Component **4**, containing the aromatic residue, was prepared by the sequence outlined in Scheme III. The reaction of isovanillin (**18**) with NH_4OAc and malonic acid (*n*-BuOH/reflux) furnished the β-amino acid **19**[7] (64%), which was then esterified (MeOH/HCl/0 °C) and protected (BOC_2O/dioxane/H_2O/25 °C) to yield the phenolic intermediate **20** (99%). The copper phenoxide derived from **20** (NaH/py, CuCl) was coupled with methyl *cis-p*-bromocinnamate (**21**)[8] in refluxing pyridine forming the diaryl ether **22** (61%).[9] Removal of the BOC group ($BF_3 \cdot Et_2O/HOAc/CH_2Cl_2$/0 °C)[10] took place (90%) without isomerization of the double bond, yielding the required β-amino ester **4**.

The coupling of the amino ester **4** with the imino ether **3**[4,11] was achieved by heating the two reactants in chlorobenzene (115 °C/9 h) to form the bicyclic 4-oxotetrahydropyrimidine **5** (25%) along with the trans isomer (6%).[12] Selective introduction of the acetyl group at N-20 was then accomplished (80%) by removal of the BOC group ($BF_3 \cdot OEt_2/CH_2Cl_2$/0 °C)[10] followed by reaction with acetyl chloride (DMAP/CH_2Cl_2/25 °C).[13] The bicyclic product **6** was opened to the 17-membered lactam **7** under the conditions developed earlier[4,5] ($NaBH_3CN$/AcOH/50 °C) (95%).

The last phase of the synthesis required activation of the carboxylate at C-14. This was accomplished by hydrolysis of the methyl ester **7** (dilute NaOH/THF/MeOH/55 °C) followed by esterification with pentafluorophenol (DCC/THF/25 °C) yielding **8**. Removal of the 2,2,2-trichloroethoxycarbonyl group at N-15 and cyclization of the resulting amino ester to chaenorhine (**1**) was achieved by treatment of **8** with Zn/HOAc at 25 °C (12 h), filtration and evaporation of excess HOAc in vacuo, and then slow addition of the resulting diamino ester **9** (diacetate) in dioxane to a solution of DMAP (1 equiv) in pyridine (14 h/95 °C) (22% conversion of **7** to **1**).[14] The synthetic material was identical in all respects (TLC, 500-MHz NMR, MS, IR) with an authentic sample of natural (*S*)-(+)-chaenorhine kindly supplied by Professor M. Hesse, the University of Zurich. We are continuing our work on the synthesis of macrocyclic polyamine alkaloids, including ephedradine A (**2**).[15]

Acknowledgment. This work was supported by NIH Grant GM-07874. The support of the NSF/NMR Northeast Regional Facility at Yale University (Grant CHE-7916210) is acknowledged.

Supplementary Material Available: ^1H NMR, infrared, and mass spectral and elemental analytical data, physical constants, and purification procedures for key intermediates (10 pages). Ordering information is given on any current masthead page.

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(7) Rodinov, V. M.; Malevinskaia, E. T. *Chem. Ber.* **1926**, *59b*, 2952.

(8) *cis*-Methyl-*p*-bromocinnamate (**21**) was prepared starting from the methyl ester of *p*-bromophenylalanine hydrochloride (Dornow, A.; Winter, G. *Chem. Ber.* **1951**, *84*, 307). Esterification (CH_3OH, HCl) and diazotization (isoamyl nitrite) was followed by treatment with $BF_3 \cdot Et_2O$ and DCC in CH_2Cl_2 according to the following procedure: Takamura, N.; Mizoguchi, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 299.

(9) (a) Whitesides, G. M.; Sadowski, J. S.; Lilburn, J. J. *J. Am. Chem. Soc.* **1974**, *96*, 2829. (b) Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555.

(10) Hiskey, R. B.; Beacham, C. M.; Matl, V. G.; Smith, J. N.; Williams, E. B.; Thomas, A. M.; Wolters, E. T. *J. Org. Chem.* **1971**, *36*, 488.

(11) For earlier work on the reactions of β-amino esters and β-lactams with imino ethers see: (a) Takahata, H.; Tomoguchi, A.; Yamazaki, T. *Chem. Pharm. Bull.* **1981**, *29*, 2526 and references contained therein. (b) Bormann, D. *Chem. Ber.* **1970**, *103*, 1797. In our experience, β-lactams give better yields in this coupling reaction. As yet we have not found an efficient route for the preparation of the β-lactam equivalent of **4**.

