JOC Article

Directed Ring-Opening of 1,5-Dioxaspiro[3.2]hexanes: Selective Formation of 2,2-Disubstituted Oxetanes

Rosa Taboada, Grace G. Ordonio, Albert J. Ndakala, and Amy R. Howell*

Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060

Paul R. Rablen

Department of Chemistry, Swarthmore College, Swarthmore, Pennsylvania 19081-1397

amy.howell@uconn.edu

Received October 11, 2002

1,5-Dioxaspiro[3.2]hexanes undergo ring-opening reactions with many heteroatom nucleophiles to provide α-substituted-β′-hydroxy ketones. However, certain Lewis acidic nucleophiles provide 2,2-disubstituted oxetanes. Herein, the results of reactions of 3-phenyl-1,5-dioxaspiro[3.2]hexane with a variety of nitrogen-containing heteroaromatic bases are reported. There appears to be a correlation between the pK_a of the nucleophile and the reaction outcome with more acidic nucleophiles providing 2,2-disubstituted oxetanes. Moreover, the mode of ring opening can be directed toward the substituted oxetane by the addition of a Lewis acid. These results are rationalized by calculation of stationary points on the potential energy surfaces for the various possible reaction pathways using ab initio molecular orbital methods.

Introduction

We have been interested in the synthesis and exploitation of novel, strained heterocyclic systems.[1−5] We developed the first general synthesis of 1,5-dioxaspiro[3.2]-hexanes (e.g. **1**),[6] and initial exploration of the reactivity of **1** revealed a dichotomy in reaction outcomes (Figure 1).[7] While neutral and anionic heteroatom nucleophiles gave exclusively α-substituted-β′-hydroxy ketones **2**, DIBALH and Me_3Al provided the 2,2-disubstituted oxetanes **3**. The latter results were rationalized by invoking the coordination of the Lewis acidic aluminum center to the epoxide oxygen with possible participation of oxonium ion **4**. Subsequent reaction with the nucleophilic species would provide the oxetane-intact products. $TMSN_3$ also gave the corresponding 2,2-disubstituted oxetane **5** (see Table 1). We postulated that silicon was serving as the Lewis acidic center in this case. We have tried to gain a greater understanding of factors that influence the reaction pathway of the dioxaspirohexanes. Here we report the trends seen in reactions with neutral, anionic, and silicon-linked heteroaromatic compounds and with carboxylic acids. Moreover, we try to rationalize reaction outcomes by calculating the potential energy surfaces for the possible reaction pathways in simple model systems using ab initio molecular orbital methods.

Results and Discussion

Since $TMSN_3$ gave the oxetane-intact product **5** (see Table 1), we decided to ascertain if other TMS-linked nucleophiles would provide the same outcome. The first compounds examined were 1-(trimethylsilyl)imidazole and 1-(trimethylsilyl)-1*H*-benzotriazole. Imidazole itself had given ring-opened product **6**. Although TMS-benzotriazole gave the oxetane product **10**, TMS-imidazole led to the same result (**6**) as neutral imidazole. Initially, we rationalized that the nucleophilicity of imidazole outweighed the potential for silicon to serve as a Lewis acid. The importance of silicon as a Lewis acid was again called into question when we discovered that benzotriazole itself gave oxetane **10**. When benzotriazole was deprotonated, the ring-opened product **11** was the major one. We decided to examine a range of heteroaromatic compounds to see if any trends emerged. The results are shown in Table 1.

Although pyrrole and indole did not react with **1**, pyrazole, 1*H*-1,2,4-triazole, and 1-(trimethylsilyl)-1,2,4-triazole gave ring-opened products **7** and **8**. However, with the 1,2,4-triazoles, ^{1}H NMR of the crude reaction mixtures revealed small amounts (∼10%) of oxetane-intact products. 1*H*-1,2,3-Triazole gave oxetane **9**, although, again, ^{1}H NMR of the crude reaction mixture showed a small quantity (<5%) of the alternate pathway of complete ring opening. Tetrazole produced oxetane **12**.

(1) Dollinger, L. M.; Ndakala, A. J.; Hashemzadeh, M.; Wang, G.; Wang, Y.; Martinez, I.; Arcari, J. T.; Galluzzo, D. J.; Howell, A. R.; Rheingold, A. L.; Figuero, J. S. *J. Org. Chem.* **1999**, *64*, 7074−7080.
(2) Dollinger, L. M.; Howell, A. R. *J. Org. Chem.* **1998**, *63*, 6782−6783.
(3) Hashemzadeh, M.; Howell, A. R. *Tetrahedron Lett.* **2000**, *41*, 1855−1858.
(4) Wang, G.; Wang, Y.; Arcari, J. T.; Howell, A. R.; Rheingold, A. L.; Concolino, T. *Tetrahedron Lett.* **1999**, *40*, 7051−7053.
(5) Ndakala, A. J.; Hashemzadeh, M.; So, R. C.; Howell, A. R. *Org. Lett.* **2002**, *4*, 1719−1722.
(6) Ndakala, A. J.; Howell, A. R. *J. Org. Chem.* **1998**, *63*, 6098−6099.
(7) Howell, A. R.; Ndakala, A. J. *Org. Lett.* **1999**, *1*, 825−827.

10.1021/jo0206465 CCC: $25.00
Published on Web 01/23/2003

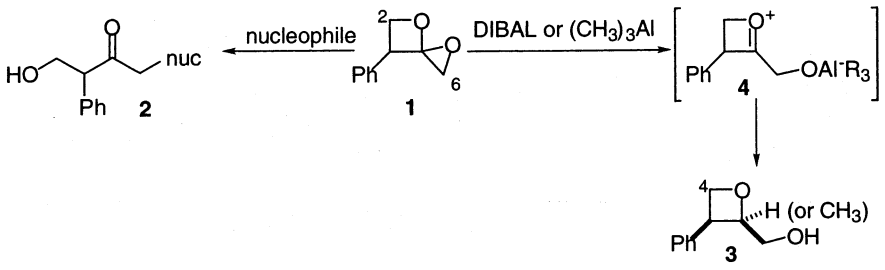
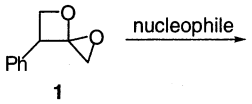
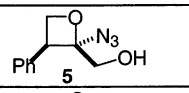
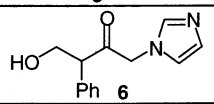
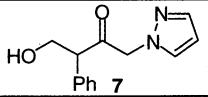
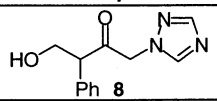
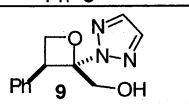
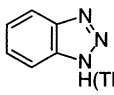
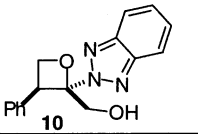
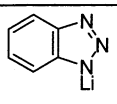
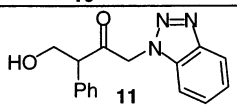
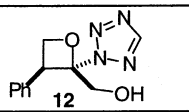


FIGURE 1. Reactions of 1,5-dioxaspiro[3.2]hexanes.

