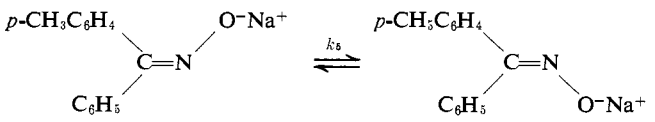
are obtained.[13] It has been pointed out previously that the range of rates of geometric isomerization of imine derivatives is a remarkable 16 powers of 10 or more.[14] We now report another dramatic demonstration of the sensitivity of these interconversion rates toward structural changes in the group singly bound to nitrogen. We have recently determined the rate constant for the *Z* to *E* isomerization of sodium *p*-methylbenzophenone oximate in methanol at 144°.[15] The value for k_5 is



3.1×10^{-5} sec^{-1} (the equilibrium constant under these conditions is 0.64). Thus under comparable[16] conditions *the iminoxy radical undergoes geometric isomerization approximately 5 or 6 powers of 10 faster than the corresponding oximate.* If one assumes a lateral shift mechanism for both isomerizations, a partial source of this difference in rates may be the difference in nonbonding electron promotional energies for the $sp^2 \rightarrow 2p$ processes during passage through the respective linear (C–N–O) transition states. Various calculated contributions to differences in energy barriers for the iminoxy radical and oxime anion interconversions will be considered in a later publication.

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(13) The accuracy of these rate constants is limited primarily by two factors. The magnitude of the diffusion-controlled rate constant, k_d, used is clearly an estimate. However, an order of magnitude error in this estimate leads to iminoxy radical syn–anti interconversion rate constants which differ from k_3 and k_4 by only a factor of 3. A second uncertainty arises from the question as to whether caged iminoxy–benzhydryl radical pairs recombine with a higher degree of stereochemical retention than do free iminoxy and benzhydryl radicals. We have recently shown that approximately 20% of **2** formed from **1** under conditions of the above stereochemical study is formed *via* a caged process.[12] The errors in k_3 and k_4 which could result from such a highly stereospecific caged process can be estimated. In the limiting case, the caged (or less likely concerted) process could be considered as competing with Scheme I and yielding *O*-benzhydryloxime with 100% geometric retention. If data used in obtaining k_3 and k_4 above are corrected for the contribution of this process to rates and stereochemistry of product formation, the revised k_3 and k_4 values are larger by a factor of approximately two.

(14) D. Y. Curtin, E. J. Grubbs, and C. G. McCarty, *J. Amer. Chem. Soc.*, **88**, 2775 (1966); see also G. E. Hall, W. J. Middleton, and J. D. Roberts (*ibid.*, **93**, 4778 (1971)) for additional references to studies of rates and mechanisms of syn–anti isomerizations of imine derivatives.

(15) D. R. Parker and E. J. Grubbs, unpublished data.

(16) It is unlikely that solvent differences can account for more than a small percentage of this difference in rates.

Thomas S. Dobashi, Edward J. Grubbs*
Department of Chemistry
California State University, San Diego
San Diego, California 92115
Received March 5, 1973

Aryldiazirines. Potential Reagents for Photolabeling of Biological Receptor Sites

Sir:

Since the photochemical generation of a reactive intermediate as a novel approach to the labeling of biological macromolecules was put forward by Westheimer and his group,[1] this technique has been limited to the use of α-keto diazo compounds and of aryl azides as carbene and nitrene precursors, respectively.[2] The carbenes have had to be derived from α-keto diazo compounds because of the chemical instability of the diazo compounds themselves, but the susceptibility of the resulting α-keto carbenes to Wolff-type rearrangements has seriously limited the utility of these materials. Further, it appears that aryl nitrenes are not always as reactive as one would like.[2] What is required is a chemically stable carbene[3] precursor that will photolyze smoothly at wavelengths clear of protein absorption. We report here the synthesis and photolysis of several 3-aryl-3*H*-diazirines. These materials have a chemical stability and photochemical lability that augur well for their use as precursors of carbene labeling reagents.