(12) Some isomerization of the cis double bond to the trans form took place at this stage. The cis/trans mixture (inseparable by liquid chromatography on silica gel) was carried through to the final cyclization step.

(13) Introduction of the acetyl group prior to the formation of the imino ether **3** was not feasible because of the sensitivity of the $NCOCH_3$ group to Meerwein's reagent. Hanessian, S. *Tetrahedron Lett.* **1967**, 1549.

(14) (a) Lagarias, J. C.; Houghten, R. A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, *100*, 8202. (b) Schmidt, U.; Griesser, H.; Lieberknecht, A.; Talbiersky, J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 280.

(15) Our approach to the synthesis of ephedradine A (**2**) involves the coupling of a suitable β-amino ester or β-lactam component with the imino ether **3**.

Argon Matrix Isolation of Bis(trifluoromethyl)oxirene, Perfluoromethylethyloxirene, and Their Isomeric Ketocarbenes

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Received August 31, 1982

Oxirenes represent the simplest and most elusive 4 n–π heterocycles, and although the search for them began over a century ago,[1] all attempts to isolate them have been unsuccessful to date.[2-5] Evidence for their transient existence was obtained in 1968 in the photochemical Wolff rearrangement of α-diazo ketones,[6] and since then they have been shown to occur as reactive intermediates in several other reactions.[7,8] Efforts for the isolation of their ring-opened isomers, the α-keto carbenes, have been more rewarding, and since 1968 several of them have been isolated in low-temperature matrices and identified by ESR spectroscopy.[9-12] However, attempts to observe their IR spectrum have failed to date.[3,4]

Ab initio MO calculations predict oxirene to be thermodynamically less stable than its ring-opened isomer, formylmethylene, and the ring-opening process to feature insufficient activation energy to kinetically stabilize the ring structure.[13] The ground state of formylmethylene is predicted to be a triplet with a small T_0–S_1 energy separation.[14]

Substituents and especially electron-withdrawing groups could enhance the ring stability of substituted oxirenes to the point that they might become stabilizable by low-temperature matrix isolation techniques as has been found to be the case with thiirenes.[8]

Consequently, we have carried out a detailed study of the low-temperature argon matrix photolysis of hexafluoro-3-diazo-2-butanone, **1**, octafluoro-2-diazo-3-pentanone, **2**, and octafluoro-3-diazo-2-pentanone, **3**, and report here the isolation of bis(trifluoromethyl)oxirene and perfluoromethylethyloxirene along with their corresponding ketocarbenes.

Photolysis of **1**[12,15] with $\lambda > 335$ nm light resulted in the slow disappearance of the original IR spectrum and the appearance of the spectrum of bis(trifluoromethyl)ketene with significant absorptions at 2192 (s), 1420 (s), 1340 (s), 1310 (m), 1305 (w), 1300 (w), 1245 (w), 1188 (vs), 1180 (s), 1170 (s), 1165 (m), 1155 (m), 992 (m), 988 (m), 728 (w), 550 (w), 535 (w), and 450 (w) cm^{-1}, in agreement with the published spectrum.[16] In addition,

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(1) Berthelot, M. *Bull. Soc. Chim. Fr.* **1870**, *14*, 113.

(2) Krantz, A. *J. Chem. Soc., Chem. Commun.* **1973**, 670.

(3) Maier, G.; Reisenauer, H. P.; Sayrac, T. *Chem. Ber.* **1982**, *115*, 2192.

(4) Maier, G.; Sayrac, T.; Reisenauer, H. P. *Chem. Ber.* **1982**, *115*, 2202.

(5) Torres, M.; Clement, A.; Strausz, O. P. *J. Org. Chem.* **1980**, *45*, 2271.

(6) Csizmadia, I. G.; Font, J.; Strausz, O. P. *J. Am. Chem. Soc.* **1968**, *90*, 7360.

(7) Cormier, R. A. *Tetrahedron Lett.* **1980**, 2021.

(8) For a recent review see: Torres, M.; Lown, E. M.; Gunning, H. E.; Strausz, O. P. *Pure Appl. Chem.* **1980**, *52*, 1623.

