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Molecular Modeling of Oxaphosphetane Intermediates of Wittig Olefination Reactions

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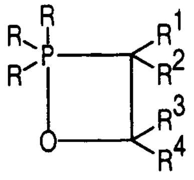
ABSTRACT

*The literature reveals that the structures of four unusual oxaphosphetanes have been established by x-ray diffraction studies, and the structure of one mythical oxaphosphetane (**6**) has been deduced by theoretical calculations. We have used these known structures to calibrate the MMX87 force field, the only necessary modification being the stretching term for the P-O bond. The bond length,* l_o*, was set at 1.80Å, which is an "average" of the P-O axial bond distances of the stable oxaphosphetanes. The AMPAC (Ver. 1.0) molecular orbital package utilizing the MNDO hamiltonian was also applied to the same problem, starting with the minimized geometries of the modified MMX87 force field. Fixed bond lengths and full minimizations were performed. The computed geometries of the four-member ring of each of the four oxaphosphetanes of known structures were found to be in very good agreement with the values obtained by x-ray diffraction. Furthermore, the method was applied to the mythical oxaphosphetane, and the results of MMX87 and MNDO calculations were found to be in very good agreement with the results of* ab initio *calculations. The MMX force field and the MNDO semiempirical method have been used to calculate the geometries and the steric energies (or heats of formation) of diastereomeric oxaphosphetanes formed in a theoretically real Wittig reaction.*

The Wittig reaction (Scheme 1) is one of the most important methods in organic synthesis. It has been studied in great detail by many workers and yet its mechanism is not completely understood [1].

The stereochemical outcome of the reaction, specifically with respect to the olefinic product is highly dependent upon the substituents present on the ylide carbon (R^1, R^2), the substituents on the carbonyl group (R^3, R^4), the substituents on the phosphorus (R), and the reaction conditions, such as the base employed to deprotonate the phosphonium cation, the solvent, the temperature, and the ratio of the reactants.

Oxaphosphetanes (**1**) are the only widely accepted intermediates in the Wittig reaction carried out under salt-free conditions (reactions in which only the ylide, the carbonyl compound, and the solvent are present) that have as yet been identified and characterized.



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A major influence on the stereochemical outcome of the reaction has been attributed to the way that this four-member ring intermediate forms and subsequently decomposes. Oxaphosphetanes of very particular structure (**2**[2], **3**[3], **4**[4], and **5**[5]) have been isolated and structurally characterized

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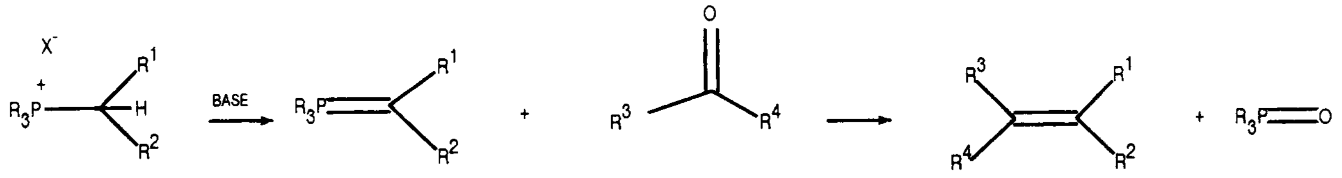
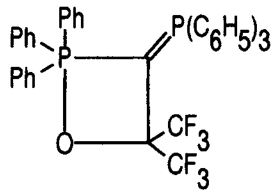


SCHEME 1

by x-ray diffraction studies. However, other, less stable oxaphosphetanes can be detected as unstable intermediates in regular Wittig reactions by means of ^{31}P, ^{13}C, and ^{1}H NMR nuclear magnetic resonance spectroscopy [1, 6, 7].