TABLE 1. Reaction of 1 with Heteroatom Nucleophiles



Nucleophile	pK_a	Product[a]	% Yield[b(c)]
$TMSN_3$	-	 **5**	56
	14.5	 **6**	50 (28)
	14.2	 **7**	90
	10.3	 **8**	45 (55)
	9.3	 **9**	59
	8.2	 **10**	45 (40)
	-	 **11**	27
	4.9	 **12**	42

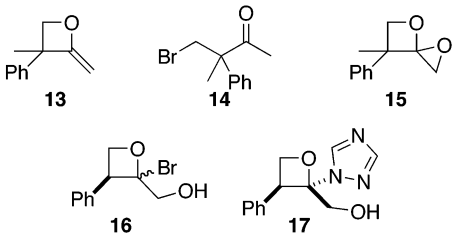
[a] The relative stereochemistry of the oxetane-intact products is assigned on the basis of our prior studies (ref 7). [b] Isolated yields. [c] Yields in parentheses are isolated yields for reaction with TMS-linked nucleophile.

The yields in Table 1 are quite variable and deserve some comment. The reaction of imidazole with **1** was as clean, based on crude ^{1}H NMR, as that of pyrazole. Separation from unreacted imidazole was difficult. The reactions of the two monocyclic triazoles and tetrazole were relatively clean as judged by crude ^{1}H NMR. There were no other major dioxaspirohexane-related products. Minor byproducts were sometimes seen, but none was consistently apparent or isolable. The yields were based on isolation of pure product, and in each case there were some product containing fractions that were discarded because they were not clean. The reactions with benzotriazole were less clean. In some reactions it appeared that the C2 epimer of **10** was present, as well as an unidentified ring-opened product. The minor products could not be separated by column chromatography. On the basis of crude ^{1}H NMR, in some reactions, these additional products may have represented up to 30% of the material. The reactions with the deprotonated benzotriazole were always messy, based on crude ^{1}H NMR, whether the anion was generated with n-BuLi or LDA and with a variety of solvents and reaction temperatures. There was always some **10**, but **11** was clearly the major product. Other byproducts could not be identified.

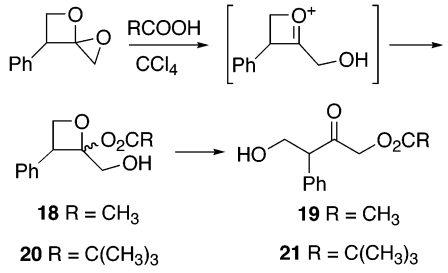
From the results in Table 1, it is apparent that the more acidic compounds provided oxetane-intact products.

In addition, silicon does not appear to be an effective Lewis acid for directing the formation of oxetanes. Nevertheless, the results do not rule out silicon serving as a Lewis acid in the cases where the oxetane remains. Since silicon did not appear to be the optimum choice of Lewis acid, other Lewis acids were examined.

We had previously found that when 2-methyleneoxetane **13** was exposed to $MgBr_2$, β-bromo ketone **14** was isolated in 85% yield.[8] When dioxaspirohexane **15** was treated with $MgBr_2$, a 2:1 mixture of diastereomers **16** was observed by ^{1}H NMR.[9] Consequently, a magnesium salt with a nonnucleophilic counterion, $Mg(OTf)_2$, was chosen. A mixture of dioxaspirohexane **1**, 1,2,4-triazole (which had given predominantly the ring-opened product **8**), and $Mg(OTf)_2$ provided oxetane **17** (45%), as a mixture of diastereomers (2:1; major one shown). No ring-opened product **8** was observed in a ^{1}H NMR of the crude reaction mixture, demonstrating that reaction outcome can be controlled.



The result with tetrazole, a compound with a pK_a similar to those of carboxylic acids, led us to examine protic acids. Reaction of **1** with acetic acid gave α-acetoxy ketone **19** (93%) in excellent yield. However, when a reaction was run in an NMR tube in carbon tetrachloride, the presence of some oxetane-intact product **18** (**18:19** = 1:3) was evident at 5 min.[10] Only ring-opened product **19** was observed at 15 min. Recognizing that intramolecular acyl transfer is likely responsible for the conversion of **18** to **19**, we decided to see if the rate of transfer could be retarded by steric effects. Indeed, 0.5 h after the addition of pivalic acid to a solution of dioxaspirohexane **1** in carbon tetrachloride, ^{1}H NMR showed oxetane **20** and ketone **21** to be present in a 1:1 ratio. After 4 h only ring-opened **21** was observed. These results support the intermediacy of an oxetane oxonium ion and suggest that protic acids can also promote its formation.



In thinking about the overall reactivity observed with the dioxaspirohexanes, it is not surprising that the ring-opening reactions occur exclusively at the oxirane ring. In general, oxiranes are opened under less stringent conditions than are oxetanes. Moreover, that dioxaspirohexanes would open with greater facility than simple epoxides is not surprising, especially given the well-described chemistry of dioxaspiropentanes.[11] The isolation of oxetane-intact products was not anticipated. Nevertheless, the results from these studies confirm that oxetane products can be formed in a reasonably predictable fashion. However, in proton-transfer processes (e.g. the conversion of **1** to **18**), products that would appear to result from protonation of the oxetane ring and subsequent reaction are not observed, although simple oxetanes are more basic than oxiranes (vide infra). Thus, we decided to examine the possible pathways of reaction with nucleophiles and upon protonation using ab initio electronic structure calculations.

Given the limitations of current computer technology, it was not feasible to perform electronic structure calculations that corresponded exactly to the experimental reaction conditions, including all substituents, counterions, and the solvent. However, we hoped to confirm our essential understanding of the reactions by computing the possible reaction pathways for simplified model systems in the gas phase. Since our rationalization of the experimental findings does not invoke solvent effects, counterion effects, or substituent effects, these simple model systems are in fact quite appropriate to examine. For the substrate, we have used the parent 1,5-dioxaspiro-[3.2]hexane **22**. As a simple representative nucleophile acting in the absence of an acid, we have chosen methoxide ion. To study the consequences of proton transfer from an acid, we have used protonated acetone as a representative proton donor. While the latter might at first seem an odd choice, it is necessary to choose a relatively thermoneutral proton-transfer reaction in order to have a chance of observing a transition state in the gas phase, and the reaction with protonated acetone meets this requirement.

The experimental results suggest that in the absence of a suitable acid catalyst, nucleophilic attack occurs at the less hindered carbon of the oxirane ring of 1,5-dioxaspiro[3.2]hexanes such as **1**, ultimately yielding fully ring-opened products such as **2**. To confirm this hypothesis, the gas-phase reaction pathways of the parent system **22** with methoxide ion as a representative nucleophile were studied.

22

Table S1 in the Supporting Information lists the energies of the structures corresponding to the stationary points along the four possible trajectories for addition of methoxide to **22**. The two pathways corresponding to attack at the spiro carbon, leading to cleavage of either the oxirane or the oxetane ring (Figures S1 and S2 in

(8) Wang, Y.; Bekolo, H.; Howell, A. R. *Tetrahedron* **2002**, 58, 7101−7107.

(9) Diastereomeric products **16** were too unstable to isolate.