(9) Trozzolo, A. M. *Acc. Chem. Res.* **1968**, *1*, 329.

(10) Hutton, R. S.; Roth, H. D. *J. Am. Chem. Soc.* **1978**, *100*, 4324.

(11) Murai, H.; Torres, M.; Strausz, O. P. *J. Am. Chem. Soc.* **1980**, *102*, 5104; *Chem. Phys. Lett.* **1980**, *70*, 358.

(12) Murai, H.; Ribo, J.; Torres, M.; Strausz, O. P. *J. Am. Chem. Soc.* **1981**, *103*, 6422.

(13) Strausz, O. P.; Gosavi, R. K.; Denes, A. S.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1976**, *98*, 4784. Strausz, O. P.; Gosavi, R. K.; Gunning, H. E. *Chem. Phys. Lett.* **1978**, *54*, 510. Tanaka, K.; Yoshimine, M. *J. Am. Chem. Soc.* **1980**, *102*, 7655. Bouma, J. W.; Nobes, R. H.; Radon, L.; Woodward, C. *J. Org. Chem.* **1982**, *47*, 1869.

(14) Baird, N. C.; Taylor, K. F. *J. Am. Chem. Soc.* **1978**, *100*, 1333.

(15) Dyatkin, B. L.; Mochalina, E. P. *Izv. Akad. Nauk. SSSR Ser. Khim.* **1965**, *6*, 1035.

(16) Nadzhimutdinov, Sh.; Slovokhotova, N. A.; Kargin, V. A. *Russ. J. Phys. Chem.* **1966**, *40*, 479.

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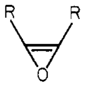
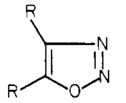
a spectrum of another species also appeared with absorptions at 1763 (m), 1751 (w), 1748 (w), 1235 (m), 1226 (s), 1209 (s), 1199 (s), 1167 (m), 1014 (w), 1011 (w), 905 (w), 860 (m), 720 (w), 692 (m), 545 (w), and 410 (w) cm^{-1}, which on subsequent photolysis with λ ≥210 nm radiation gradually disappeared with a concomitant increase in the ketene spectrum. The most significant feature of the intermediate spectrum is the 1763-cm^{-1} band, which falls in the C=O and C=C stretching region. Given the ability of the intermediate to convert to the ketene on photolysis, three structures need to be considered: the ketocarbene, oxirene, and the 1,2,3-oxadiazole (**4**–**6**, respectively), all of which are novel molecules, although we have succeeded earlier to isolate the triplet ground-state **4** under similar conditions and identify its two geometrical conformers on the basis of their ESR spectra.[12] However, no IR spectrum due to a ketocarbene has been reported before. Formation of trifluoromethyl trifluorovinyl ketone, CF_2=$CFCOCF_3$, can be ruled out because of the absence of its reported strong absorption[17] at 1785 and 1695 cm^{-1} and also because it would not be expected to rearrange to the ketene on photolysis.[18] An absorption at 1763 cm^{-1} is equally unlikely for **6** because it could only be due to a ν(C=C), and 1,2,3-oxadiazoles would be expected to be pseudoaromatic and like 1,2,3-thiadiazoles not to show ν(C=C) absorptions.

$R\ddot{C}COR$

4



5

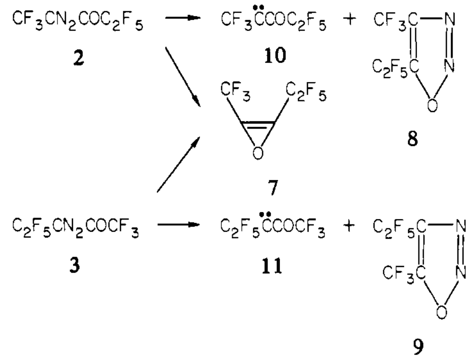


6, R = CF_3

5 being a symmetrical molecule, it is expected to show a weak ν(C=C), and although both the intensity and position of the 1763-cm^{-1} band are as expected for the ν(C=O) of **4**, the possibility of **5** being the carrier cannot be ruled out. Differentiation between these possibilities could be made on the basis of isotopic labeling. With ^{18}O, the carbonyl stretching frequency should shift to lower wavenumbers by an amount commensurate with that in the ketene product, while the ν(C=C) frequency should not be affected. For this reason, we prepared 20% ^{18}O-labeled **1** and photolyzed it under the same conditions as before. This resulted in the formation of the same intermediate in which the 1763-cm^{-1} absorption appeared at 1735 cm^{-1}. The shift, −28 cm^{-1}, compares well with that observed for the ν(C=O) in the ketene, −32 cm^{-1}, and allows the definite assignment of the spectrum to the perfluoroacetylmethylmethylene, **4**.

