the solvent) and in the gas phase (due to the existence of a more feasible competitive reaction) can easily occur inside the active site of an enzyme.

The present results indicate that hydroxyl attack is a strongly favored process, which occurs at a high rate due to the small activation barrier. Therefore, it seems obvious that the hydroxyl attack at the C6 atom of nucleosides cannot be the rate-determining step of the deamination reactions catalyzed by ADA and CDA.

The ease of hydroxyl attack on the neutral 6-aminopyrimidine molecule introduces one intriguing question: Why is the protonation of N1 necessary[6,12,26,27,53,54] for the deamination reaction? Stated another way, what is the biochemical role of the protonation of N1? Three possible explanations follow.

(i) Protonation at N1 creates a net charge over the pyrimidine ring and consequently the hydroxyl attack on C6 is presumably favored (for both orbital and electrostatic reasons) over the proton transfer. This charge could open new reactive pathways such that a hydroxyl group located in a "nonreactive" orientation becomes "reactive".

(ii) Protonation at N1 could be responsible for a conformational change occurring in the enzyme during the formation of the tetrahedral intermediate. This change is well documented for ADA,[55-57] whereas several indirect experimental indications of this change as the slow binding of transition state inhibitors[11] exist for CDA. As a consequence, a hydroxyl group initially in a nonreactive position could become reactive.

(iii) This work is focused on the study of hydroxyl attack on nucleosides. However, the great reactivity of the hydroxyl group in the gas phase (clearly demonstrated in this work) makes it difficult to envision its existence in free form at the active site of an enzyme. Therefore, the hydroxyl group must be generated, presumably from a water molecule, by the action of a basic residue of the enzyme (probably a histidine group[16,26]). In this context, a new reaction, the proton transfer from a water molecule to a residue of the active site, appears. It could be suggested that the protonation at N1 and consequent increase of the electrophilicity at C6 facilitates this hydroxyl generation.

The results discussed above answer certain questions concerning the mechanism of reaction of nucleoside deaminatives enzymes but introduce new ones such as the mechanistic role of the protonation step. Three hypothesis are postulated; no experimental evidence supports any one of them over the others, and perhaps the true role of the protonation step within the whole deaminative reaction is a mixture of all of them.

Acknowledgment. We thank Drs. S. Olivella and J. Bofill for making available their personal version of the MOPAC package. We are also indebted to Dr. F. J. Luque for many helpful discussions.

Registry No. ADA, 9026-93-1; CDA, 9025-06-3; 6-aminopyrimidine, 591-54-8; hydroxyl, 14280-30-9; formaldehyde, 50-00-0.

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Conformational Analysis of Bridged Biphenyls and 2,2′-Bipyridines. Empirical Force Field Calculations (MM2-V4)

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The conformational analysis of bridged biphenyls and 2,2′-bipyridines has been undertaken with MM2-V4 force field (a modification of original MM2 force field containing the V4 torsional term). The known conformational properties of these compounds have been correctly reproduced. Ethano- and propano-bridged compounds have low interconversion barriers (ca. 4.5 and 10 kcal/mol, respectively), while butano-bridged derivatives present highly energetic barriers (ca. 25 kcal/mol).

Biaryls, mainly 2,2′-bipyridines, are extensively used as effective ligands to coordinate a large diversity of metals, and this effect is extended to annulated biaryls. E.g., 2,2′-bipyridine ruthenium complexes are important photosensitizers,[1] a bridged 2,2′-bipyridine (the 1,10-phenanthroline–cuprous complex) is an oxidative correactant in B DNA single-stranded break,[2] and some annulated 2,2′-bipyridine diquaternary salts have potent herbicide properties.[3]

In spite of the great interest of the chemistry of biaryls, these molecules have not been deeply studied from a theoretical point of view although some MO calculations on the conformations of biphenyl[4] have been carried out. Several articles concerned with experimental determinations on ground-state conformation and/or rotational barriers in biphenyl have been published.[5] Theoretical

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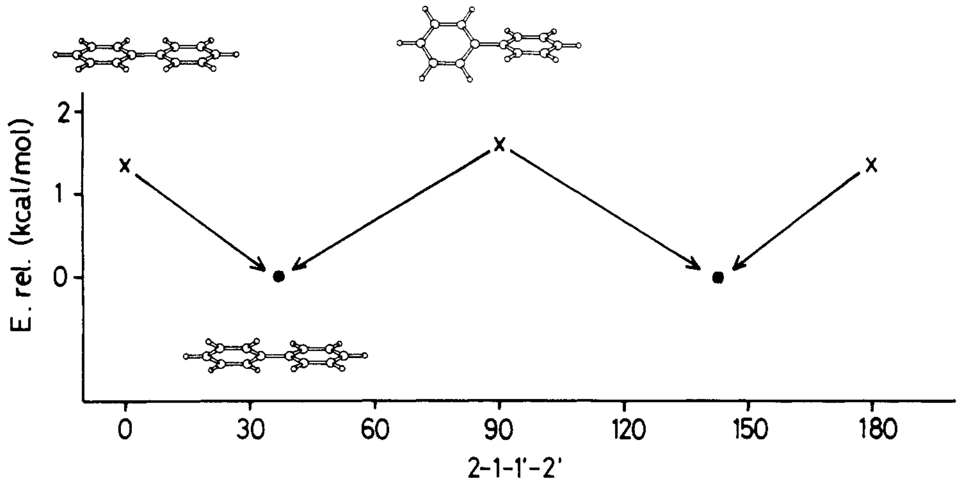
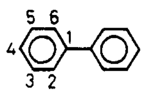


Figure 1. Energy variation and isoenergetic stationary points obtained in the MM2-V4 calculations on the rotation of the pivot bond of 1.

conformational analysis of biphenyls has usually been carried out using molecular orbital methods at different levels of approximation (ab initio or semiempirical calculations). The large size of biphenyl-containing molecules preclude them from being calculated by MO methods, and it would, thus be very interesting to be able to study their geometrical and conformational properties by an empirical computational method. Only three recent articles try to approach this problem from the molecular mechanics (MM) point of view.[6]

In this work, our own strategy[6b] is applied to the conformational study of several bridged biphenyls and 2,2′-bipyridines. The studied compounds are: biphenyl itself, 1, 2,2′-ethano-, 2,2′-propano-, and 2,2′-butano-bridged biphenyl, 2, 3, and 4, respectively, and the corresponding 2,2′-bipyridines, compounds 5, 6, 7, and 8[7].