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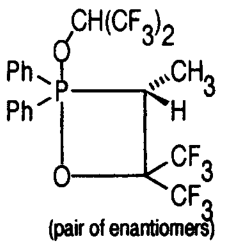

(pair of enantiomers)

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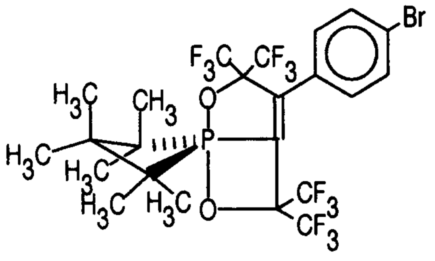

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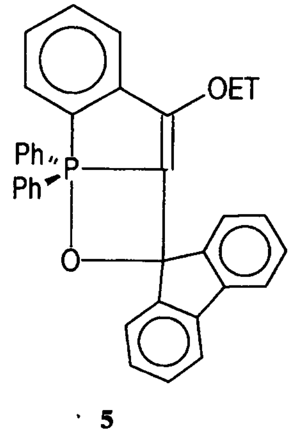

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Other geometric features of oxaphosphetanes have been assessed by *ab initio* molecular orbital calculations for the mythical Wittig reaction in which all the substituents depicted in scheme I are -H [8, 9].

In our initial attempts to gain an understanding of the behavior of the Wittig reaction under different conditions, we have adopted a molecular modeling approach based upon force field (molecular mechanics [10, 11]) and semiempirical molecular orbital (MNDO [11, 12] methods. In the present work, these methods are first applied to the oxaphosphetanes, since they are the key intermediates of the Wittig reaction; subsequently, we intend to expand our scope to include other species which may be involved.

Molecular mechanics force fields have been shown to be a useful tool in predicting geometries and other useful molecular properties. This approach is based upon a mechanical model of a given molecule described in terms of a set of parameters that includes stretching, bending, and torsional forces and van der Waals interactions. Careful use of the parameters that describe such forces is necessary for the prediction of known molecular geometries and properties. On the other hand, semiempirical molecular orbital (MO) calculations have been used as the "molecular spectrometer" [11] for the prediction of molecular properties based upon quantum mechanical calculations with an empirical parameterization that makes possible a fit to experimental results. In particular, the use of the MNDO [11, 12] method, where only individual atomic parameterization is necessary, has been shown to be useful for certain types of systems.

METHODOLOGY

The known structures of stable oxaphosphetanes based on x-ray diffraction studies were used to calibrate the MMX87 force field [13]. The only necessary modification was found to be the stretching term of the force field for the P-O bond. The natural bond length, l_o, was set to be 1.80 Å, which is the "average" of the P-O (axial) bond distances of the stable oxaphosphetanes. The force constant, k_s, used for such a bond was 3.27 dy/Å [14]. No attempt was made to calibrate the bending and tor-

TABLE 1 Structural Parameters of the Oxaphosphetane Rings of Known Structures: Experimental and Calculated Values

Compound	*dP-O* (Å)	*dP-C* (Å)	*dC-C* (Å)	*dO-C* (Å)	<*OPC* (°)	<*PCC* (°)	<*CCO* (°)	<*COP* (°)
2 [2] (exptl.)	2.01	1.76	1.57	1.39	71.3	98.5	96.1	—
2 (calc.)	1.82	1.80	1.53	1.43	70.6	98.7	90.2	101.1
3 [3] (exptl)	1.83	1.78	1.51	1.44	75.5	88.1	100.5	—
3 (calc.)	1.83	1.83	1.55	1.42	71.7	95.4	92.5	99.9
4 [4] (exptl.)	1.79	1.83	1.52	1.36	71.6	—	—	—
4 calc.)	1.81	1.79	1.54	1.44	69.7	99.6	87.3	103.3
5 [5] (exptl.)	1.85	1.81	1.48	1.43	—	—	—	—
5 (calc.)	1.82	1.81	1.53	1.43	70.6	97.7	90.2	101.4

sional parameters where a generalized constant set was used. This change in force field was necessary due to the distortion introduced in the normal trigonal bipyramidal geometry of pentavalent phosphorus compounds by the presence of the four member ring of an oxaphosphetane [14].

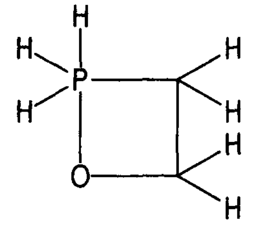
The AMPAC [15] (Ver. 1.0) molecular orbital package utilizing the MNDO hamiltonian was used for semiempirical MO calculations. The starting geometries for this semiempirical calculation were the minimized geometries of the modified MMX87 force field. The MMX geometries were treated with the MNDO method in some calculations while full optimizations were carried out in others, as shown in the tables.