(10) The presence of oxetane products is easy to detect by ^{1}H NMR. The protons on C-2 of a dioxaspiro[3.2]hexane appear above 5.0 ppm in oxetane-intact products and shift to below 5.0 ppm in ring-opened products.

(11) Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Lin, F. *J. Org. Chem.* **1991**, *56*, 1153−1166.

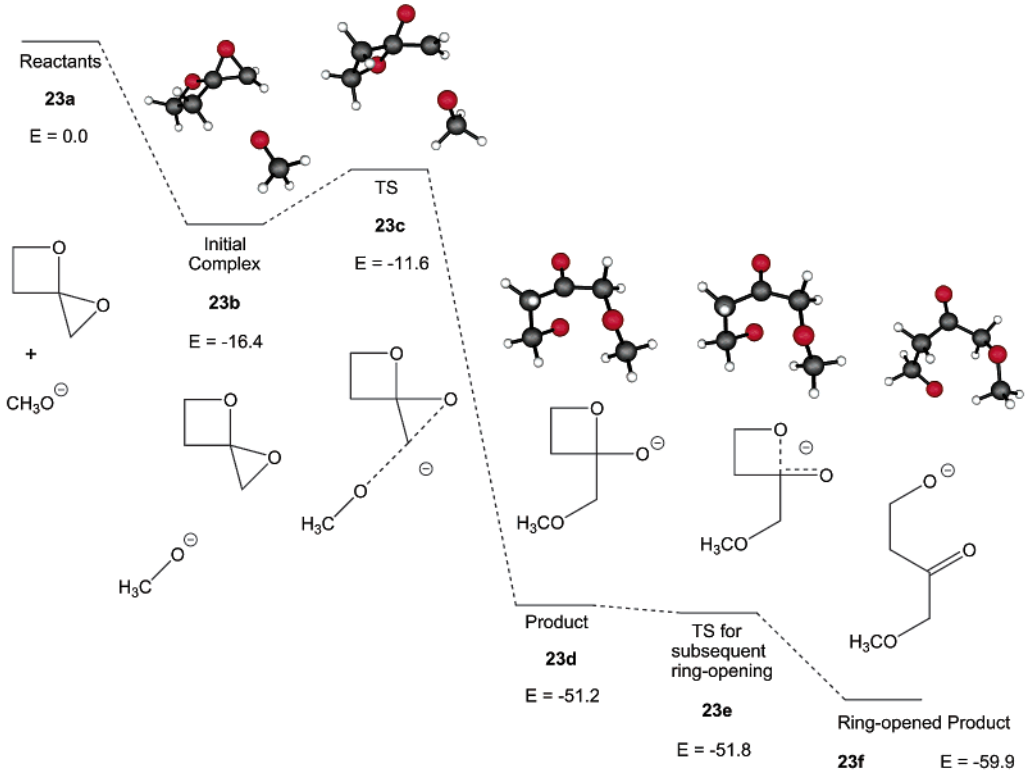
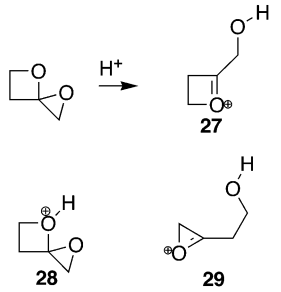


FIGURE 2. Nucleophilic attack of methoxide ion at the less hindered oxirane carbon atom of 1,5-dioxaspiro[3.2]hexane **22**. The energies shown are in kcal/mol and are calculated at the B3LYP/6-311+G(2df,p)//B3LYP/6-31+G** level, with the zero-point energy correction included.

the Supporting Information), exhibit much higher barriers (by 8−27 kcal/mol) than do the pathways corresponding to attack at carbons 2 or 6.

The calculations also show a modest preference (2 kcal/mol) for initial attack on the oxirane ring (Figure 2) instead of on the oxetane ring (Figure 3). This preference is in accord with the experimental observations for conditions lacking a good Lewis acid.

The experimental evidence also suggests that, in the presence of an acid, coordination to the oxirane oxygen leads to formation of an oxonium ion, such as **4**, and ultimately to oxetane-intact products such as **3**. To explore this hypothesis, calculations were carried out on the structures of oxirane, oxetane, 1,5-dioxaspiro[3.2]-hexane **22**, and their products of protonation. The results are listed in Table 2. These calculations properly reproduce the greater basicity of oxetane compared to oxirane. However, attempted protonation of **22** almost always led to spontaneous ring opening. Protonation on the oxirane oxygen invariably led to opening of the oxirane ring, yielding one of several possible conformations of the oxonium ion **27**. Protonation of the oxetane oxygen sometimes led to a stable structure **28**, but at best only a very small (<2 kcal/mol) barrier ever separated **28** from ring opening to a conformation of oxonium ion **29**. The preferred reaction pathway of **22** under conditions of protonation is thus likely governed by the relative stabilities of the two possible ring-opened oxonium ions **27** and **29**, of which **27** is more stable by fully 18.8 kcal/mol. This energy difference reasonably accounts for the experimentally observed pattern, in which reaction occurs via preferential opening of the oxirane ring under conditions of protonation.



To further explore the reactivity of the parent 1,5-dioxaspiro[3.2]hexane **22** with acids, the gas-phase reaction pathways of **22** with protonated acetone were also examined. Table S2 in the Supporting Information lists the energies of the structures corresponding to the stationary points along the trajectories for proton transfer from protonated acetone to either the oxirane or the oxetane oxygen of **22**, as shown in Figures 4 and 5. In both cases, the potential energy surface that connects the reactant complex with the product complex has no barrier whatsoever, according to B3LYP calculations, and at most a very small barrier at the Hartree−Fock level. However, proton transfer to the oxirane ring initiates a strongly exothermic (−22 kcal/mol) reaction pathway leading to **27**, while proton transfer to the oxetane ring initiates a nearly thermoneutral (−3 kcal/mol) reaction pathway leading to **29**. Again, the results are highly consistent with acids demonstrating a strong preference