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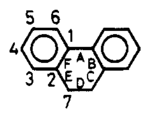

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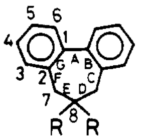
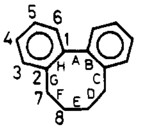


3, R=H; **9**, R=Me



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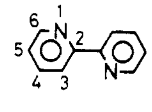

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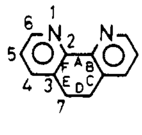

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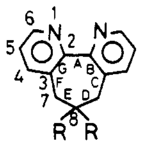
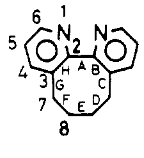


7, R=H; **10**, R=Me



8

Computational Techniques

Calculations were performed in a VAX-8800 computer. Ōsawa's technique[8] was followed throughout the work, i.e., after calculating the torsional energy surface by MM2-V4 program,[9] the stationary points were located using a modified version of the BIGSTRN-3 program[10] able to perform calculations with the fourth-order torsional term (hereinafter called BS4).

The one-bond drive technique was used only for the parent compounds, 1 and 5, as a consequence of having only one bond capable to rotate. One torsional energy surface was calculated for the rest of compounds by using the two-bond drive technique on 2–1–1′–2′ and one additional dihedral angle from the aliphatic moiety. Compounds 4 and 8 needed a deeper study, and three different torsional energy surfaces were calculated until we were sure that the conformational circuit was completed. Saddle points were located, using the BS4 program, either by the full Newton–Raphson optimization of close geometries or by using the tandem steepest-descent/Newton–Raphson algorithm when gradients were larger. After locating the real transition states, the BS4 eigenvector distortion option was used in connection with the variable metric optimization procedure.

Table I contains the main geometrical features (calculated endocyclic dihedral angles and bond lengths), relative energies, and symmetry for all the stationary points obtained in this work for bridged biaryls. MM2 force field treats lone pairs (LP) of electrons as pseudoatoms and they are represented by full circles near the nitrogen atoms in all figures.

MM2-V4/BS4 Calculations on Biphenyls

Biphenyl (1). Rotation about the pivot bond of biphenyl (Figure 1) affords two distinct energy maxima located at 2–1–1′–2′ dihedral angles of 0.0° and 90.0°, and two undistinguished energy minima were obtained with a 37.3° dihedral angle between phenyl rings (in good agreement with experimental observations[5b]). The calculated torsional barriers were 1.28 and 1.60 kcal/mol for the 0° and 90° passing rotation, also in good agreement with the experimental values.

Bridged Biphenyls. 2,2′-Ethano-Bridged Biphenyl 2. The calculated torsional energy surface of 2 (Figure 2),

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(7) IUPAC names for **2**, **3**, **4**, **6**, **7**, and **8** are 9,10-dihydrophenanthrene or [0.2]-*o*-cyclophane, [0.3]-*o*-cyclophane, [0.4]-*o*-cyclophane, 5,6-dihydro-1,10-phenanthroline, 3,3′-trimethylene-2,2′-bipyridine, and 3,3′-tetramethylene-2,2′-bipyridine, respectively.

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Table I. MM2-V4/BS4 Calculated Endocyclic Dihedral Angles and Lengths for Bonds on the Aliphatic Moiety (deg and Å), Relative Energy (kcal/mol), and Symmetry of the Energetically Unique Stationary Points for the Compounds Studied in This Work

		dihedral angle[a]/bond length									
compd.	conf	A	B	C	D	E	F	G	H	rel *E*	sym
2	**T2**	0.0/1.507	0.0/1.405	0.0/1.506	0.0/1.534	0.0/1.506	0.0/1.405			5.25	C_{2v}
	M2	19.2/1.505	0.2/1.404	-37.2/1.508	53.9/1.532	-37.2/1.508	0.2/1.404			0.00	C_2
3	**T3**	0.0/1.530	1.2/1.420	35.4/1.509	-80.8/1.521	80.8/1.521	-35.4/1.509	-1.2/1.420		11.87	C_s
	M3	49.1/1.502	1.5/1.405	-72.2/1.512	42.6/1.536	42.6/1.536	-72.2/1.512	1.5/1.405		0.0	C_2
9	**T9**	0.0/1.528	0.3/1.420	36.8/1.511	-77.3/1.531	77.3/1.531	-36.8/1.511	-0.3/1.420		13.18	C_s
	M9	48.7/1.502	1.5/1.405	-73.2/1.512	42.9/1.546	42.9/1.546	-73.2/1.512	1.5/1.405		0.00	C_2
4	**T4c**	8.8/1.540	-3.0/1.433	60.5/1.523	-68.8/1.529	-24.8/1.525	112.1/1.502	-69.1/1.502	-3.8/1.422	27.62	C_1
	T4b	-74.5/1.497	-1.1/1.403	67.9/1.515	9.2/1.544	-82.4/1.538	9.2/1.544	67.9/1.515	-1.1/1.403	6.05	C_2
	T4a	-68.7/1.498	-3.8/1.403	89.1/1.511	-27.8/1.538	-30.6/1.544	-27.8/1.538	89.1/1.511	-3.8/1.403	7.67	C_2
	M4c	-60.6/1.502	3.3/1.404	92.5/1.508	-43.4/1.534	-66.4/1.540	65.2/1.535	17.6/1.522	-1.4/1.412	3.05	C_1
	M4b	-60.6/1.502	-1.4/1.404	17.6/1.522	65.2/1.535	-66.4/1.540	-43.2/1.534	92.5/1.508	3.3/1.404	3.05	C_1
	M4a	-62.7/1.499	-1.0/1.404	95.5/1.515	-84.7/1.536	53.7/1.539	-84.7/1.536	95.5/1.515	-1.0/1.404	0.00	C_2
6	**T6**	0.0/1.500	0.0/1.401	0.0/1.507	0.0/1.538	0.0/1.507	0.0/1.401			4.72	C_{2v}
	M6	19.0/1.501	0.5/1.402	-36.5/1.509	59.7/1.534	-36.5/1.509	0.5/1.402			0.00	C_2
7	**T7b**	0.0/1.517	-0.9/1.413	-34.4/1.508	79.5/1.525	-79.5/1.525	34.4/1.508	0.9/1.413		7.57	C_s
	T7a	36.7/1.503	-2.4/1.401	-70.8/1.506	82.6/1.531	-20.6/1.538	-27.4/1.520	0.7/1.410		5.45	C_1
	M7b	31.9/1.507	-2.6/1.404	-65.1/1.505	90.9/1.531	-42.5/1.531	-8.2/1.517	-0.1/1.412		5.20	C_1
	M7a	48.8/1.501	1.7/1.404	-72.7/1.511	42.4/1.537	42.4/1.537	-72.7/1.511	1.7/1.404		0.00	C_2
10	**T10b**	0.0/1.516	-0.3/1.419	-35.9/1.510	76.1/1.536	-76.1/1.536	35.9/1.510	0.3/1.412		8.90	C_s
	T10a	37.6/1.503	-2.5/1.401	-70.7/1.505	81.9/1.542	-21.3/1.546	-24.8/1.521	0.7/1.410		6.87	C_1
	M10b	30.4/1.506	-2.1/1.403	-66.0/1.504	88.1/1.542	-39.6/1.542	-7.6/1.519	-0.2/1.412		6.70	C_1
	M10a	48.4/1.500	1.8/1.404	-73.2/1.511	42.7/1.546	42.7/1.546	-73.2/1.511	1.8/1.404		0.00	C_2
8	**T8c**	0.0/1.526	0.2/1.419	65.8/1.511	-90.4/1.532	0.0/1.534	90.4/1.532	-65.8/1.511	-0.2/1.419	21.16	C_s
	T8b	-74.8/1.496	-1.3/1.402	68.5/1.514	8.6/1.545	-81.6/1.539	8.6/1.545	68.5/1.514	-1.3/1.402	5.70	C_2
	T8a	-68.7/1.498	-4.1/1.403	89.6/1.510	-28.4/1.539	-29.4/1.545	-28.4/1.539	89.6/1.510	-4.1/1.403	7.38	C_2
	M8c	-60.4/1.501	3.1/1.403	92.2/1.508	-43.0/1.534	-66.6/1.540	65.0/1.535	18.0/1.521	-1.8/1.411	3.02	C_1
	M8b	-60.4/1.501	-1.8/1.411	18.0/1.521	65.0/1.535	-66.6/1.540	-43.0/1.534	92.2/1.508	3.1/1.403	3.02	C_1
	M8a	-62.7/1.498	-1.1/1.403	95.5/1.514	-84.2/1.537	53.2/1.540	-84.2/1.537	95.5/1.514	-1.1/1.403	0.00	C_2

