Conformational and Medium Effects on Intramolecular Carbene Reactions[1,2]

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Abstract: The photochemical decomposition of α-diazoamides leads to the intramolecular formation of lactams. Thus, the photolysis of *N*,*N*-diethyldiazoacetamide (**1**) in dioxane produces 1-ethyl-4-methyl-2-azetidinone (**2**) and 1-ethyl-2-pyrollidinone (**3**) in roughly equal amounts. Striking solvent effects are observed on these reactions. As the polarity of the medium is increased, the ratio of β-lactam/γ-lactam increases.

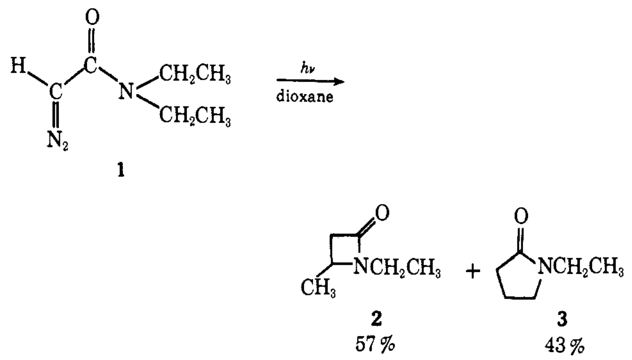
The gross effects of structure and electronic state on the reactivity of carbenes are fairly well understood.[3] On the other hand, the consequences of preferred conformations and solvent effects are less certain. It is the purpose of this report to point out rather profound influences of both conformation and solvent on the chemistry of the carbenes photochemically derived from α-diazo amides.

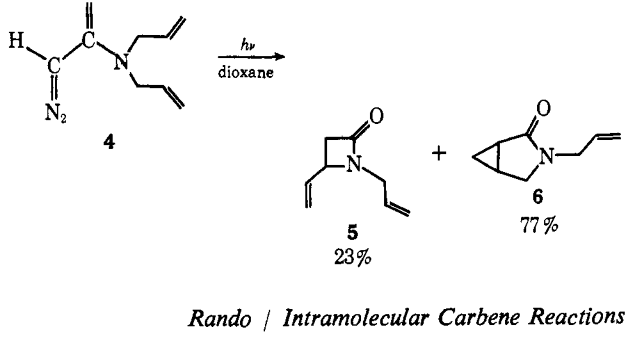
The influence of preferred conformations on the intramolecular reactions of certain carbenoids can be inferred from the work of Closs[4] and Kirmse.[5] These authors demonstrated that the relative amounts of cyclopropanes produced by intramolecular 1,3 C–H insertion were quite sensitive to the effective crowding in the respective transition states. For example, the reaction of *sec*-butyllithium and methylene chloride leads to the formation of approximately nine times as much *trans*-dimethylcyclopropane as *cis*-.[4] The transition state on the way to the cis isomer is, of course, the more crowded one. Kaplan and Meloy[6] argued that the failure of 4-diazo-2,2,5,5-tetramethyl-3-hexanone to undergo Wolff rearrangement can be traced to an unfavorable diazo ketone conformation.

One notes with interest the fact that although carbalkoxycarbenes undergo facile intermolecular C–H insertion[7] and double-bond addition reactions,[3] the intramolecular counterparts of these reactions are not achieved. For example, the photolysis of allyl diazoacetate in cyclohexane affords allyl cyclohexylacetate as the sole product.[8] Intramolecular lactone formation does not occur. Lactone formation only starts to come into the picture when the alkoxy moiety is of exceptional bulk, as in *tert*-butyl diazoacetate.[9] Photochemical decomposition of this diazo ester in cyclohexane affords 9.5% γ,γ-dimethylbutyrolactone along with 90.5% *tert*-butyl cyclohexylacetate. All this suggests that the dominant factor in these reactions is a conformational one, whereby the *O*-alkyl moiety of the diazo esters never achieves sufficient proximity to the divalent center, except in the bulky *tert*-butyl case, for intramolecular reactions to ensue. A test of this hypothesis is to investigate the photochemical decomposition of *N*,*N*-dialkyldiazo amides. In these cases intramolecular lactam formation should readily occur, since one alkyl group must remain adjacent to the incipient carbene as a consequence of the planar peptide bond. We should like to report studies on the photochemical decompositions of diazo amides which substantiate these views. In addition, rather striking solvent effects in these reactions were also observed.