The only 3-aryl-3*H*-diazirine in the literature is the *p*-nitrophenyl compound, which was prepared by a route using difluoramine.[4] 2,4,6-Triaryl-1,3,5-triazabicyclo[3.1.0]hexanes can be made from aryl aldehydes, chloramine, and ammonia in methanol at −10°. In contrast to the alkyl compounds,[5] oxidative cleavage of the aryl derivatives with acid dichromate gives very poor yields of diazirines, presumably owing to the rapid acid hydrolysis of the intermediate aryl diaziridines. However, the diaziridines can be trapped by oxidation to the diazirine if yellow mercuric oxide is added to the reaction mixture immediately after precipitation of the triazabicyclohexane has begun. In this way, 3-(*p*-tolyl)- (**1**) and 3-(*p*-anisyl)-3*H*-diazirine and the water-soluble *p*-diazirinophenoxyacetic acid (**2**) were prepared (in 2–4% yield). The low yields are offset to some extent by the simplicity of the method, preparative thin-layer chromatography of the reaction mixture giving the diazirine directly. The parent 3-phenyl-3*H*-diazirine (**3**) was prepared in 48% yield by cleavage of the corresponding bicyclohexane with *tert*-butyl hypochlorite in methanol at 0° (**1**, oil; ir ($CHCl_3$) 1600 cm^{-1}; pmr (CCl_4) τ 8.12 (S, 1 H); uv 368 (ϵ 311), 272 (ϵ 319) nm; **2**, yellow crystals; ir (mull) 1610 cm^{-1}; pmr (CD_3OD) τ 7.90 (S, 1 H); uv 378 (ϵ 300), 269 (ϵ 1607) nm; **3**, oil; ir ($CHCl_3$) 1580 cm^{-1}; pmr (CCl_4) τ 8.24 (S, 1 H); uv 362 (ϵ 299), 265 (ϵ 331) nm). The mass spectra showed $M^+ - 28$ peaks characteristic of loss of nitrogen from the molecular ion. No detectable amounts of diazirine could be obtained from the *tert*-butyl hypochlorite cleavage of the *p*-tolyl- or of the *p*-anisyltriazabicyclohexane. The mechanism of this cleavage probably involves initial N-chlorination followed by participation of a lone pair of one of the diaziridine nitrogen atoms in the loss of chloride ion. The resultant cation may then break down to give products other than the diazirine, derived from the aryl carbonium ion (formed by opening the three-membered ring) which can be stabilized by the presence of an electron-releasing group.

The photochemical interconversion of diazirines and diazo compounds is known for diazirine itself[6] and

(1) A. Singh, E. R. Thornton, and F. H. Westheimer, *J. Biol. Chem.*, 237, PC 3006(1962); J. Shafer, P. Baronowsky, R. Laursen, F. Finn, and F. H. Westheimer, *ibid.*, **241**, 421 (1966).
(2) J. R. Knowles, *Accounts Chem. Res.*, **5**, 155 (1972).
(3) Preferably an aryl carbene; alkyl carbenes rearrange to the olefin.
(4) W. A. Graham, *J. Amer. Chem. Soc.*, **88**, 4677 (1966).
(5) E. Schmitz, *Chem. Ber.*, **95**, 690 (1962).
(6) M. J. Amrich and J. A. Bell, *J. Amer. Chem. Soc.*, **86**, 292(1964).

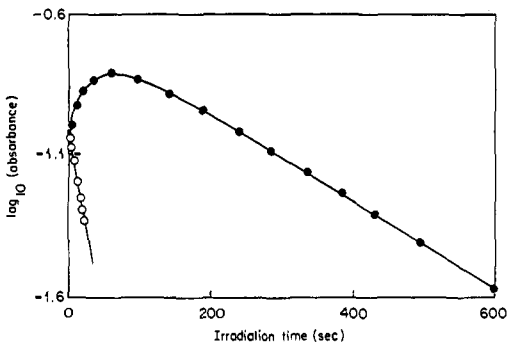

Figure 1. The time dependence of absorbance at the diazirine λ_{max} (362 nm) of 3-phenyl-3*H*-diazirine solutions in hexane, in the absence, a (●), and presence, b (○), of 0.1 *M* acetic acid.

some diazoacetamides[7] and is likely for alkyl diazirines.[8] Irradiation of 3-phenyl-3*H*- and of 3-(*p*-tolyl)-3*H*-diazirine[9] resulted in loss of the characteristic fine structure of the diazirine absorption band centered around 370 nm (Figure 2a,b). There was an initial rapid increase in absorbance at this wavelength followed by a slower decrease (see Figure 1a). New absorption bands at around 275 nm (see Figure 2b) and 490 nm appeared on irradiation, these bands being identical with those of the authentic diazo compounds.[10] When the irradiation of low (0.2 m*M*) concentrations of diazirine was carried out in the presence of 0.1 *M* acetic acid, the decrease in absorbance of the diazirine band was cleanly first order (Figure 1b). Successive uv spectra of the irradiated diazirine showed an isosbestic point under these conditions. However, when a solution of diazirine that had been irradiated for 2 min (see Figures 1a and 2b) was then treated with acetic acid, the diazo compound bands were eliminated as expected, but the absorbance increase at around 370 nm was maintained (Figure 2c). Consequently, the absorbance increase shown in Figure 1a cannot be attributed to a diazo compound and a second intermediate (X), that is insensitive to acid in the dark and has an absorbance maximum in the 340–380-nm region, is therefore implicated. Confirmation of the existence of more than one intermediate was provided by a general method of algebraic analysis of the spectral changes at different wavelengths, devised by Albery.[11] Brief irradiation of authentic phenyldiazomethane did not produce material absorbing in the 340–380-nm region, indicating that formation of the diazirine or of X from the diazo compound is unfavorable under these conditions.