[a] Endocyclic dihedral angles are given following a clockwise movement starting from the pivot bond (i.e., angle A is that for 1–1′, angle B is that for 1′–2′, and so on).

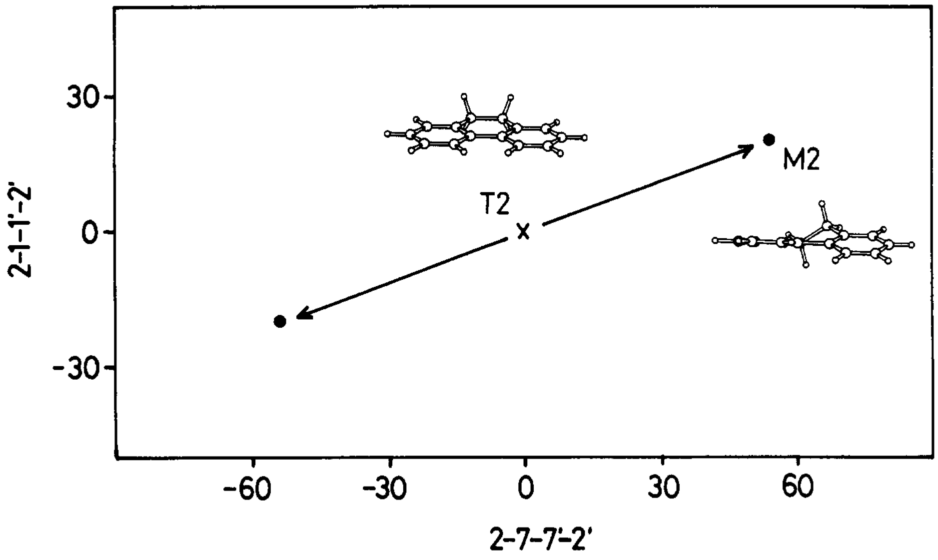

Figure 2. Schematic representation of the torsional energy surface of 2 as a function of the 2–1–1′–2′ and 2–7–7′–2′ dihedral angles. The transition state is represented by ×, energy minima by ●, and arrows show the minima connected by the transition state.

obtained by driving the 2–1–1′–2′ and 2–7–7′–2′ dihedral angles, presents only one saddle point, **T2**, and two symmetrically disposed energy minima, **M2** and **M2′**. The transition state is completely planar, all bonds are eclipsed, and it has C_{2v} symmetry, while both energy minima have C_2 symmetry. From the energy values a barrier of 5.25 kcal/mol can be obtained. Compound **2** thus presents free conformational behavior.

2,2′-Propano-Bridged Biphenyl 3. Compound **3** presents a larger degree of mobility. Figure 3 shows a schematic representation of its torsional energy surface as a function of 2–7–8–7′ and 2′–7′–8–7 dihedral angles. According the MM2-V4 calculations, **3** presents two isoenergetic energy maxima, **T3** and **T3′**, interconnecting two also isoenergetic energy minima, **M3** and **M3′**. Energy maxima present the 2–1–1′–2′ dihedral angle equal to 0.0° while the minima have C_2 symmetry and no coplanarity between phenyl rings. The calculated barrier for the interconversion between minima is 11.87 kcal/mol.