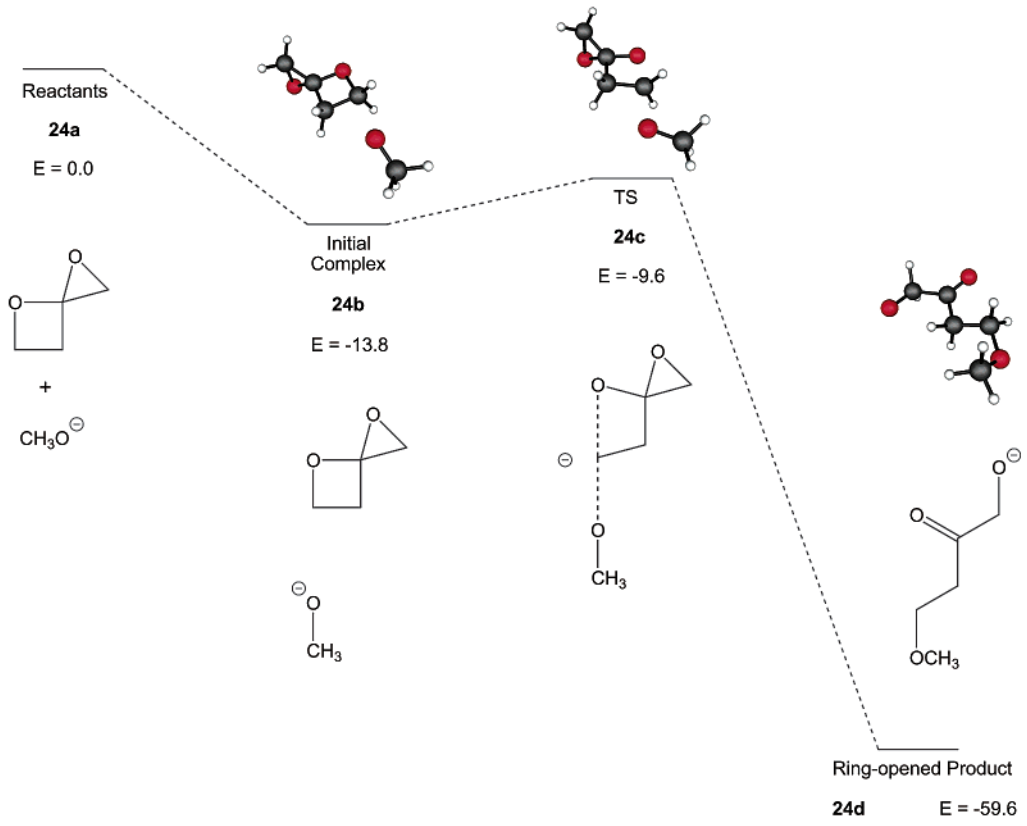


FIGURE 3. Nucleophilic attack of methoxide ion at the less hindered oxetane carbon atom of 1,5-dioxaspiro[3.2]hexane **22**. The energies shown are in kcal/mol and are calculated at the B3LYP/6-311+G(2df,p)//B3LYP/6-31+G** level, with the zero-point energy correction included.

TABLE 2. Relative Enthalpies at 0 K of Oxirane, Oxetane, 1,5-Dioxaspiro[3.2]hexane, and Their Protonation Products (kcal/mol)

	ΔH (0 K)				
species	HF/6-31G* [a]	B3LYP/6-31+G** [b]	B3LYP/6-311+G(2df,p)[b]	MP2/6-311+G(2df,p)[b]	CBS-Q[c]
oxirane	0.0	0.0	0.0	0.0	0.0
oxirane-H^+	−186.7	−182.7	−181.8	−178.9	−181.6
oxetane	0.0	0.0	0.0	0.0	0.0
oxetane-H^+	−198.9	−194.9	−193.8	−191.1	−193.3
22	0.0	0.0	0.0	0.0	0.0
27	−221.8	−216.2	−216.2	−208.2	−212.4
28	−193.0	−192.1	−191.6	−187.3	−189.6
29	−199.4	−196.7	−197.4	−192.2	−194.3

[a] Includes HF/6-31G* zero-point vibrational energy scaled by 0.893. [b] Includes B3LYP/6-31+G** zero-point vibrational energy scaled by 0.97. [c] The CBS-Q energies include a zero-point vibrational energy correction by definition.

for reaction at the oxirane oxygen, rather than at the oxetane oxygen. This preference results from the fact that subsequent ring opening is kinetically facile in either case but is thermodynamically far more favorable for the more highly strained oxirane ring.

The behavior of the 1,5-dioxaspiro[3.2]hexane system when treated with a nucleophile can thus be understood on the basis of classical epoxide chemistry and the chemistry of acetals. Under basic, or anionic, conditions, nucleophilic attack occurs at the less substituted oxirane carbon. The oxirane ring opens in preference to the oxetane ring, due to the greater relief of strain in the former case. Once opening is accomplished, the immediate product is the anion of a cyclic hemiacetal, and further opening of the oxetane ring to yield an alkoxy ketone is unavoidable.

Under acidic, or cationic, conditions, on the other hand, nucleophilic attack occurs at the acetal carbon, as would be expected for any acetal. Once even partial protonation occurs on either oxygen atom of 1,5-dioxaspiro[3.2]-hexane, the highly stablized incipient carbocation at the spiro (acetal) carbon is highly susceptible to nucleophilic attack. Furthermore, calculations suggest that once an acid begins to approach, virtually no barrier intervenes between the initial complex and the final product corresponding to opening of *either* the oxirane *or* the oxetane ring. Consequently, the selection of a reaction pathway is not affected by the relative basicity of isolated oxirane and oxetane functionalities but is instead governed simply by the overall thermodynamic favorability of the various possible routes. The pathway in which the more highly strained oxirane ring opens is thus favored again.

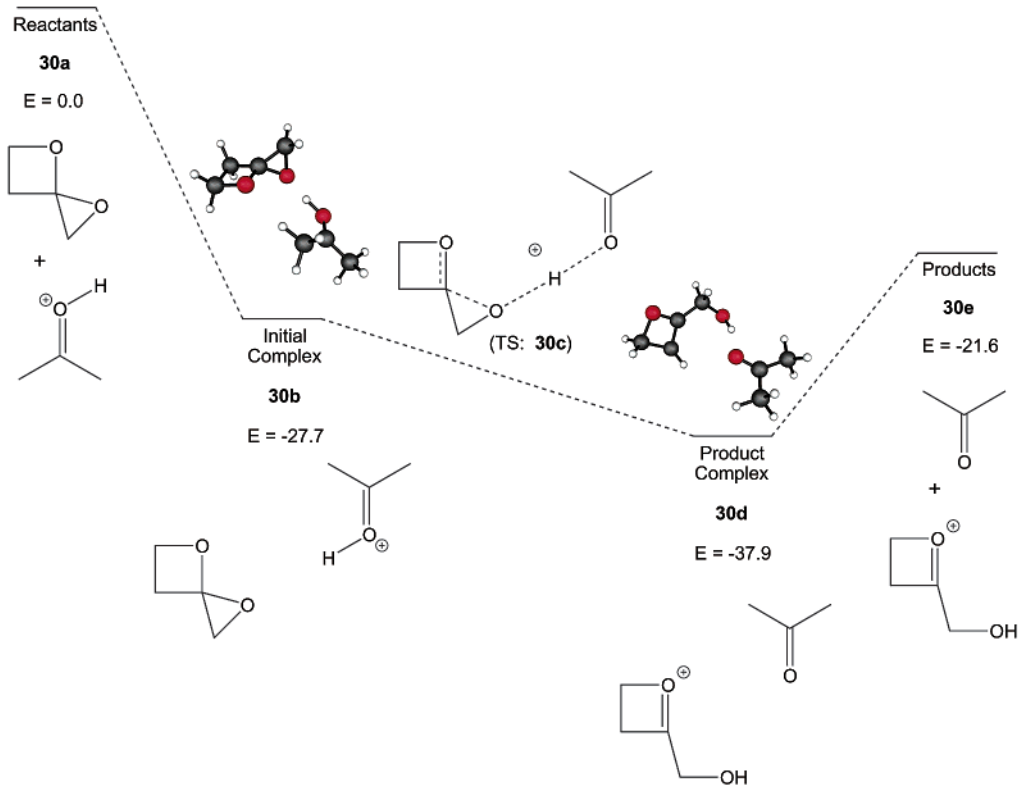


FIGURE 4. Proton transfer from protonated acetone to the oxirane oxygen atom of 1,5-dioxaspiro[3.2]hexane **22**. The energies shown are in kcal/mol and are calculated at the B3LYP/6-311+G(2df,p)//B3LYP/6-31+G** level, with the zero-point energy correction included. A transition state must exist between the reactant and product complexes, since the latter are both true minima, but no transition state could be located at the B3LYP/6-31+G** level of theory. At the HF/6-31G* level of theory, a transition state (**30c**) was found, but it was only slightly higher in energy (by 1.0 kcal/mol) than the reactant complex.