Results and Discussion

The photochemical decomposition of *N*,*N*-diethyldiazoacetamide (**1**) in *p*-dioxane led to the production of the two possible intramolecular insertion products (**2** and **3**) in roughly equal amounts. Absolutely no intermolecular reaction products were formed. When double bonds were introduced into the amine portion of the diazo amide, as in *N*,*N*-diallyldiazoacetamide (**4**), intramolecular reaction again occurred (**5** and **6**), to the complete exclusion of intermolecular products.





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[1] A portion of this work appeared in preliminary form: R. R. Rando, *J. Amer. Chem. Soc.*, **92**, 6706 (1970).

[2] This work was supported by a grant from the Petroleum Research Fund, administered by the American Chemical Society (No. 1489-G1).

[3] W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964; "Carbene, Carbenoide and Carbenanalogue," Verlag Chemie, Weinheim/Bergstr., Germany, 1969.

[4] G. L. Closs, *J. Amer. Chem. Soc.*, **84**, 809 (1962).

[5] W. Kirmse and G. Wächtershäuser, *Tetrahedron*, **22**, 63 (1966).

[6] F. Kaplan and G. K. Meloy, *J. Amer. Chem. Soc.*, **88**, 950 (1966).

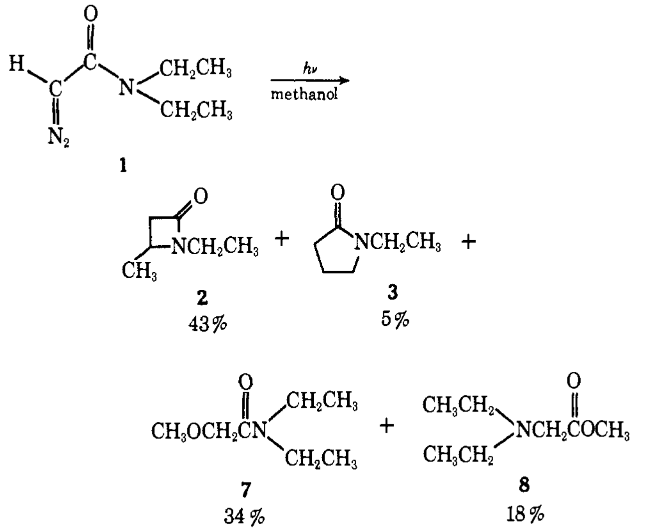
[7] W. von E. Doering and L. H. Knox, *ibid.*, **78**, 4947 (1956); **83**, 1989 (1961).

[8] W. Kirmse and H. Dietrich, *Chem. Ber.*, **98**, 4027 (1965).

[9] W. Kirmse, H. Dietrich, and H. W. Bucking, *Tetrahedron Lett.*, 1833 (1967).

The total lack of intermolecular insertion products in these cases is, of course, opposite to what is observed in the photochemistry of diazo esters. These observations are, then, quite in accord with the idea that the dominant force in these reactions is a conformational one. It is interesting to note that the photolysis of *N*-methyldiazoacetamide in water[10] gives rise only to O–H insertion and Wolff rearrangement products, but no β-lactam, a result entirely consistent with our hypothesis.

Profound solvent effects are evidenced in the photochemistry of diazo esters. In hydrocarbon solvents the photochemical decomposition of ethyl diazoacetate leads to intermolecular C–H insertion,[7] with no other isolable products being formed. However, in protic solvents, such as methanol[10] or 2-propanol,[11] this mode of reaction is all but abolished at the expense of Wolff rearrangement and O–H insertion. When *N*,*N*-diethyldiazoacetamide was photolyzed in methanol, the yield of β-lactam **2** was little affected, whereas the formation of γ-lactam **3** was sharply decreased.



The amide **7** is the O–H insertion product and the ester **8** arises by addition of methanol to the Wolff-rearranged product. The suppression of γ-lactam **3** formation is analogous to suppression of C–H insertion products in the diazo ester cases.