8,8-Dimethyl 2,2′-Propano-Bridged Biphenyl 9. The presence of two geminal methyl groups does not affect the torsional energy surface shape nor the geometrically more important features of the parent compound, **3**. Only the relative energy for the different conformations is affected by this substitution (Table I). Its torsional energy surface contains one pair of enantiomeric energy maxima, **T9** and

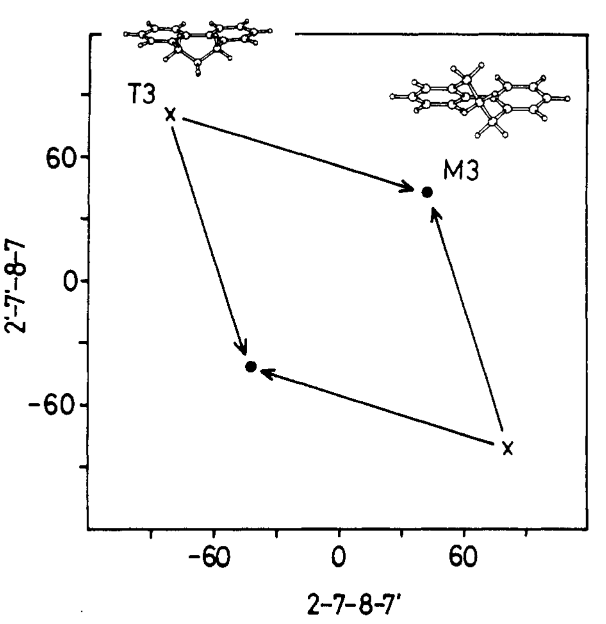

Figure 3. Schematic representaion of the torsional energy surface of **3** as a function of the 2–7–8–7′ and 2′–7′–8–7 dihedral angles. Transition states are represented by ×, energy minima by ●, and arrows show the minima connected by each transition state.

T9′, and another pair of minima, **M9** and **M9′**. The calculated barrier of interconversion for this compound is 13.18 kcal/mol.

2,2′-Butano-Bridged Biphenyl 4. The presence of a larger aliphatic ring in **4** makes the conformational behavior of this molecule more complicated than those of the previously studied compounds. A clear picture of the conformational behavior of **4** was obtained after calculating three different torsional energy surfaces. Compound **4** exists in two isoenergetic minima, **M4a** and **M4a′**, having C_2 symmetry in its ground state wherein the 2–1–1′–2′ dihedral angle takes values of ±62.7°. These conformers pass through transition states, **T4a** and **T4a′**, 7.67 kcal/mol higher than the global minima and are converted into other highly energetic minima, **M4b** and **M4b′** (3.05 kcal/mol above the global minima), belonging to a pseudorotational circuit of conformations having two pairs of energetically equivalent minima, **M4b** and **M4c**, and two pairs of different maxima, **T4b** and **T4c**, (figure 4).

The calculated transition states for the interconversion of the two global minima, **T4c** and **T4c′**, having C_1 symmetry and produced a rotational barrier of 27.62 kcal/mol. Figure 4 also contains the representation of all isoenergetic stationary points of **4**.

Discussion on Biphenyls. The experimentally determined conformational properties[5b] of biphenyl, **1**, were correctly reproduced by our calculations. It should be noted here that only a few experimental determinations have been made for the conformational aspects of bridged biphenyls. Mislow[11] already studied this class of compounds in 1964 and gave estimations for the interconversion barrier heights. The barrier for **2** and **3** were estimated to be 4 and 13 kcal/mol, respectively. The MM2-V4 calculated barriers for these compounds (5.25 and 11.87 kcal/mol, respectively) are in good agreement with these values. Moreover, Rebek[12] recently determined the interconversion barrier fo the 8,8-bis(carboxymethyl)-**3** to be 14.6 kcal/mol. The calculated barrier for the 8,8-dimethyl-**3**, **9**, that can be considered as a model of Rebek's compound, is 13.18 kcal/mol, again in good agreement with the experimental result. Analysis of calculated transition-state geometries indicates a strong $H_6/H_{6'}$ nonbonded interaction in ethano- and propano-bridged compounds (l = 2.05 Å in **2** and 1.87 Å in **3**). Clearly, the presence of two double bonds in the six-membered ring of **2** produces a higher annular tension in the ground state than in the seven-membered ring of **3**.

No experimental or calculated data on the barriers of **4** have been reported to our knowledge, preventing meaningful comparison with our results. However, Thummel[13] studied the 2,2′-bipyridinium salt analogue of **4** by NMR experiments and found it rigid on the NMR time scale. Although the effect of two positively charged N atoms on the barrier heights is not clear, our results do not contradict those from Thummel. Compound **4** has a calculated barrier of 27.62 kcal/mol. The transition state again presents a 2–1–1′–2′ dihedral angle near 0° (actually 8.8°), another dihedral angle (7–8–8′–7′) is nearly eclipsed (−24.8°), and one more almost produces eclipsing between C–C and C–H bonds (2–7–8–8′). This compound would exist as a mixture of two undistinguished enantiomeric conformers. By placing one simple methyl group in any of the phenyl rings we could turn it into conformational enantiomers. If the substituent was placed onto one of the aliphatic carbon atoms, the enantiomers then would become diastereomers.

Both phenyl rings interact strongly through close hydrogen–hydrogen contacts in all transition states, and as a consequence they are considerably deformed. It is known that parameters for the mechanical treatment of benzene within MM2 are too soft and they allow phenyl rings to deform very easily. Thus, it would be interesting to recalculate this barrier height when new phenyl ring parameters would be available for the MM2 scheme.

MM2-V4 Calculations on 2,2′-Bipyridines

In the conformational study of **5**, **6**, **7**, and **8**, the same methodology as in the previous section was applied. Again, no molecular mechanics studies are described in the literature although several molecular orebital calculations on these compounds have been published.[14] From the experimental side, only a few articles dealing with conformational determinations on 2,2′-bipyridines can be found. Thus, this work provides an extremely important basis for forthcomming experimental or theoretical results.