When the photolysis of **1** was carried out with 270-nm light, in addition to the spectrum of **4**, which was somewhat less intense than before, a new spectrum appeared with absorptions at 1325 (m), 1275 (s), 1160 (m), 875 (w), 730 (w), 660 (m), and 560 (w) cm^{-1}. Subsequent photolysis of the photolyzate with 360-nm light resulted in the disappearance of this spectrum and an increase in the intensity of the ketene spectrum, leaving the spectrum of the ketocarbene unaltered. Continuing the line of argument as discussed above, the carrier of this latter spectrum is either the oxirene **5**, or less likely, the oxadiazole, **6**.[20]

Scheme I



In order to distinguish between these alternatives, we synthesized diazoketones **2** and **3**, which on photolysis would give the same oxirene **7**, but two different isomeric oxadiazoles, **8** and **9**[22] (Scheme I). Photolysis with ≥335-nm light of **2** gave keto carbene **10** with a C=O (st) absorption at 1752 cm^{-1}, and of **3** keto carbene **11** with a C=O (st) absorption at 1762 cm^{-1}. Photolysis of **2** and **3** with 270-nm radiation yielded in addition to the keto carbenes a new intermediate with a weak but clearly superimposable IR spectra consisting of absorptions at 1260, 1225, 1030, 840, 750, 685, and 655 cm^{-1}. This intermediate could also be converted to the ketene on photolysis with light of 360 nm, as was the case with the intermediate in the photolysis of **1**.

Thus, we are forced to conclude that the second intermediate produced in the shorter wavelength photolysis of **1** is the bis(trifluoromethyl)oxirene and in the photolysis of **2** and **3**, the perfluoromethylethyloxirene. The IR spectra of both of these species are nondescript because of the nonappearance of the ν(C=C) absorption, which may be due to its inherently low intensity and possible coincidence with one of the C=O stretchings in either the precursor diazo ketone or keto carbene products.

The photochemical behavior of oxirenes, as could be observed here, is somewhat reminiscent of the behavior of thiirenes. The latter are formed when the source compounds (1,2,3-thiadiazoles or trithiocarbonates) are irradiated with shorter wavelength radiation, and on subsequent photolysis at longer wavelengths the thiirenes convert to thioketenes.[8]

The lower intensity of the IR spectrum of oxirene **7** relative to oxirene **5** can at least be partly attributed to the lower relative concentrations of the more favorable *s-Z* conformation for oxirene formation in the matrix of diazo ketones **2** and **3** than of diazo ketone **1** on account of the increased steric hindrance exerted by the bulkier C_2F_5.[5,23] It should also be noted that in the photolysis of **1**, two geometrical conformers of **4** were produced (as was found before by ESR detection[13]), one of them being predominant, but in the photolysis of **2** and **3** only one conformer of each **10** and **11** was discernible.

The thermal stability of **4** and **5** was also briefly explored. Slow-warming of the argon matrix to 35 K caused a substantial decay in the intensity of the spectrum of **5**, but that of **4** remained unaffected, and in the photolysis of a thin film of **1**, the spectrum of **4** was stable up to ~150 K. Thus, thermally, oxirene is considerably less stable than its isomeric keto carbene.

The present results appear to demonstrate that the intensity of the ν(C=C) absorption in oxirenes may be too feeble to be observable by IR spectroscopy, which may be the reason earlier

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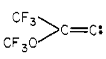
(17) Anderson, B. C. *J. Org. Chem.* **1968**, *33*, 1016.