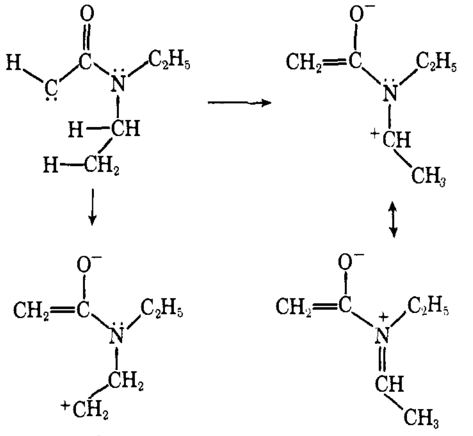
Further studies of solvent effects on the decompositions of **1** led to the results shown in Table I. As can be seen, there is a tendency for the **2**/**3** ratio to increase with increasing dielectric constant of the medium. This effect is especially striking in the methanol and lithium bromide addition cases.

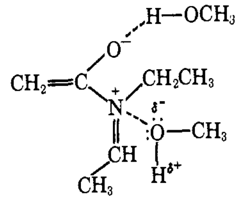
Table I. Photolysis of *N*,*N*-Diethyldiazoacetamide (**1**) in Different Media

Solvent	Dielectric const,[b] ε	% **2**[a]	% **3**[a]
Cyclopentane	1.97	53	47
p-Dioxane	2.2	57	43
Ethyl acetate	6.02	63	37
Methylene chloride	9.08	62	38
Acetone	20.7	60	40
Methanol	32.6	90	10
Acetonitrile	37.5	69	31
Cyclopentane Methanol (9:1)		81	19
p-Dioxane–LiBr (1%)		66	34
Acetone–LiBr (3.5%)		87	13

[a] These values refer to relative yields. The absolute yields in cases where directly measured were always greater than 90%. In all cases, save for the LiBr and MeOH runs, **2** and **3** were the sole products. See Experimental Section. [b] R. C. Weast, Ed., "Handbook of Chemistry and Physics," The Chemical Rubber Publishing Co., Cleveland, Ohio, 1969, p E62.

The fact that β-lactam **2** and γ-lactam **3** formation are affected differently by solvents requires that their mechanisms of formation be different. One might argue that this difference is a ramification of the polarity differences in their respective transition states. Polar resonance contributors such as **9** should be important to β-lactam **2** formation, whereas the corresponding polar contributor **10** for γ-lactam formation should be relatively unimportant. If this is true, the transition state on the way to β-lactam **2** formation should be differentially stabilized by polar solvents, such as methanol, and hence able to effectively compete with the normally rapid O–H insertion and Wolff rearrangement processes. Further inspection of the results in Table I shows that the medium effect is not entirely linear with dielectric constant. Methanol appears to occupy a rather unique position in this series. For example, it suppresses γ-lactam **3** formation more than acetonitrile, even though the latter has a larger dielectric constant. It might be that methanol elicits a special solvent effect as depicted in **11** not possible with nonhydroxylic solvents such as acetonitrile. The special effect of methanol can also be seen in the results obtained from the decomposition of **1** in the cyclopentane–methanol mixture. Finally, it is interesting to note that the medium effect appears to be asymmetrical, in that at the lower reaches of solvent polarity, *i.e.*, cyclopentane, the **2**/**3** ratio is governed only by statistics. This must mean that the net polarity of the β-lactam **2** transition state can be induced by the medium. In





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(10) H. Chaimovich, R. J. Vaughan, and F. H. Westheimer, *J. Amer. Chem. Soc.*, **90**, 4088 (1968).

(11) O. P. Strausz, T. DoMinh, and H. E. Gunning, *ibid.*, **90**, 1660 (1968).

nonpolar solvents, **2** is probably generated *via* a transition state which is nondipolar in nature, *i.e.*, akin to the transition state leading to **3**.

Experimental Section

Materials. *p*-Nitrophenyl chloroformate was purchased from K and K Labs., Inc., and purified by recrystallization from carbon tetrachloride before use. *p*-Nitrophenyl diazoacetate was prepared and purified by the published procedure.[10] 1-Ethyl-2-pyrollidinone (**3**) was purchased from Aldrich Chemical Co. *N*,*N*-Diethylglycinate **8** was synthesized by reacting diethylamine with methyl bromoacetate.[12] *N*,*N*-Diethylmethoxyacetamide (**7**) was prepared by reacting methoxyacetyl chloride purchased from Aldrich Chemical Co. with excess diethylamine in dry ether. All of the solvents used were dried and distilled before use.