2,2′-Bipyridine (5). As already described,[15] compound **5** presents a conformational behavior quite different from that of biphenyl (**1**). The presence of the two N atoms in the ortho/ortho′ positions substantially affects the geometry of this molecule. Thus, upon one-bond drive rotation of the 1–2–2′–1′ angle from 0° to 180°, two energy maxima were detected a 0.0° and 73.8°; two energy minima also appeared at angle values of 42.0° and 180.0°. The relative energies for these stationary points were 7.08, 6.47, 5.99, and 0.0 kcal/mol, respectively. These values agree well with ab initio calculations[14b] and also with the experi-

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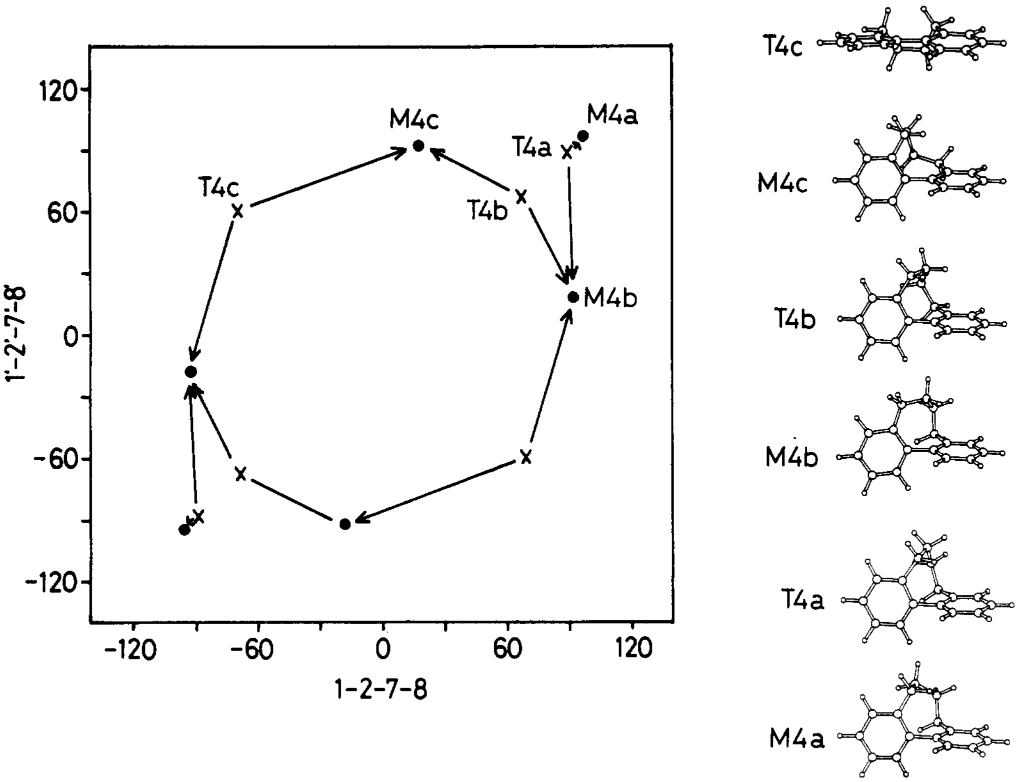

Figure 4. Schematic representation of the torsional energy surface of 4 as a function of the 1–2–7–8 and 1′–2′–7′–8′ dihedral angles. Transition states are represented by ×, energy minima by ●, and arrows show the minima connected by each transition state.

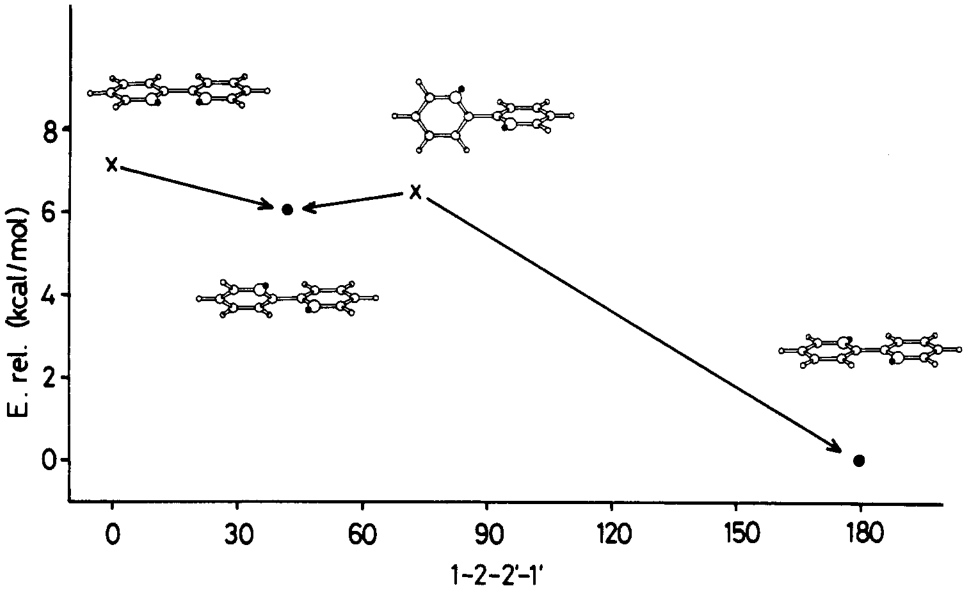

Figure 5. Energy variation and isoenergetic stationary points obtained in the MM2-V4 calculations on the rotation of the pivot bond of 5. Nitrogen lone pairs are shown as filled circles.

mentally preferred s-trans conformer and the suggested detection of some s-cis-like conformer.[14a] Figure 5 contains the drawing of the energetically equivalent stationary points of 5 as well as the energy variation obtained in the pivot bond rotation.

Bridged Bipyridines. 3,3′-Ethano-2,2′-bipyridine (6). The calculated torsional energy surface of 6 contains two enantiomeric minima, **M6** and **M6′**, connected by one transition state, **T6** (Figure 6). The saddle point has a completely planar structure with fully eclipsed bonds and is 4.72 kcal/mol above the minima. Energy minima have a dihedral angle of ±19.0° between both aromatic ring planes.