The photolytic decomposition of diazirine is not all *via* the diazo compound. This was demonstrated by nmr examination of the product mixture, which gives the ratio of substituted benzyl acetate (derived from acid-trapped diazo compound) to aryl heptanes (the insertion products of the aryl carbene in hexane) as a function of added acetic acid concentration. The proportion of acetate rose to a maximum value at about

(7) R. A. Franich, G. Lowe, and J. Parker, *J. Chem. Soc., Perkin Trans. 1*, 2034(1972).
(8) H. M. Frey, *Advan. Photochem.*, **4**, 225(1966).
(9) In hexane solution (0.1–2 m*M*), with a medium-pressure mercury lamp and Pyrex filter, at room temperature.
(10) The photoisomerization of 3-(*p*-tolyl)-3*H*-diazirine was also followed by the appearance and decay of the ir band at 2060 cm^{-1} in CCl_4 (diazo N=N stretch).
(11) Dr. W. J. Albery, private communication.

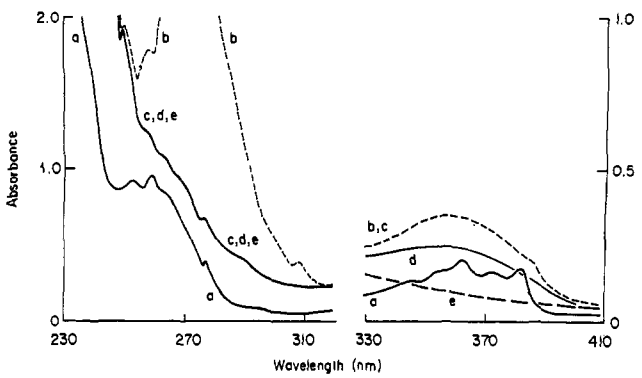

Figure 2. Ultraviolet spectra of a, 3-phenyl-3*H*-diazirine (0.6 m*M* in hexane); b, spectrum a after irradiation for 2 min; c, spectrum b after addition of acetic acid (to 0.25 *M*); d, spectrum c after further irradiation for 75 sec; and e, spectrum c after further irradiation for 5 min.

0.1 *M* acetic acid and was not significantly increased by using higher acid concentrations up to 1 *M*. At the maximum, about 70% of 3-(*p*-anisyl)-3*H*-diazirine and about 50% of 3-(*p*-tolyl)-3*H*-diazirine was converted to acetate (*via* the diazo compound). Since in the presence of acid the formation of X was spectroscopically undetectable (Figure 1b), the acid-insensitive route to carbene (and thence to aryl heptane) is likely to involve the direct photochemical fragmentation of the diazirine. The nature of X is uncertain. One possibility is 7α*H*-indazole which could be formed by ring expansion of the diazirine and which has been postulated as a carbene precursor in the gas-phase pyrolysis of 1*H*-indazole.[12] 3-Phenyl-3-chloro- and 3-(*p*-anisyl)-3-chlorodiazirines[13] show no evidence of formation of any intermediate on photolysis at room temperature. The presence of acetic acid has no effect on the spectral changes and α-chlorobenzyl acetates cannot be detected.

The 3-aryl-3*H*-diazirines reported here have considerable promise in the field of photogenerated labeling reagents, since they admirably fulfill the main criteria of chemical stability and appropriate photolability.

Acknowledgment. We thank the Science Research Council for a Research Studentship (to R. A. G. S.).

(12) W. D. Crow, R. Lea, and M. N. Paddon-Row, *Tetrahedron Lett.*, 2235 (1972).
(13) W. A. Graham, *J. Amer. Chem. Soc.*, **87**, 4396 (1965).

Richard A. G. Smith, Jeremy R. Knowles*
The Dyson Perrins Laboratory, University of Oxford
Oxford, England
Received April 2, 1973

Still Another Change in Rate-Determining Step for a Simple Carbonyl Addition Reaction. Evidence for a Kinetically Significant Proton Transfer Step in Acid-Catalyzed *O*-Methyloxime Formation[1]

Sir:

We wish to report the observation of two breaks on the acid limb of the pH–rate profile for *O*-methyloxime formation from *p*-chlorobenzaldehyde, which indicates the existence of *two* changes in rate-determining step

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