However, in the cationic route, the immediate product is *not* a hemiacetal, so further opening of the oxetane ring is blocked.

Conclusions

In summary, we have found that 1,5-dioxaspirohexanes react with nitrogen-containing heteraromatic compounds to give either α-substituted-*β*′-hydroxy ketones or 2,2-disubstituted oxetanes. The more acidic aromatic compounds and carboxylic acids provide the latter. Moreover, reaction outcome can be directed toward the substituted oxetane by the addition of an appropriate Lewis acid. Ab initio calculations confirm that under anionic conditions, the lowest barrier pathway yields substituted ketone products. Under conditions of protonation, however, calculations reveal that barriers are universally low or nonexistent, and the alternative oxetane products are easily rationalized on the basis of thermodynamic stability.

Experimental Section

General. Tetrahydrofuran was distilled from a dark-colored solution of sodium benzophenone ketyl. Deuterated chloroform was dried over 3 Å molecular sieves. Ethyl acetate and petroleum ether were distilled from $CaCl_2$. Methylene chloride was freshly distilled from CaH_2. The concentration of *n*-butyllithium was determined using *sec*-butyl alcohol and 1,10-phenanthroline as an indicator. All other reagents were used without further purification. Compound **1** was prepared as previously described.[6,12]

2-Azido-2-(hydroxymethyl)-3-phenyloxetane (5). Trimethylsilyl azide (0.22 g, 1.85 mmol) was added to a stirred solution of 3-phenyl-1,5-dioxaspiro[3.2]hexane (**1**) (0.20 g, 1.23 mmol) in dry Et_2O (2 mL). The reaction mixture was left to stir overnight at room temperature. It was concentrated to provide a colorless oil, which was then dissolved in dry THF (5 mL). The mixture was cooled to 0 °C and tetrabutylammonium fluoride (1 M in THF, 1.85 mL, 1.85 mmol) was added dropwise. After 2 h, the reaction mixture was concentrated, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 9:1 to 4:1). A white solid (0.14 g, 56%) was obtained. Recrystallization from EtOAc/petroleum ether yielded white prisms: mp 37−38 °C; IR ($CDCl_3$) 3441, 3062, 3031, 2971, 2903, 2116, 1590, 1493, 1452, 1257, 1048, 946 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.29 (m, 3H), 4.86 (dd, J = 6.2, 7.7 Hz, 1H), 4.80 (dd, J = 6.2, 8.8 Hz, 1H), 4.49 (dd, J = 8.3, 8.3 Hz, 1H), 3.53 (dd, J = 7.1, 12.5 Hz, 1H), 3.40 (dd, J = 6.8, 12.4 Hz, 1H), 1.52 (dd, J = 7.0, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8, 128.8, 127.9, 127.6, 100.9, 67.2, 64.1, 48.3; MS (EI) *m*/*z* 177 ($M^+ - N_2$), 159 ($M^+ - N_2 - CH_2O$), 129, 120, 117 (100), 103, 90, 89, 77, 63, 51. Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.82; H, 5.09; N, 20.11.

4-Hydroxy-1-imidazol-1-yl-3-phenylbutan-2-one (6). Imidazole (0.10 g, 0.50 mmol) was added to a stirred solution of 3-phenyl-1,5-dioxaspiro[3.2]hexane **(1)** (0.046 g, 0.068 mmol) in dry THF (2 mL). The mixture was stirred at room temperature for 1 h and then concentrated. The orange residue was

(12) Compound **1** was isolated as a mixture of diastereomers (14:1). The identity of the major diastereomer is not known. Evidence (see ref 6) suggests that diastereoselectivity is largely sterically controlled. It is noteworthy that the diastereomeric ratio is inconsequential for the subsequent transformations of **1** in the applications described in this paper.

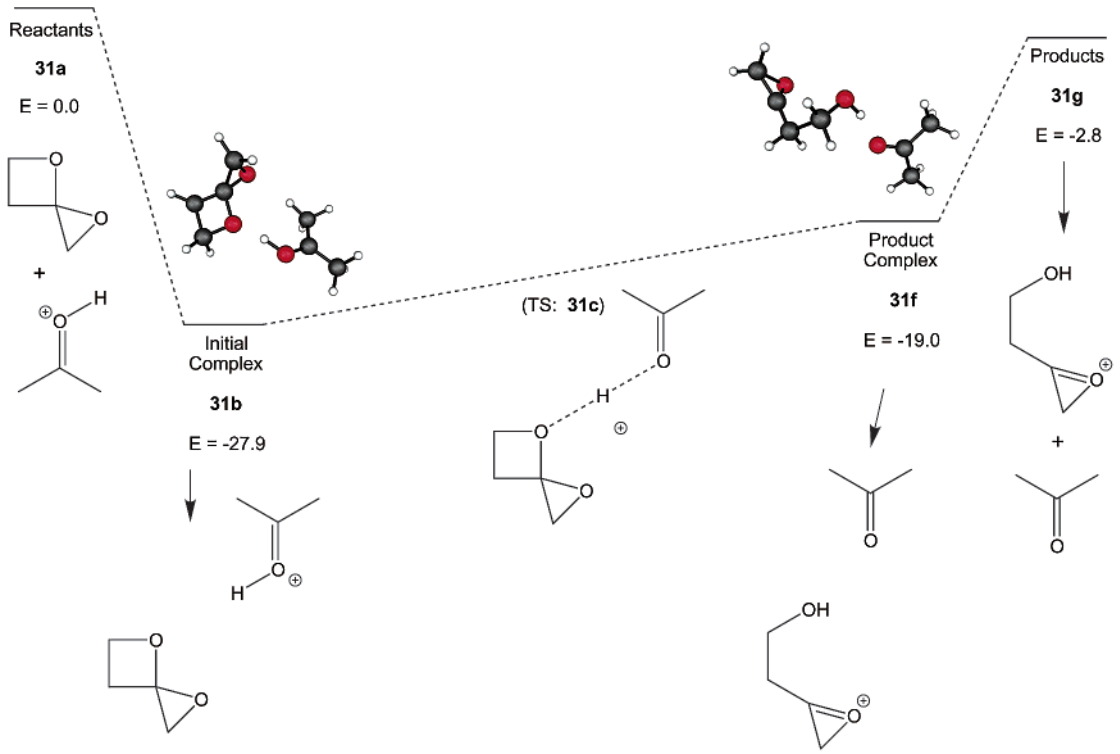


FIGURE 5. Proton transfer from protonated acetone to the oxetane oxygen atom of 1,5-dioxaspiro[3.2]hexane **22**. The energies shown are in kcal/mol and are calculated at the B3LYP/6-311+G(2df,p)//B3LYP/6-31+G** level, with the zero-point energy correction included. A transition state must exist between the reactant and product complexes, since the latter are both true minima, but no transition state could be located at the B3LYP/6-31+G** level of theory. At the HF/6-31G* level of theory, a transition state (**31c**) was found, but it was only slightly higher in energy (by 2.8 kcal/mol) than the product complex. Also only at the Hartree−Fock level, the initial product of proton transfer (**31d**) was a stable intermediate structure having both the oxirane and oxetane rings intact. A second, very low energy transition state separated this initial product from the final product complex (**31f**) in which the oxetane ring is cleaved.