3,3′-Propano-2,2′-bipyridine (7). The calculated torsional energy surface of 7 presents a pseudorotational circuit having two enantiomeric pairs of transition states, **T7a**/**T7a′** and **T7b**/**T7b′**, and two more pairs of energy minima, **M7a**/**M7a′** and **M7b**/**M7b′** (Figure 7). The global minima **M7a**/**M7a′**, have C_2 symmetry and dihedral angles of ±48.8° between both aromatic rings. These minima pass through saddle points, **T7a** and **T7a′**, 5.53 kcal/mol above them and fall into other more energetic minima, **M7b** and **M7b′** (5.20 kcal/mol higher than the global minima). After crossing the higher transition states, **T7b** and **T7b′** (7.57 kcal/mol), the pseudorotation continues. Figure 7 contains the representation of the

Table II. $H_6/H_{6'}$ **or** $LP_1/LP_{1'}$ **Nonbonded Distances (*r*, Å),** H_6**–C6• • •C6′–**$H_{6'}$ **or** LP_1**–N1• • •N1′–**$LP_{1'}$ **Pseudodihedral Angles (*w*, deg), and Selected Bond Angles (deg) (C1–C6–**H_6 **or C2–N1–**LP_1**, C5–C6–**H_6 **or C6–N1–**LP_1**, and C1′–C1–C6 or C2′–C2–N1; O1, O2, and O3) for Global Energy Minima and Transition States of Bridged Biphenyls (2–4 and 9) and Bipyridyls (6–8 and 10) as Calculated by MM2-V4**

	2		3		9		4		6		7		10		8	
	T2	**M2**	**T3**	**M3**	**T9**	**M9**	**T4c**[a]	**M4a**	**T6**	**M6**	**T7b**	**M7a**	**T10b**	**M10a**	**T8c**	**M8a**
r	2.05	2.19	1.87	2.58	1.87	2.58	1.83	2.83	2.17	2.32	1.85	2.62	1.86	2.62	1.75	2.78
w	0.0	28.4	0.0	65.4	0.0	65.2	22.0	80.6	0.0	29.3	0.0	67.0	0.0	67.0	0.0	83.3
O1	122.0	121.3	123.7	120.4	123.8	120.4	120.4[b]	120.2	120.4	120.6	119.5	120.5	119.5	120.5	119.1	120.5
O2	115.8	117.7	110.4	119.2	110.5	119.1	109.0[c]	119.3	119.8	120.3	117.6	120.4	117.7	120.5	116.4	120.4
O3	122.2	122.6	118.6	120.1	118.6	120.2	118.5[d]	118.7	118.3	119.5	112.9	118.0	113.0	118.1	111.1	116.8

[a] Nonsymmetrical conformation. [b] C1′-C6′-$H_{6'}$ = 124.1°. [c] C5′-C6′-H_6′ = 108.4°. [d] C1-C1′-C6′ = 115.1°.

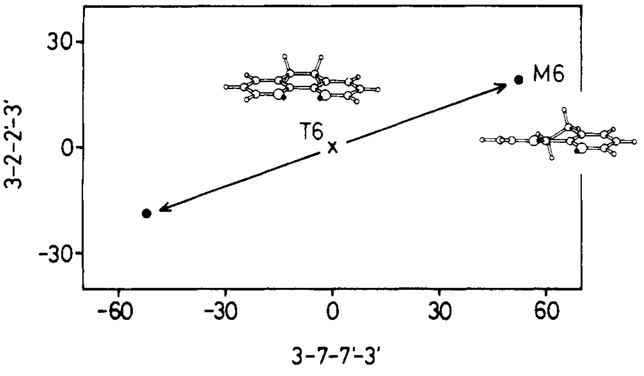

Figure 6. Schematic representation of the torsional energy surface of 6 as a function of the 3–2–2′–3′ and 3–7–7′–3′ dihedral angles. The transition state is represented by ×, energy minima by <<ftd, and arrows show the minima connected by the transition state. Nitrogen lone pairs are shown as filled circles.

isoenergetic stationary points of 7, as well as the schematic representation for the pseudorotational circuit as the function of the 3–7–8–7′ and 3′–7′–8–7 dihedral angles.

8,8-Dimethyl-3,3′-propano-2,2′-bipyridine (10). The conformational energy surface of this compound is just the same as that for 7. It contains a closed circuit having two pairs of enantiomeric maxima, **T10a**/**T10a′** and **T10b**/**T10b′**, and minima, **M10a**/**M10a′** and **M10b**/**M10b′**. The energy barrier for the pseudorotational process is calculated to be 8.90 kcal/mol.

3,3′-Butano-2,2′-bipyridine (8). The conformational behavior of 8 is simpler than that if its hydrocarbon analogue 4. Compound 8 exists as a mixture of two enantiomeric conformers, **M8a** and **M8a′**, which are converted through several energy maxima and minima. Global energy minima, **M8a**/**M8a′**, have dihedral angles of ±62.7° between pyridine rings and have C_2 symmetry. A family of minima, **M8b**/**M8b′** and **M8c**/**M8c′**, was found 3.02 kcal/mol above **M8a**/**M8a′**, having angles of ±60.4° between the aromatic rings. The interconversion barrier between global minima, **T8c**/**T8c′**, is 21.16 kcal/mol and belongs to conformations with coplanar pyridine rings having C_s symmetry.

Figure 8 shows the schematic representaion for the torsional energy surface of 8 as the function of the 2–3–7–8 and 2′–3′–7′–8′ dihedral angles and the conformations for the isoenergetic stationary points.

Discussion on 2,2′-Bipyridines. No experimentally determined barrier is reported for 5. The ab initio calculated variation of energy versus the rotation of the pivot bond[14b] has been correctly reproduced using our approach.[6b]

Only one determination for the interconversion barriers in bridged 2,2′-bipyridines has been recorded in the literature. Compound 6 is experimentally very flexible[13] and our calculated interconversion barrier is only 4.72 kcal/mol.

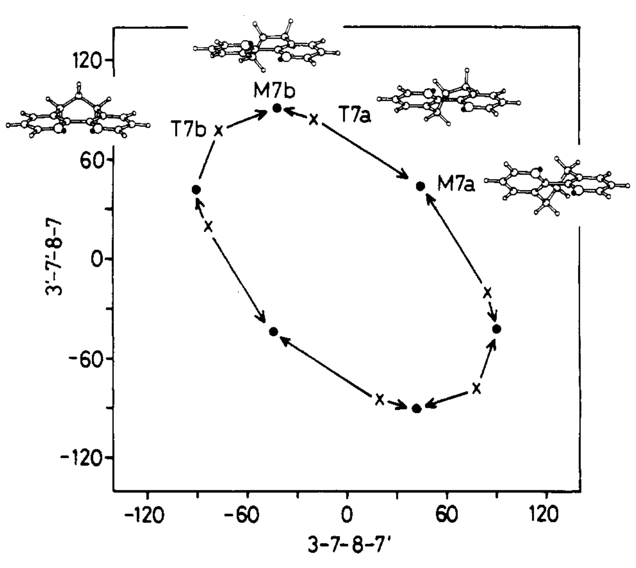

Figure 7. Schematic representation of the torsional energy surface of 7 as a function of the 3–7–8–7′ and 3′–7′–8–7 dihedral angles. Transition states are represented by ×, energy minima by ●, and arrows show the minima connected by each transition state. Nitrogen lone pairs are shown as filled circles.