Analytical. Separation of the photolysates was accomplished on an F and M Model 720 vapor phase chromatograph with an electrical conductivity detector. A 5 ft × $^1/_4$ in. 5% Carbowax 20M on Chromosorb W (60–80 mesh) column operated at 150° column temperature was used. Under these conditions, excellent separations of all isomers were achieved. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer; nmr spectra on a Varian Model A-60 spectrometer; and mass spectra on a Varian M-66 mass spectrometer.

Photolyses. Photolyses were carried out through Pyrex vessels using G.E. sunlamps with external water cooling so that the internal temperature never rose above 35°. The reactions were run until the diazo stretching absorption (4.69 μ) was no longer visible in the infrared spectrum. Under the conditions of the photolyses (Pyrex filter), none of the products reported were interconvertible.

Synthesis of *N*,*N*-Diethyldiazoacetamide (1). *p*-Nitrophenyl diazoacetate[10] (2.0 g, 10 mmol) was added to 25 ml of 40% diethylamine in water. The bright yellow solution was stirred at room temperature for 2 hr, evaporated to dryness, taken up in a minimum quantity of 9:1 benzene–ethyl acetate, and applied to a Woelm activity grade IV neutral alumina column. Elution with 9:1 benzene–ethyl acetate led to the recovery of pure *N*,*N*-diethyldiazoacetamide **1** (0.43 g, 3 mmol) as a yellow oil. The diazoamide exhibits strong infrared absorption ($CHCl_3$) at 4.69 ($C{=}N{=}N$) and 6.2 μ ($C{=}O$), and nmr absorption ($CDCl_3$) at τ 4.9 (s) of relative area 1 ($HC{=}N_2$), 6.7 (q) of relative area 4 ($N{-}CH_2{-}$), and 8.8 (t) of relative area 6 ($N{-}CH_2{-}C\mathit{H}_3$).

Synthesis of *N*,*N*-Diallyldiazoacetamide (4). *p*-Nitrophenyl diazoacetate (2.0 g, 10 mmol) was added to 25 ml of 40% diallylamine in methanol. The reaction was run as usual, and after purification *N*,*N*-diallyldiazoacetamide (0.35 g, 2.3 mmol) was isolated as a yellow oil. The diazoamide exhibited the usual strong absorption in the infrared ($CHCl_3$) at 4.7 and 6.2 μ.

Photolysis of *N*,*N*-Diethyldiazoacetamide (1) in Dioxane. The diazoamide (0.27 g, 1.9 mmol) was dissolved in 15 ml of dry, distilled *p*-dioxane and photolyzed as described. The dioxane was removed by distillation leaving 0.205 g of a pale yellow oil. Vapor phase chromatography indicated the presence of two major products accounting for greater than 95% of the material applied to the column. The product with the longer retention time proved to be 1-ethyl-2-pyrollidinone (**3**) by comparison of its ir and nmr spectra along with its vpc retention time with authentic material (Aldrich Chemical Co.). The product with the shorter retention time was isolated as a colorless oil and proved to be 1-ethyl-4-methyl-2-azetidinone (**2**). This β-lactam showed carbonyl absorption in the ir ($CHCl_3$) at 5.75 μ ($C{=}O$). Amide carbonyl absorption in this region is quite indicative of a strained β-lactam ring.[13] The compound also showed nmr absorption ($CDCl_3$) at τ 6.3 (m) ($CH_3C\mathit{H}$-ring) of relative area 1, 6.8 (q) ($NC\mathit{H}_2CH_3$) of relative area 2, 7.2 (m) ($CHC{=}O$) of relative area 1, 7.4 (m) ($CHC{=}O$) of relative area 1, 8.7 (d) ($C\mathit{H}_3CH$) of relative area 3, and 8.9 (t) ($NCH_2C\mathit{H}_3$) of relative area 3.[14] The mass spectrum revealed the expected molecular ion with *m*/*e* 113 in addition to showing a cracking pattern uniquely ascribable to a four-membered β-lactam ring;[15] that is, intense peaks at *m*/*e* 42 ($CH_2{=}C{=}O$, $CH_3CH{=}CH_2$) and 72 (CH_3CH_2NCO, $CH_3CH_2NCH{=}CH_2$) were found.

The relative amounts of the two isomers were determined by measuring the relative areas of their respective vpc traces and correcting for statistical weighting (**3**/**2**) and conductivity differences. No other products were formed. This was demonstrated by the observation that no additional peaks were observable on the vpc trace and that the nmr of the crude product (before chromatography) showed no signals other than those accountable for by the β- and γ-lactams.