purified by flash chromatography on silica gel ($CHCl_3$/MeOH 49:1 to 19:1). 4-Hydroxy-1-imidazol-1-yl-3-phenylbutan-2-one (**6**) was isolated as a colorless oil (71 mg, 50%): IR ($CDCl_3$) 3346, 3121, 3035, 2918, 2843, 1731, 1598, 1507, 1447, 1238, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 3H), 7.25 (m, 2H), 7.20 (m, 1H), 7.03 (s, 1H), 6.72 (s, 1H), 4.77 (d, J = 18.4 Hz, 1H), 4.71 (d, J = 18.3 Hz, 1H), 4.25 (dd, J = 11.0, 9.1 Hz, 1H), 4.01 (dd, J = 9.1, 4.6 Hz, 1H), 3.76 (dd, J = 11.1, 4.7 Hz, 1H), 2.95 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 138.0, 134.1, 129.4, 129.3, 128.4, 120.0, 63.8, 58.5, 55.1; MS (EI) m/z 200 ($M^+ - CH_2O$), 91 (100), 82, 81($M^+ - CH_2C_4H_3N_2$), 65, 59; HRMS (FAB) calcd for $C_{13}H_{15}N_2O_2$ ($M^+ + H$) m/z: 231.1134. Found: 231.1144.

4-Hydroxy-1-pyrazol-1-yl-3-phenylbutan-2-one (7). Pyrazole (0.055 g, 0.80 mmol) in dry CH_2Cl_2 (2.0 mL) was added dropwise to a stirred solution under nitrogen of 3-phenyl-1,5-dioxaspiro[3.2]hexane (**1**) (0.10 g, 0.62 mmol) in dry CH_2Cl_2 (2.0 mL) at 0 °C. After 1 h, the reaction mixture was allowed to warm to room temperature, then it was concentrated to afford a yellow residue. Flash chromatography on silica gel (CH_2Cl_2/methanol 98:2) afforded 4-hydroxy-1-pyrazol-1-yl-3-phenylbutan-2-one (**7**) as a light yellow oil (0.13 g, 90%): IR (neat) 3349 (br), 1733, 1397, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 1.4 Hz, 1H), 7.33 (m, 3H), 7.21 (d, J = 2.2 Hz, 1H), 7.17 (m, 2H), 6.28 (m, 1H), 4.93 (d, J = 17.9 Hz, 1H), 4.90 (d, J = 17.9 Hz, 1H), 4.18 (dd, J = 8.5, 11.2 Hz, 1H), 3.96 (dd, J = 4.9, 8.5 Hz, 1H), 3.78 (dd, J = 4.9, 11.1 Hz, 1H), 2.34 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 140.1, 134.3, 130.9, 129.2, 128.5, 128.1, 106.3, 63.8, 59.8, 58.0; MS (EI) m/z 212 ($M^+ - H_2O$), 200 ($M^+ - CH_2O$), 103 (100), 91, 81, 77. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.50; H, 6.50; N, 11.83.

4-Hydroxy-1-(1,2,4-triazol-1-yl)-3-phenylbutan-2-one (8). 1-(Trimethylsilyl)-1,2,4-triazole (0.10 g, 0.62 mmol) was added dropwise to a stirred solution of 3-phenyl-1,5-dioxaspiro[3.2]-hexane (**1**) (0.087 g, 0.62 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. The temperature was maintained at 0 °C for 2.5 h, and then the solvent was evaporated in vacuo. The residue was dissolved in THF (3.0 mL) at 0 °C, and TBAF (0.62 mL, 0.62 mmol) was added dropwise. The reaction mixture was stirred for 1 h and then diluted with CH_2Cl_2 (15 mL). The solution was washed with saturated aqueous NH_4Cl (3 × 3 mL) and dried, and the solvent was removed in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2/methanol 98:2) provided 4-hydroxy-1-(1,2,4-triazol-1-yl)-3-phenylbutan-2-one (**8**) as a pale yellow solid (78 mg, 55%). Recrystallization from ethyl acetate/petroleum ether provided white needles: mp 125.5−126.3 °C; IR (KBr) 3409 (br), 3129, 2924, 1729, 1513, 1483, 1272, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 2H), 7.36 (m, 3H), 7.18 (m, 2H), 5.00 (d, J = 18.2 Hz, 1H), 4.96 (d, J = 18.2, 1H), 4.22 (dd, J = 8.6, 11.1 Hz, 1H), 4.02 (dd, J = 4.8, 8.6 Hz, 1H), 3.79 (dd, J = 4.8, 11.1 Hz, 1H), 2.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 152.0, 144.6, 133.7, 129.6, 128.6, 128.4, 63.7, 58.6, 57.1; MS (EI) m/z 213 ($M^+ - H_2O$), 201 ($M^+ - CH_2O$), 185, 131, 103 (100), 91, 77, 55. Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 61.94; H, 5.28; N, 17.80.

2-(Hydroxymethyl)-3-phenyl-2-(1,2,3-triazol-2-yl)-2-oxetane (9). A solution of 1*H*-1,2,3-triazole (0.043 g, 0.62 mmol) in dry CH_2Cl_2 (2.0 mL) was introduced to a stirred solution under nitrogen of 3-phenyl-1,5-dioxaspiro[3.2]hexane (**1**) (0.10 g, 0.62 mmol) in dry CH_2Cl_2 (2.0 mL) at −78 °C. After 3 h at −78 °C, the reaction was allowed to warm to room temperature, then the solvent was evaporated in vacuo. The resultant oil was purified by flash chromatography on silica

gel (CH_2Cl_2/ethyl acetate 95:5). 2-(Hydroxymethyl)-3-phenyl-2-(1,2,3-triazol-2-yl)oxetane (**9**) was isolated as a pale yellow solid (0.076 g, 59%): mp 77.0−78.3 °C; IR ($CDCl_3$) 3145, 3031, 2969, 1496, 1452, 1323, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 2H), 7.41 (m, 2H), 7.35 (m, 3H), 5.41 (dd, J = 7.7, 8.2 Hz, 1H), 5.08 (dd, J = 6.0, 8.5 Hz, 1H), 4.98 (dd, J = 6.0, 7.0 Hz, 1H), 4.15 (dd, J = 7.6, 13.0, Hz, 1H), 4.10 (dd, J = 7.6, 13.0, 1H), 2.51 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 134.1, 128.8, 128.1, 128.0, 99.7, 68.5, 62.9, 47.9; MS (EI) m/z 200 ($M^+ - CH_2O$), 185, 104 (100), 78. Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.58; H, 5.30; N, 17.94.