(18) Other unlikely but possible carriers:

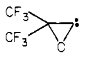
a

$CF_3C{\equiv}COCF_3$

b



c



d

These could be ruled out as follows: a has been shown not to be an intermediate in the Wolff rearrangement of azibenzil by Blaustein and Berson.[19] Acetylene b and vinylidene carbene c would be expected to show significant IR absorption at ~2200 and ~1650 cm^{-1}, respectively. Since no triplet signals other than those of *s-E*- and *s-Z*-**4** were detected by ESR[12] if carbene d is present, it would have to be in a singlet ground state. Ab initio MO calculations on the lowest singlet C_2H_2O isomers predict a much higher kinetic stability and activation energy of formation for oxaranylidene than for oxirene, which should be enhanced by the presence of trifluoromethyl groups. These contrast with the easy formation and thermal instability observed for the carrier, and we feel that its formation is very unlikely.

(19) Blaustein, M. A.; Berson, J. A. *Tetrahedron Lett.* **1981**, *22*, 1081.

(20) Oxadiazole **6** is expected to have an UV absorption spectrum similar to that of 1,2,3-thiadiazoles[21] although shifted to lower wavelengths. Consequently **6** would not be expected to absorb light at >360 nm and therefore would not photolyze at long wavelength.

(21) Zeller, K. P.; Meier, H.; Müller, E. *Liebigs Ann. Chem.* **1972**, *766*, 32.

(22) The IR spectra of **8** and **9** would be expected to be very similar, but on the basis of the differences between the IR spectra of **2** and **3** and **10** and **11** it would be expected to show a few significant differences.

(23) Torres, M.; Ribo, J.; Clement, A.; Strausz, O. P. *Can. J. Chem.*, in press.

efforts for the low-temperature matrix isolation of oxirenes were unsuccessful.

Further studies are in progress.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council for continuing financial support, and J.L.B. acknowledges a fellowship from the Ministerio de Universidades e Investigación, Spain.

Registry No. 1, 14088-58-5; **2**, 84802-89-1; **3**, 84802-90-4; **4**, 78844-51-6; **5**, 84802-91-5; **7**, 84802-92-6; **10**, 84802-93-7; **11**, 84802-94-8.

Heavy-Atom Tunneling as the Dominant Pathway in a Solution-Phase Reaction? Bond Shift in Antiaromatic Annulenes

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It is probably fair to say that many organic chemists view the concept of tunneling, even of hydrogen atoms, with some skepticism.[1] Heavy-atom tunneling is thus considered to be of negligible significance to chemical reactions.[1] The purpose of this communication is to point out that the bond shift reaction of [4*n*]annulenes could proceed by a mechanism that is *primarily* heavy-atom tunneling and that for cyclobutadiene in particular the *tunneling process could constitute >97% of the total rate constant below 0 °C*! The tunneling mechanism leads to the prediction of abnormally low activation entropies for the bond-shift reactions, in accord with experimental observation.

The reaction coordinate for automerization of cyclobutadiene can be approximated by a single stretching motion. This is equivalent to treating cyclobutadiene as homonuclear diatomic molecule with the two pseudoatoms each having a mass[2] of 26 daltons (see Figure 1).

The potential-energy profile for the bond-shifting reaction can be approximated as an intersection between two harmonic potential functions whose minima are separated on the reaction coordinate by a distance equal to the difference in length between the long and the short carbon-carbon bonds of cyclobutadiene. One could guess that this difference (ΔR) would be about 0.18 Å, given typical lengths of 1.52 and 1.34 Å for the long (single) and short (double) bonds respectively. Recent molecular orbital calculations[3-5] suggest that ΔR is about 0.198 Å.

In the model used here the height of the potential-energy barrier is determined by ΔR and the force constant for the stretching vibration. If one assumes a plausible value of 1000 cm^{-1} for the in-plane rectangular deformation[6] (symmetry b_{1g}), then the force constant for the pseudodiatomic molecule is calculated to be 1.532×10^6 dyn/cm. This leads to a calculated potential barrier of 10.8 kcal/mol for the automerization reaction, which perhaps by coincidence is near the middle of the range (8.3-14 kcal/mol) obtained from the most sophisticated quantum mechanical calculations.[4,5,7]