Input files were generated using the graphics interface of PC-MODEL (Serena Software, Bloomington, IN). The calculations were carried out by use of the DEC VAX-6210 computer at the University of Massachusetts University Computer Center.

RESULTS AND DISCUSSION

The geometry of the four membered ring of each of the oxaphosphetanes of known structure (**2**, **3**, **4**, and **5**) and the calculated values are shown in Table 1. Caution must be taken in this approach since these oxaphosphetanes of known structures are rather unusual: they are stable, they undergo the Wittig reaction only very slowly, if at all, and they have unusual functionalities ($-CF_3$, $-C{=}PPh_3$) and/or small rings attached by a spiro union to the four member ring, a situation that is not typically found in most common Wittig reactions. Good agreement is found between each of the calculated and the known values, showing the reliability of the use of the modified MMX87 force field to predict the structures of these rather unusual oxaphosphetanes, especially if we consider that, in the x-ray structure, the molecules in the solid phase must adopt certain conformations in order to satisfy the packing requirements that allow the molecules to form single crystals. Of course in the molecular mechanics calculations, such conformational restrictions do not apply.

Having calibrated the MMX87 force field to predict the oxaphosphetane geometries, the force field was applied to another oxaphosphetane of "known" structure (**6**). The structure of this "mythical" oxaphosphetane has been computed by *ab initio* calculations at different levels of theory [8, 9, 16]. The results of our MMX and MNDO calculations and of previous *ab initio* calculations on the mythical oxaphosphetane are compared in Table 2. It may be noticed that the geometry predicted by the less elaborate and costly modified MMX87 force field is closer to the higher level *ab initio* theory $4\text{-}31G^{**}/4\text{-}31G^{*}$ level of theory [9], than the one predicted by a lower level (but still costly) 4-31G+d approach [8].



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Somewhat surprisingly, the results of the MNDO semiempirical molecular orbital calculations show excellent agreement with those of the more elaborate *ab initio* calculations. This result was unexpected owing to previous results found with this method [8, 16, 17], which is known not to treat well four-member rings and hypervalent atoms (the *d* orbital contribution is not explicitly treated in MNDO).

The results described herein give us some confidence in the methods utilized, especially if we consider the convenience of using the modified MMX87 force field since these calculations are in-

TABLE 2 Structural Features of the Mythical Oxaphosphenate (6): *ab initio*, Modified MMX and MNDO Calculated Geometries

Method	*dP-O* (Å)	*dP-C* (Å)	*dC-C* (Å)	*dO-C* (Å)	*<OPC* (°)	*<PCC* (°)	*<CCO* (°)	*<CPO* (°)
4-31G[a]	1.933	1.917	1.541	1.422	72.3	92.2	100.1	95.4
STO-3G[b]	1.888	1.937	1.548	1.427	73	—	—	—
4-31G*[c]	1.757	1.843	1.533	1.399	75.9	89.0	98.0	—
MMX87	1.83	1.79	1.53	1.42	73.25	94.49	94.33	96.85
MNDO	1.73	1.85	1.54	1.38	76.40	87.62	98.24	97.75

[a] Ref. 22.
[b] Ref. 8.
[c] Ref. 9.

expensive and relatively fast. At the very least, they yield a good starting geometry for more elaborate semiempirical and *ab initio* calculations. Moreover, semiempirical and *ab initio* calculations (especially *ab initio*) are restricted to smaller molecular systems due to their extensive computational needs. Hence, for some real systems, the molecular mechanics force field calculations are seen to be the only reasonable choice to model the Wittig reaction. Force fields, such as MMX, have been shown to be useful in the study of reactivity problems in which steric effects are important [10]. Most mechanistic explanations for the observed stereochemistry of Wittig reactions have involved use of steric arguments at one point or another in the consideration of different intermediates proposed for the respective mechanisms [6b, 18, 19, 20]. If this is a valid consideration, modified forms of MMX could be used as a "steric spectrometer" to evaluate such interactions in the system. Reliable results are likely to be expected from comparisons of diastereomers or similar stereoisomeric forms of a system. Thus, we chose as a model the hypothetical reaction used by Vedejs in his most recent evaluation of the Z:E alkene rations in the Wittig reactions of unstabilized ylides with pivalaldehyde [19] (Scheme 2).