2-Benzotriazol-2-yl-2-(hydroxymethyl)-3-phenyloxetane (10). Benzotriazole (0.15 g, 1.3 mmol) in dry CH_2Cl_2 at 0 °C was added to a stirred solution of 3-phenyl-1,5-dioxaspiro[3.2]hexane (**1**) (0.21 g. 1.3 mmol) in dry CH_2Cl_2 (4.0 mL) at 0 °C. The reaction mixture was left to stir for 3.0 h at 0 °C. It was then concentrated to provide a light brown oil. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 80:20). 2-Benzotriazol-2-yl-2-(hydroxymethyl)-3-phenyloxetane (**10**) was isolated as a white solid (0.15 g, 41%): mp 119−123 °C; IR (film) 3437 (br), 3094, 3064, 2941, 1560, 1499 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.1 Hz, 2H), 7.35 (m, 7H), 5.42 (dd, J = 7.0, 8.7 Hz, 1H), 5.20 (dd, J = 6.0, 8.7 Hz, 1H), 5.09 (dd, J = 6.0, 6.8 Hz, 1H), 4.25 (dd, J = 7.7, 13.0 Hz, 1H), 4.20 (dd, J = 7.0, 13.0 Hz, 1H), 2.6 (dd, J = 7.3, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 134.3, 129.3, 128.6, 128.5, 127.8, 119.1, 102.2, 69.8, 63.8, 48.8; MS (EI) m/z 281 (M^+), 251, 162, 104 (100), 91; HRMS (FAB) calcd for $C_{16}H_{16}N_3O_2$ (M^+ + H) m/z 282.1242, found 282.1248. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.13; H, 5.40; N, 14.97.

1-Benzotriazol-1-yl-4-hydroxy-3-phenylbutan-2-one (11). *n*-Butyllithium (0.77 mL, 1.6 M in hexane, 1.2 mmol) was added to a stirred solution of benzotriazole (0.15 g, 0.12 mmol) in dry CH_2Cl_2 (4.0 mL) at −78 °C. The mixture was left to stir at −78 °C for 30 min. 3-Phenyl-1,5-dioxaspiro[3.2]hexane (**1**) (0.2 g, 1.2 mmol) in dry CH_2Cl_2 (2.0 mL) was added dropwise and the reaction was left to stir at −78 °C for 1.5 h. Saturated NH_4Cl (5.0 mL) was added, and the organic layer was drawn off, washed with brine (5.0 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 80:20 to 75:25) to give 1-benzotriazol-1-yl-4-hydroxy-3-phenylbutan-2-one (**11**) as a colorless oil (0.093 g, 27%): IR (film) 3300 (br), 1700, 1500, 1400, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.1, 1H), 7.38 (m, 4H), 7.16 (m, 2H), 7.06 (d, J = 8.0 Hz, 1H), 5.46 (d, J = 18.1 Hz, 1H), 5.40 (d, J = 18.1 Hz, 1H), 4.22 (dd, J = 8.8, 10.8 Hz, 1H), 4.11 (dd, J = 4.8, 8.7 Hz, 1H), 3.81 (dd, J = 4.8, 10.8 Hz, 1H), 2.26 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 145.8, 133.6, 133.4, 129.5, 128.5, 128.4, 127.8, 124.3, 120.0, 109.0, 63.7, 58.5, 55.8; MS (EI) m/z 251 ($M^+ - CH_2O$), 132 (M+ − $CH_2C_6H_4N_3$), 104, 91, 77 (100); HRMS (FAB) calcd for $C_{16}H_{16}N_3O_2$ (M^+ + H) m/z 282.1243, found 282.1252.

2-(Hydroxymethyl)-2-tetrazol-2-yl-3-phenyloxetane (12). 1*H*-Tetrazole (0.078 g, 1.1 mmol) in dry THF (2.0 mL) was added dropwise to a stirred solution under nitrogen of 3-phenyl-1,5-dioxaspiro[3.2] hexane (**1**) (0.15 g, 0.94 mmol) in THF (2.0 mL) at 0 °C. The reaction mixture was stirred for 1 h and then concentrated. The resultant yellow oil was purified by flash chromatography on silica gel (CH_2Cl_2/methanol 100:0 to 98:2) to provide 2-(hydroxymethyl)-2-tetrazol-2-yl-3-phenyloxetane (**12**) as a pale yellow oil (0.090 g, 42%): IR ($CDCl_3$) 3436 (br), 2916, 1319, 1054, 953 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.42 (m, 5H), 5.37 (dd, J = 6.9, 8.6 Hz, 1H), 5.16 (dd, J = 6.1, 8.6 Hz, 1H), 5.08 (dd, J = 6.2, 6.2 Hz, 1H), 4.21 (dd, J = 7.5, 13.5 Hz, 1H), 4.17 (dd, J = 7.4, 13.5 Hz, 1H), 1.86 (dd, J = 7.4, 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 133.2, 129.1, 128.5, 128.1, 100.9, 69.6, 62.6, 47.8; MS (EI) m/z 204 ($M^+ - N_2$), 185 ($M^+ - CN$), 173 ($M^+ - CH_2OH$), 104 (100), 91, 78. Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 56.76; H, 5.14; N, 23.78.

2-(Hydroxymethyl)-2-(1,2,4-triazol-1-yl)-3-phenyloxetane (17). A solution of magnesium triflate (0.40 g, 1.23 mmol) in dry THF (5.0 mL) was introduced to a stirred solution at room temperature of 3-phenyl-1,5-dioxaspiro[3.2]hexane (**1**) (0.20 g, 1.23 mmol) in THF (2.0 mL). The temperature was then lowered to 0 °C, and a solution of 1*H*-1,2,4-triazole (0.22 g, 1.48 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 2.5 h, warmed to room temperature, and stirred for an additional 3 h. Then, the mixture was concentrated to provide a yellow oil, which was purified by flash chromatography on silica gel (CH_2Cl_2/methanol 99.5:0.5 to 99:1). 2-(Hydroxymethyl)-2-(1,2,4-triazol-1-yl)-3-phenyloxetane (**17**) was isolated as a 2:1 mixture of diastereomers (0.13 g, 45%): IR (film) 3403, 2903, 1499, 1279, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major, δ 8.18 (s, 1H), 8.11 (s, 1H), 7.40 (m, 5H), 5.11 (m, 1H), 5.06 (m, 1H), 4.74 (dd, J = 8.4, 16.3 Hz, 1H), 3.94 (d, J = 12.8 Hz, 1H), 3.83 (d, J = 12.8 Hz, 1H); minor, δ 8.42 (s, 1H), 7.67 (s, 1H), 7.12 (m, 5H), 5.11 (m, 1H), 5.06 (m, 1H), 4.74 (dd, J = 8.4, 16.3 Hz, 1H), 4.75 (d, J = 12.8 Hz, 1H), 4.31 (d, J = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major, δ 133.3, 129.0, 127.9, 127.7, 127.4, 127.4, 98.5, 68.9, 63.7, 48.7; minor, δ 133.3, 129.0, 127.9, 127.7, 127.4, 127.4, 98.5, 70.6, 67.2, 45.8; MS (EI) m/z 167, 149 (100), 71; HRMS (FAB) calcd for $C_{12}H_{14}N_3O_2$ (M^+ + H) m/z 232.1086, found 232.1101.