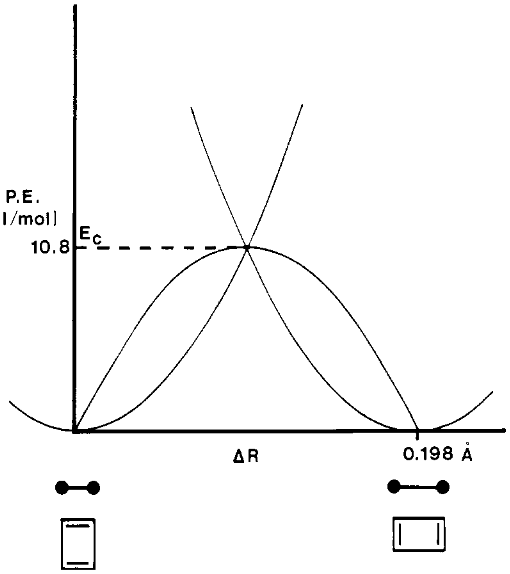

Figure 1. Model potential-energy functions for the automerization of cyclobutadiene.

In order to carry out the tunneling calculations one must represent the potential barrier by some analytical function. In the interests of preserving the simplicity of this model, I have chosen the truncated parabola form.[8] As shown in Figure 1, the parabola that passes through the point (0.099, E_c) and the minima of the harmonic potentials is probably somewhat too wide, and so the contribution from tunneling will tend to be *underestimated*. Nevertheless, *the width is nearly an order of magnitude smaller than that for most organic reactions. It is the extreme narrowness of the barrier that makes bond-shifting reactions especially susceptible to tunneling.*

The energy levels of the pseudodiatomic molecule can be calculated from the usual harmonic oscillator formula,[9,10] and the probability of transmission through the barrier $G(E)$ at each of these levels can be calculated from the Bell formula:[11]

$$G(E) = \frac{1}{1 + \exp[2\pi(E_c - E)/h\nu_t]}$$

$$\nu_t = \frac{1}{\pi a}\left(\frac{E}{2\mu}\right)^{1/2}$$

where μ is the reduced mass of the oscillator and the width of the barrier at its base is $2a$. The microcanonical tunneling-rate constant for each level is then taken to be the product of $G(E)$ and the oscillator frequency.

Finally, one can calculate the unimolecular tunneling-rate constant at various temperatures by imposing a Boltzmann population on each of the energy levels of the oscillator.[12] This is equivalent to assuming that the experiment is conducted at the

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[1] There are, of course, some exceptions. See, for example: Kaldor, S. B.; Saunders, W. H. *J. Am. Chem. Soc.* **1979**, *101*, 7594-7599. Buchwalter, S. L.; Closs, G. L. *Ibid.* **1975**, *97*, 3857-3858. Especially relevant to the present problem: Fong, F. K. *Ibid.* **1974**, *96*, 7638-7646.

[2] The real normal coordinate will consist of some C-H motion in addition to the predominant C-C motion. This means that the effective masses of the pseudoatoms in the diatomic model should be somewhat less than 26. By use of the highest value the tendency will be to *underestimate* the tunneling contribution.

[3] Dewar, M. J. S.; Komornicki, A. *J. Am. Chem. Soc.* **1977**, *99*, 6174-6179.

[4] Newton, M. D.; Jafri, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 5012-5017.

[5] Borden, W. T.; Davidson, E. R.; Hart, P. *J. Am. Chem. Soc.* **1978**, *100*, 388-392.

[6] Schaad et al. calculate a frequency of 978 cm^{-1} for this mode: Schaad, L. J.; Hess, B. A.; Ewig, C. S. *J. Org. Chem.* **1982**, *47*, 2904-2906.

[7] Kollmar, H.; Staemmler, V. *J. Am. Chem. Soc.* **1977**, *99*, 3583-3587.

[8] Bell, R. P. *Trans. Faraday Soc.* **1959**, *55*, 1-3.

[9] Schutte, C. J. H. "The Wave Mechanics of Atoms, Molecules and Ions"; Arnold: London, 1968; p 50.

[10] Actually there should be some splitting of the energy levels due to interaction between the wave functions for the two oscillators (see ref 9, pp 69 ff) but this has been neglected for the present purposes.

[11] Bell, R. P. "The Proton in Chemistry", 2nd ed.; Cornell University Press; Ithaca, NY, 1973; p 274.

[12] In fact the populations of these levels should be divided by vibrational partition function for the true molecule and not for the diatomic model. The reported unimolecular rate constants were calculated in this way although the effect is small: with the vibrational frequencies from ref 6, the vibrational partition function is calculated to be 1.14 at -50 °C and 1.27 at -10 °C.

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