Stabilization of Singlet Ethoxycarbonylnitrene by 1,4-Dioxan

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A study of the solvent polarity and triplet quenching effects on the insertion of ethoxycarbonylnitrene into cyclic ethers demonstrates that the singlet state of the nitrene is stabilized by 1,4-dioxan. The lowering of the yield of the triplet nitrene product compared with that of the singlet nitrene product in 1,4-dioxan as solvent supports this postulate. The activation parameters for insertion in the presence and absence of a triplet quencher further support singlet stabilization. This is discussed in the terms of the interaction of the nitrene *p* orbital with the lone pair electrons of ether oxygen atoms.

THE rate of change of intersystem crossing by nitrene in its interaction with solvents has been extensively studied. Solvents containing heavy atoms promote intersystem crossing of ethoxycarbonylnitrene in addition reactions with olefins.[1] It has recently been reported that hexafluorobenzene[2] and dichloromethane[3,4] stabilize the singlet state of nitrenes during the C–H insertion reactions. Gleiter and Hoffmann[5] have proposed the theory that nitrene singlet states are stabilized by interaction with the lone pair electrons of NH_3, H_2O, halogeno-compounds, *etc.*

For a solvent which stabilizes singlet ethoxycarbonyl nitrene, the reactivity of the nitrene with the α-C–H bonds of ethers, which react with both singlet and triplet nitrene,[6] may be altered by comparison with a solvent in which such stabilization is not feasible. The yield of the triplet nitrene product would be decreased in the solvent stabilizing the singlet nitrene. The present work was undertaken to investigate this phenomenon for 1,4-dioxan.

Solvents containing heavy atoms[1] and carbonyl groups[7] may affect the spin state of ethoxycarbonylnitrene and its precursor, ethyl azidoformate. Protic solvents may solvate the ethereal substrates[8] so that the

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[1] 'Nitrenes,' ed. W. Lwowski, Interscience, New York, 1970, p. 191.

[2] D. S. Breslow and E. I. Edwards, *Tetrahedron Letters*, 1972, 2041.

[3] G. R. Felt, S. Linke, and W. Lwowski, *Tetrahedron Letters*, 1972, 2037.

[4] R. C. Belloli, M. A. Whitehead, R. H. Wollenberg, and W. A. LaBahn, *J. Org. Chem.*, 1974, **39**, 2128.

[5] R. Gleiter and R. Hoffmann, *Tetrahedron*, 1968, **24**, 5899.

[6] H. Nozaki, S. Fujita, H. Takaya, and R. Noyori, *Tetrahedron*, 1967, **23**, 45.

[7] Ref. 1, p. 189.

[8] E. L. Eliel and O. Hofer, *J. Amer. Chem. Soc.*, 1973, **95**, 8041.

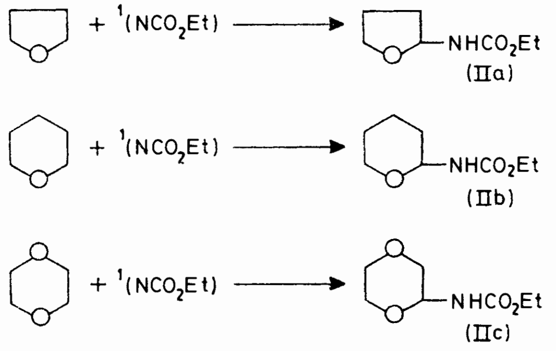
reactivity of the nitrene is affected. Thus, the above solvents other than 1,4-dioxan were excluded.

Cyclohexane was used in competitive reactions to obtain the relative reactivity of the nitrene towards cyclic ethers since only singlet nitrene inserts to give cyclohexylurethane (I) [equation (1)].[9]

$$C_6H_{12} + {}^1(NCO_2Et) \longrightarrow \underset{(I)}{C_6H_{11}NHCO_2Et} \qquad (1)$$

RESULTS AND DISCUSSION

A solution of ethyl azidoformate, cyclohexane, and a cyclic ether as substrate in the molar ratio 1 : 30 : 30 was dissolved in a given solvent (90% v/v), and irradiated under the conditions given in the Experimental section. The relative rate constant of insertion (k_{rel}) into one α-C–H bond of tetrahydrofuran (THF), tetrahydropyran (THP), or 1,4-dioxan compared with insertion into one C–H bond of cyclohexane was determined by means of g.l.c. from the relative yield of ethyl tetrahydrofuran-2-carbamate (IIa), ethyl tetrahydropyran-2-carbamate (IIb), or ethyl 1,4-dioxan-2-carbamate (IIc) compared with that of cyclohexylurethane (I). For example, the relative rate constant k_{rel} of THF was derived from equation (2). In this



SCHEME 1

$$k_{rel} = \{d[(IIa)]/d[(I)]\}([cyclohexane]_0/[THF]_0)(12/4) \qquad (2)$$

equation, 12 and 4 are the number of α-C–H bonds in the substrate. The k_{rel} values of THP and 1,4-dioxan were derived similarly.