1-Acetoxy-4-hydroxy-3-phenylbutan-2-one (19). A solution of glacial acetic acid (105 mg, 1.74 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of 3-phenyl-1,5-dioxaspiro[3.2]hexane (**1**) (0.20 g, 1.23 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C. The mixture was stirred (2 h) and then left to warm to room temperature over 12 h. The reaction mixture was then concentrated, and the orange oil was purified by flash chromatography on silica gel (petroleum ether/EtOAc 9:1 to 4:1 to 3:2) to give **19** as a colorless oil (0.26 g, 93%): IR ($CDCl_3$) 3450, 3061, 3030, 2928, 1751, 1729, 1495, 1375, 1227, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 3H), 7.22 (m, 2H), 4.71 (d, J = 17.1 Hz, 1H), 4.57 (d, J = 17.1 Hz, 1H), 4.19 (ddd, J = 5.8, 8.5, 11.4 Hz, 1H), 3.99 (dd, J = 4.9, 8.5 Hz, 1H), 3.78 (ddd, J = 4.9, 7.8, 11.4 Hz, 1H), 2.22 (dd, J = 5.8, 7.8 Hz, 1H), 2.12(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 170.1, 134.3, 129.3, 128.5, 128.2, 67.6, 64.0, 57.7, 20.3; MS (EI) m/z 204 ($M^+ - H_2O$), 192 ($M^+ - CH_2O$), 162 ($M^+ - AcOH$), 150, 131, 121 ($M^+ - COCH_2OAc$), 104 (100), 103, 101 ($COCH_2OAc^+$), 91, 77 (Ph^+), 73, 65, 51. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.62; H, 6.10.

4-Hydroxy-3-phenyl-1-(dimethylpropionyl)butan-2-one (21). Trimethylacetic acid (0.069 g, 0.68 mmol) was added to a stirred solution under nitrogen of 3-phenyl-1,5-dioxaspiro-[3.2]hexane (**1**) (0.10 g, 0.62 mmol) in dry CH_2Cl_2 (5.0 mL). The mixture was stirred at room temperature for 12 h, then the solvent was evaporated in vacuo to afford a pale yellow residue. Purification was performed by flash chromatography on silica gel (petroleum ether/EtOAc 9:1 to 3:2) to give 4-hydroxy-3-phenyl-1-(dimethylpropionyl)butan-2-one (**21**) as a white solid (0.11 g, 68%): mp 94.5−95.0 °C; IR (KBr) 3555 (br), 2968, 1740, 1287, 1727, 1161 cm^{-1}; ^1H NMR (400 MHz) δ 7.35 (m, 3H), 7.26 (m, 2H), 4.67 (d, J = 16.9 Hz, 1H), 4.57 (d, J = 16.9 Hz, 1H), 4.19 (ddd, d, J = 5.8, 8.3, 11.3 Hz, 1H), 3.98 (dd, J = 4.9, 8.3 Hz, 1H), 3.80 (ddd, J = 4.9, 7.8, 11.3 Hz, 1H), 2.26 (dd, J = 5.9, 7.6, 1H) 1.22 (s, 9H); ^{13}C NMR (100 MHz) δ 204.2, 177.8, 134.5, 129.3, 128.6, 128.2, 67.6, 64.2, 57.7, 38.7, 27.1; MS (EI) m/z 234 ($M^+ - CH_2O$), 143, 121, 104, 85, 77, 57 ($(CH_3)_3C)^+$ (100). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.81; H, 7.84.

Computational Methodology. Both ab initio (HF and MP2) and density functional calculations were carried out with the Gaussian 98 package,[13] using standard Pople basis sets.[14]

The density functional calculations employed the B3LYP functional,[15] which consists of Becke's three-parameter hybrid exchange functional in conjunction with the correlation functional of Lee, Yang, and Parr.[16,17] The stationary points located were identified as minima or as transition states via calculation of vibrational frequencies. Symmetrical structures that were found to have undesired imaginary frequencies were reoptimized in lower symmetry. Transition state geometry optimizations were in most cases carried out using Schlegel's synchronous transit-guided quasi-Newton method (QST2 and QST3 procedures).[18] Zero-point vibrational energy corrections were scaled by 0.8934 at the HF/6-31G* level[19] and by 0.97 for the B3LYP calculations.[20] Single-point B3LYP/6-311+G(2df,p), MP2/6-31+G**, and MP2/6-311+G(2df,p) energies were calculated at the B3LYP/6-31+G**-optimized geometries.

Protonation energies of oxirane, oxetane, and 1,5-dioxaspiro-[3.2]hexane **22** were additionally calculated using the CBS-Q procedure of Petersson and co-workers.[21] The CBS-Q energies, which include by definition a zero-point vibrational energy correction, are expected to be the most accurate of those presented in Table 3. Examination of Table 3 shows that the CBS-Q proton affinities agree particularly closely with the results of the B3LYP/6-311+G(2df,p)//B3LYP/6-31+G** calculations. For this reason, and also because the large basis set DFT calculations are expected to be more reliable than either the HF calculations or the DFT calculations using smaller basis sets, the discussion in the text is based upon the B3LYP/6-311+G(2df,p)//B3LYP/6-31+G** energies. This level of theory should provide a representative and reliable picture. However, the discussion would not be substantially changed if any of the other sets of energies were used instead.

Acknowledgment. A.R.H. thanks the NSF (CHE 0111522) for support of this research. Acknowledgment is made by P.R.R. to the donors of the Petroleum Research Fund, administered by the ACS, for partial support of this research. R.T. is supported by a fellowship from the Multicultural Scholars Program at the University of Connecticut. We thank Scott Denmark for helpful discussion.

Supporting Information Available: Calculated energies in hartrees and Cartesian coordinates for all optimized structures, as well as NMR spectra of compounds lacking microanalyses. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0206465

(13) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A. Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98 (Revision A.6)*; Gaussian, Inc.: Pittsburgh, PA, 1998.

(14) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(15) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.

(16) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

(17) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200−206.

(18) Peng, C.; Ayala, P. Y.; Schlegel, H. B.; Frisch, M. J. *J. Comput. Chem.* **1996**, *17*, 49. Peng, C.; Schlegel, H. B. *Israel J. Chem.* **1994**, *33*, 449−454.

(19) Curtiss, L. A.; Raghavachari, K.; Trucks, G. W.; Pople, J. A. *J. Chem. Phys.* **1991**, *94*, 7221−7230.

(20) Rablen, P. R.; Lockman, J. W.; Jorgensen, W. L. *J. Phys. Chem. A* **1998**, *102*, 3782−3797.

(21) Ochterski, J. W.; Petersson, G. A.; Montgomery, J. A., Jr. *J. Chem. Phys.* **1996**, *104*, 2598−2619.