Cramer, F. J. Dulles and D. E. Falvey. *J. Am. Chem. Soc.* **116,** 9787 (1994).
66. P. Wang, Y. Zhang, R. Glaser, A. E. Reed, P. v. R. Schleyer and A. Streitwieser. *J. Am. Chem. Soc.* **113,** 55 (1991).
67. C. J. Cramer and G. R. Famini. *J. Am. Chem. Soc.* **112,** 5460 (1990).
68. G. R. J. Thatcher and R. Kluger. *Adv. Phys. Org. Chem.* **25,** 99 (1989).
69. T. L. Windus and M. S. Gordon. *Theor. Chim. Acta* **83,** 21 (1992).