Compound 7 is also mobile as deduced from its NMR spectrum.[13] Our calculated barrier (7.57 kcal/mol) perfectly agrees with this experimental observation. Nevertheless, Rebek stated that the 8,8-bis(carboxymethyl)-7 shows in interconversion barrier of 11–12 kcal/mol,[12] while our calculations on a model compound (the 8,8-dimethyl-7, 10) presents only 8.90 kcal/mol for a similar barrier. Compound 8 is conformationally rigid and has C_2 symmetry according to ^1H NMR data.[13] The calculated interconversion barrier (21.16 kcal/mol) and geometry for the energy minimum agree with those observations.

It is worth noting here the dramatic effect that the replacement of the two H_{ortho} for the two lone pairs of electrons (LP) exerts on the barrier height. The 5.80 kcal/mol of increment ($\Delta\Delta H^{*}$) when passing from 1 to 5 is reasonable, and it is a consequence of having two LP/H_{ortho} interactions in the energy minimum of 5, while the energy minimum of 1 is already geometrically very close to its transition state. The small $\Delta\Delta H^{*}$ between 2 and 6 (only 0.53 kcal/mol) indicates that the $H_6/H_{6'}$ and $LP_1/LP_{1'}$ interactions have low contribution to the barrier height as the almost unchanged bond angles around the interacting H or LP also suggest (Table II).

The geometries for both the energy minimum and the transition state within a pair of equally bridged biaryls are very similar. Nevertheless, there is a large decrease in the barrier height when going from a biphenyl to the corresponding bipyridine except for the enthano-bridged 2 and 6. The replacement of $H_6/H_{6'}$ by $LP_1/LP_{1'}$ interactions in the bipyridine transition states must be the reason.

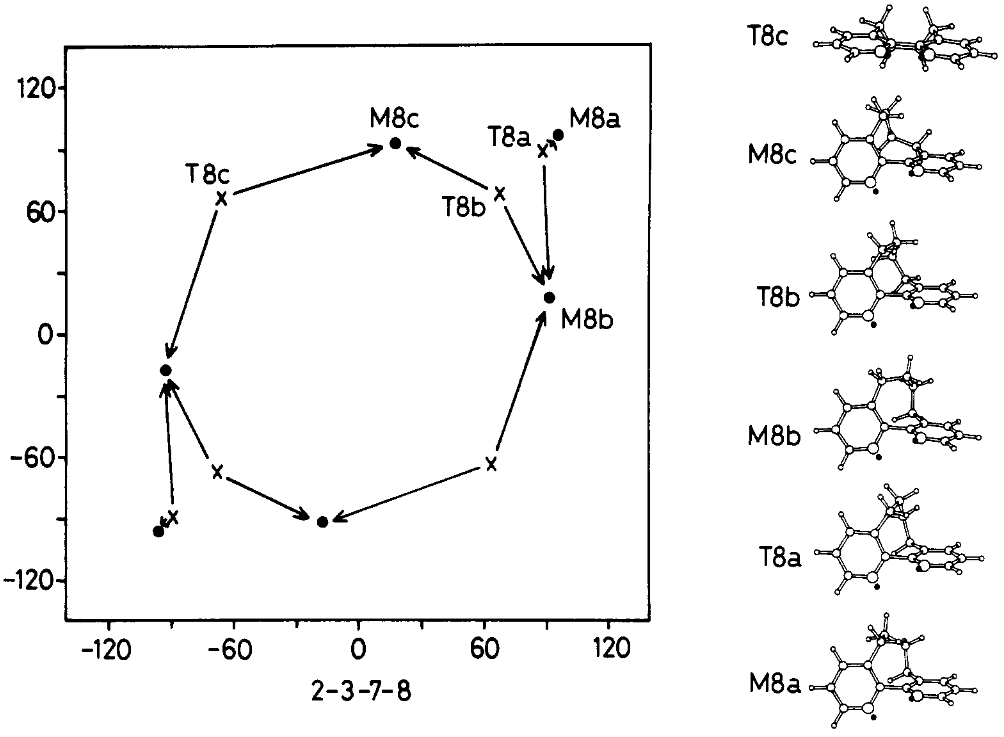

Figure 8. Schematic representation of the torsional energy surface of 8 as a function of the 2–3–7–8 and 2′–3′–7′–8′ dihedral angles. Transition states are represented by ×, energy minima by ●, and arrows show the minima connected by each transition state. Nitrogen lone pairs are shown as filled circles.

There is no difference between the behavior of the trimethylene-bridged compounds, **3**, and **7**, with their corresponding 8,8-dimethyl derivatives, **9** and **10**, except for the barriers heights which are slightly higher for the later. An identical $\Delta\Delta H^{\ddagger}$ is obtained (4.3 kcal/mol) when passing from **3** to **7**, or from **9** to **10**, denoting the importance of the N atoms on the barrier. The C5–C6–H or C6–N1–LP bond angles are much smaller in the global transition states than in the global energy minima. Their value is substantially reduced (about 9°) in **3** and **9**, while is only slightly decreased (about 3°) in **7** and **10** (Table II). The $LP_1/LP_{1'}$ interaction is again less energetic than the corresponding $H_6/H_{6'}$. It is interesting to note that compounds **4** and **8** have the highest calculated barriers among all the studied compounds. These two products contradict the general idea of "the larger the ring the greater the flexibility". The presence of the tetramethylene bridge forces the substituents in 6,6′ for biphenyl and 1,1′ for bipyridines to become very close. Hydrogens interact much stronger, as in **4** (2.2 kcal/mol and $r = 1.83$ Å), than LP as in **8**. This interaction is so severe that it produces the lack of symmetry for the transition state of **4** as well as the largest deformation of bond angles (about 10° in **4** and about 4° in **8**) (Table II). A fully symmetrical transition state would have extremely short H/H contacts (less than 1.8 Å).