Photolysis of *N*,*N*-Diethyldiazoacetamide (1) in Methanol. The diazoamide (0.17 g, 1.2 mmol) was dissolved in 10 ml of methanol and photolyzed as usual. Careful fractional distillation of the photolysate led to the recovery of 0.15 g of a pale yellow liquid which was subjected to vpc as above. In addition to the β- and γ-lactam peaks, two others were observed. The compound with the shortest retention time proved to be methyl *N*,*N*-diethylglycinate (**8**) by comparison with independently prepared material. The compound with retention time intermediate between the two lactams proved to be *N*,*N*-diethylmethoxyacetamide (**7**), also by comparison with authentic material.

Photolysis of *N*,*N*-Diethyldiazoacetamide (1) in Various Solvents. The diazoamide (0.006 g, 0.043 mmol) was dissolved in 300 μl of the appropriate solvent, photolyzed, and analyzed as usual. In the cyclopentane, *p*-dioxane, ethyl acetate, methylene chloride, acetone, and acetonitrile runs, **2** and **3** were the sole products of the photochemical decompositions, as shown by vpc analysis. In these cases, the same absolute amounts of total product were obtained within experimental error. Also, no polymer formation was observed. The vapor phase chromatography was done under identical conditions for each of the samples in triplicate. Equal aliquots of the different samples always gave the same total deflection on the vpc trace. The absolute total yield of **2** + **3** was judged to be at least 90% based on pure diazoamide **1**. In methanol and cyclopentane–methanol (9:1), products **7** and **8** were formed in addition to **2** and **3**. When LiBr was added, at least one additional product was formed aside from **2** and **3**. However, at all times during the photochemical decomposition the **2**/**3** ratio remained constant suggesting that the additional product(s) was neither being depleted at the expense of nor collapsing to **2** or **3**. Neither **2** nor **3** is photochemically interconvertible in the presence of added LiBr under the conditions used.

Photolysis of *N*,*N*-Diallyldiazoacetamide (4). The diazoamide (0.18 g, 1.2 mmol) was dissolved in 12 ml of *p*-dioxane, photolyzed, and worked up in the usual way to yield 0.145 g of a pale yellow oil. Vapor phase chromatography of this material at 150° showed the presence of only two peaks. The material with the shorter retention time proved to be 1-allyl-4-vinyl-2-azetidinone (**5**). Its ir spectrum showed the typically high β-lactam carbonyl absorption[13] at 5.75 μ ($C{=}O$), and the mass spectrum showed the correct molecular ion at *m*/*e* 137 and a cracking pattern uniquely ascribable to a four-membered ring system,[15] *i.e.*, intense peak at *m*/*e* 54 ($CH_2{=}CHCH{=}CH_2$), etc. The compound with the longer retention time proved to be *N*-allyl-2-azabicyclo[3.1.0]hexan-1-one (**6**). This compound showed strong ir absorption ($CHCl_3$) at 6.0 μ ($C{=}O$), a parent molecular ion at *m*/*e* 137, and nmr absorption ($CDCl_3$) at τ 4.2 (m) (vinyl CH) of relative area 1, 4.6 (m) (vinyl CH) of relative area 1, 4.9 (m) (vinyl CH) of relative area 1, 6.1 (d) (allyl CH_2) of relative area 2, 6.4 (m) ($N{-}CH_2$) of relative area 2, 7.9 (m) ($C\mathit{H}C{=}O$) of relative area 1, 8.1 (m) (bridgehead H) of relative area 1, 8.8 (m) (cyclopropyl H) of relative area 1, and 9.3 (m) (cyclopropyl H) of relative area 1. No other products were observed.

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[12] T. Terakawa, *J. Pharm. Soc. Jap.*, **74**, 287 (1954).

[13] L. M. Bellamy, "Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 214.

[14] The nmr spectrum of this compound was quite similar to analogous β-lactams in K. D. Barrow and M. T. Spotswood, *Tetrahedron Lett.*, 37, 3325 (1965).

[15] H. E. Audier, M. Fetizon, H. B. Kagan, and J. L. Luche, *Bull. Soc. Chim. Fr.*, 2297 (1967); M. Fisher, *Chem. Ber.*, **101**, 2669 (1968).