As indicated in Table 3, in all cases (even when the original MMX87 parameterization, which yields poor geometrical fitting for oxaphosphetanes of known structure, is used), the E-oxaphosphetane is shown to be more stable than its Z counterpart by 4-6 kcal/mol by comparison of either the steric energy (MMX method) or the heat of formation (MNDO method). This shows that the steric energy provided by the MMX method could be used as a parameter to compare steric stabilities of diastereomeric species. This parameterization becomes more reliable when bulkier "R" groups and no additional functional groups are attached to the oxaphosphetane ring (a more realistic case in regular Wittig reactions), since steric strain may be the determinant factor in the geometries adopted by the molecules as well as in its chemical behavior. On the other hand, the geometries predicted by MNDO show a rather long P-C bond that may be attribut-

SCHEME 2

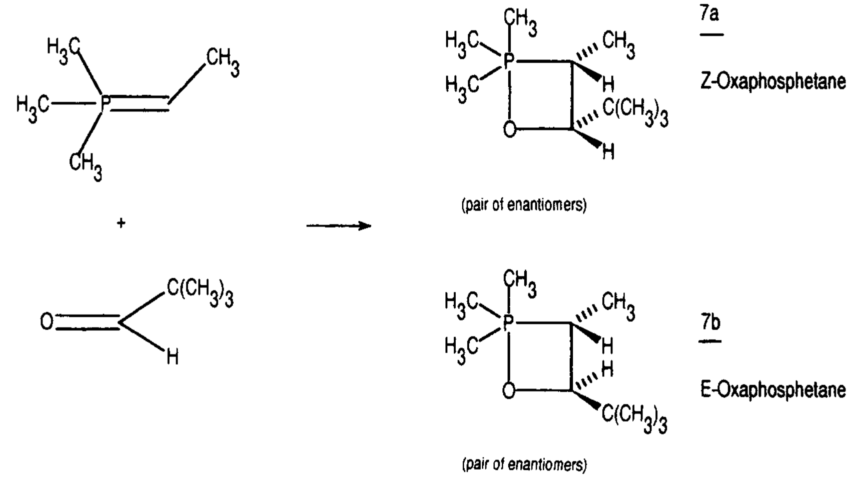

TABLE 3 Calculated Structural Parameters, Steric Energy (SE) and Heat of Formation (ΔH_f) of the Oxaphosphetane Product of the Hypothetical Reaction of $Me_3P{=}CHCH_3$ and Pivalaldehyde (7a and 7b)

Method and Compound	*dP-O* (Å)	*dP-C* (Å)	*dC-C* (Å)	*dO-C* (Å)	*<OPC* (°)	*<PCC* (°)	*<CCO* (°)	*<COP* (°)	*SE or* H_f[a]
MMX[b] (7a)	1.67	1.84	1.53	1.42	73.54	88.95	90.69	99.72	20.39
MMX[b] (7b)	1.67	1.82	1.53	1.41	70.90	93.01	92.41	96.50	16.75
MMX[c] (7a)	1.85	1.83	1.54	1.41	70.90	93.01	92.41	96.50	17.03
MMX[c] (7b)	1.85	1.81	1.53	1.41	76.22	95.45	93.62	98.47	13.34
MNDO[d] (7a)	1.84	1.82	1.52	1.41	73.87	92.22	94.99	97.27	−0.45
MNDO[d] (7b)	1.81	1.81	1.53	1.41	73.69	93.38	95.05	97.62	−4.97
MNDO[e] (7a)	1.77	1.94	1.56	1.38	72.57	86.56	96.64	99.63	−6.90
MNDO[e] (7b)	1.76	1.94	1.56	1.38	72.94	88.14	96.98	101.56	−12.52

[a] Steric energy (Kcal/mol) when MMX is used, ΔH_f (Kcal/mol) when MNDO is used.
[b] Original MMX87 constants are used.
[c] Modified MMX87 constants set used.
[d] Bonds' lengths optimized by MMX.
[e] Full MNDO geometric optimization.

able to steric repulsion of the substituents on the phosphorus atom and the ylide carbon as the oxaphosphetane is formed.

We feel that steric considerations alone cannot provide an adequate explanation for the *cis*-stereoselectivity of many reactions of unstabilized ylides with aldehydes. We are now in the process of evaluating various mechanistic concepts, both old' and new [21], in an attempt to solve this mystery with the calibrated force field and semiempirical techniques.

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