Another important feature to be considered in the bipyridyl series is the complexing capability of each compound according to our calculations. Two geometrical factors mainly control chelate formation: the nonbonded LP/LP′ distance and the pseudodihedral LP–N⋯N′–LP′ angle. All our studied bipyridyls are able to form chelates if the LP/LP′ distance is considered (Table II).[16] However, the situation drastically changes when the pseudodihedral angle is considered. Clearly, those bipyridyls having a smaller LP–N⋯N′–LP′ angle (larger planarity) in their ground state will be the best ligands for chelates (i.e. **6**). Nevertheless, in considering complexing capabilities thermodynamic considerations must be also taken into account. The parent compound, **5**, easily forms chelates with metal cations in spite of having the global minimum geometry not well prepared (LPs are antiperiplanar). The $\Delta G°$ liberated when the chelate is formed largely overcomes the 7.08 kcal/mol separating the s-cis and s-trans conformations of **5**. Compounds **7** and **10** can also be good candidates as effective ligands because their transition states are largely planar (Table II) and at only 7–8 kcal/mol from the global minimum. Since entropy changes are frequently the *main driving force* for chelate formation,[17] even **8**, having the worst geometrical requirements and the largest $\Delta H^{\ddagger}$, may finally be a reasonably good ligand and form stable chelates.

Conclusions

MM calculations on bridged biphenyls and 2,2′-bipyridines have been carried out using a modified MM2 force field containing the V4 torsional term (MM2-V4). The agreement between experimentally available results and theoretical calculations undertaken in this work is good. Gound-state conformations of equivalently bridged biaryls are very similar. Only transition-states geometries and barrier heights change when comparing biphenyls to bipyridines as a consequence of the presence of H/H and LP/LP interactions, respectively. Biphenyls are less flexible than bipyridyls, and the contribution of the H/H′ interaction on the barrier height can be estimated to be

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[16] In ethylenediamine, the energy minima having a geometry suitable to form chelates (*-sp*/*-sp*/*+sp* and symmetry related ones) present a LP/LP′ nonbonded distance of 2.96 Å according to MM2 calculations. It is very well known that this compound is a very good ligand and forms stable chelates.

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of 4–6 kcal/mol in this class of compounds.

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Registry No. 1, 92-52-4; 2, 776-35-2; 3, 1015-80-1; 4, 1082-12-8; 5, 366-18-7; 6, 97919-82-9; 7, 97919-83-0; 8, 97919-84-1; 9, 125568-48-1; 10, 125568-49-2.

Nucleophilic Addition of Phosphines to Carbonyl Groups. Isolation of 1-Hydroxy Phosphonium and 1-(Trimethylsiloxy) Phosphonium Salts and the Crystal Structure of (1-Hydroxy-1-methylethyl)triethylphosphonium Bromide

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1-Hydroxy phosphonium salts and 1-(trimethylsiloxy) phosphonium salts can be isolated by nucleophilic addition of a small basic phosphine (PMe_3 or PEt_3) to the carbonyl carbon of aldehydes or ketones in the presence of Br_2–acetone (a source of anhydrous HBr), anhydrous acids, or chlorotrimethylsilane as trapping agents. The crystal structure of $[(CH_3)_2C(OH)(PEt_3)]Br$, Ib, was determined through X-ray diffraction. Ib crystallizes in the monoclinic system, space group $P2_1/n$ with lattice constants $a = 7.304$ (3) Å, $b = 12.004$ (4) Å, $c = 14.164$ (5) Å, $\beta = 93.33$ (3)°, and $Z = 4$. Least-squares refinement of the structure led to a R (R_w) factor of 0.042 (0.043) for 732 unique reflections of $I > 3\sigma(I)$ and for 62 least-squares variables. The phosphorous atom and all carbon atoms adopt sp^3 hybridization. The C–O bond distance of 1.429 (10) Å indicates a normal C–O single bond; however, the P–C bond to the carbonyl derived carbon (1.877 (10) Å) is significantly longer than the other P–C bonds (1.80 (1) Å av).

Introduction

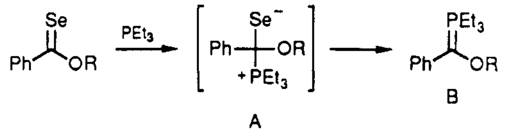
Phosphonium salts are usually prepared from the reaction between phosphines and alkyl halides, and these salts are readily transformed to phosphorus ylides by treatment with base.[1] (2-Hydroxyalkyl)phosphonium salts are an important class of compounds because of their use in the mechanistic investigation of the Wittig reaction and their versatile synthetic utility.[1] Recently a general synthesis of (2-hydroxyalkyl)-, (3-hydroxyalkyl)-, and (4-hydroxyalkyl)phosphonium salts was reported from the reaction between triphenylphosphine and cyclic ethers in the presence of strong acids.[2] Tertiary phosphines are also known to attack at unsaturated carbon atoms and add smoothly to unsaturated aldehydes and esters in the presence of strong mineral acids (eqs 1, 2, and 3).[3] Hansen

$$Ph_3P + CH_2{=}CHCOOH + HBr \rightarrow [Ph_3PCH_2CH_2COOH]Br \quad (1)$$

$$Ph_3P + PhC{\equiv}CCOOH + HCl \rightarrow [Ph_3PCPh{=}CHCOOH]Cl \quad (2)$$

$$Ph_3P + MeOOCC{\equiv}CCOOMe + HBr \rightarrow [MeOOCCH{=}C(COOMe)PPh_3]Br \quad (3)$$

reported the reaction between *O*-alkyl selenoesters and PEt_3, which includes an intermediate A from nucleophilic attack of the phosphine on a selenoyl carbon;[4] however, this intermediate was not isolated (eq 4). Wittig and Rieber reacted solutions of trimethylphosphonium methylide with benzophenone and isolated a low yield of impure (2,2-diphenyl-2-hydroxyethyl)trimethylphosphonium iodide after quenching with acid and potassium iodide.[5]



(4)

$$(CH_3)_3P{=}CH_2 + (C_6H_5)_2CO \xrightarrow[H^+]{KI} [(CH_3)_3PCH_2C(OH)(C_6H_5)_2]I \quad (5)$$

It has also been difficult to obtain structural data for tetrahedral intermediates formed by nucleophilic addition to a carbonyl carbon.[1a,7] Weak amine–carbonyl interac-

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