Solvent Polarity Effects.—The log k_{rel} values are plotted against two solvent polarity parameters, Kirkwood's function $(D - 1)/(2D + 1)$,[10] and E_T (30) values[11] (Figures 1 and 2). The k_{rel} values for THF and THP are considerably lowered in 1,4-dioxan as solvent. If the THF–1,4-dioxan and THP–1,4-dioxan interactions decrease the k_{rel} values in 1,4-dioxan, the linear relationship between 1,4-dioxan and cyclohexane as substrate (Figures 1 and 2) should not be observed in the case of THF and THP as solvent. Therefore, this possibility was ruled out, and a nitrene–1,4-dioxan interaction was assumed.

In order to establish the special effect of 1,4-dioxan, the k_{rel} values of THF and THP were measured in an n-hexane–1,4-dioxan mixture (Figure 3). The curves in Figure 3 indicate the predominant effect on the k_{rel} value by 1,4-dioxan over n-hexane.

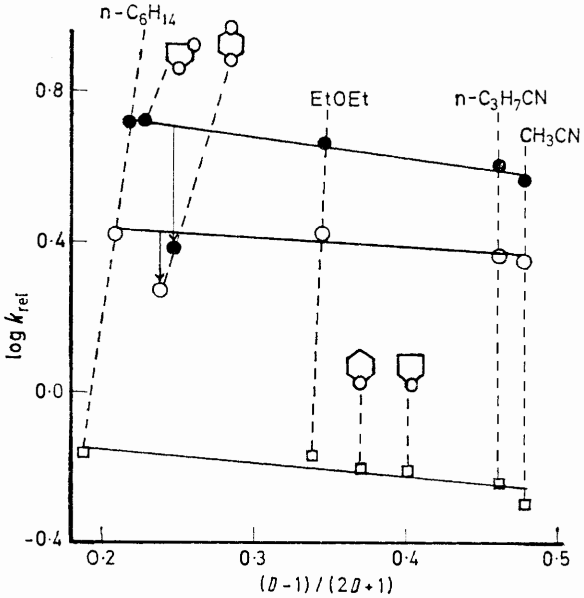


FIGURE 1 Plot of log k_{rel} against $(D - 1)/(2D + 1)$ as a measure of the solvent polarity effect. The dielectric constant was calculated from the proportions (solvent–substrate 9 : 1 v/v) of the reaction mixture. Substrate composition (1 : 1): ●, THF–cyclohexane; ○, THP–cyclohexane; □, 1,4-dioxan–cyclohexane

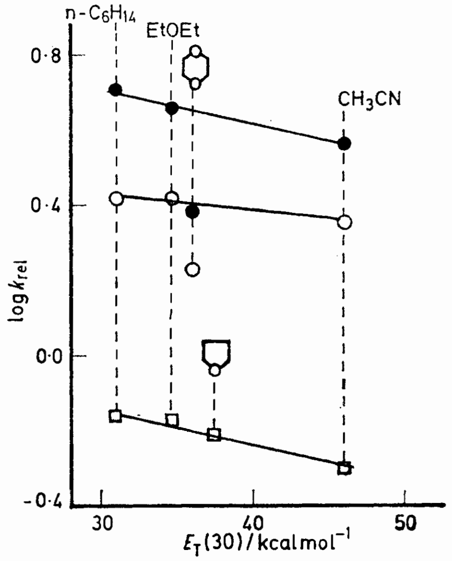


FIGURE 2 Plot of log k_{rel} against $E_T(30)$ as a measure of solvent polarity. E_T Values for solvent–substrate 9 : 1 (v/v) were used. Substrate composition (1 : 1): ●, THF–cyclohexane; ○, THP–cyclohexane; □, 1,4-dioxan–cyclohexane

The solvent polarity effect in triplet quenching experiments with piperylene (0.25M) described in the

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[9] J. M. Simson and W. Lwowski, *J. Amer. Chem. Soc.*, 1969, **91**, 5107.

[10] K. B. Wiberg, 'Physical Organic Chemistry,' Wiley, New York, 1966, p. 381.

[11] E. M. Kosower, 'An Introduction to Physical Organic Chemistry,' Wiley, New York, 1968, p. 305.

following section was obtained for insertion into THF (Figure 4). No unusual effect is observed for 1,4-dioxan.

These results suggest that the nitrene–1,4-dioxan interaction occurs without changing the reactivity of C–H insertion.

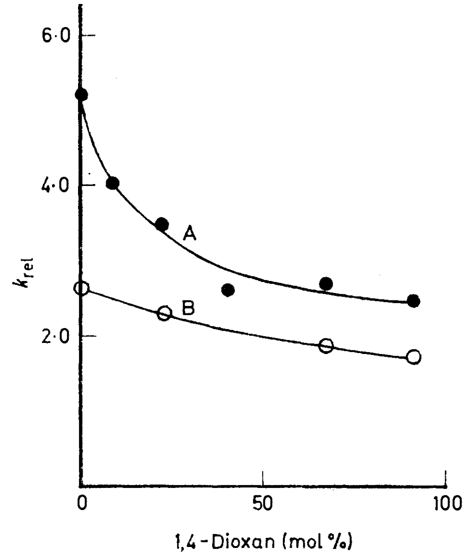


FIGURE 3 Plot of k_{rel} against mol% 1,4-dioxan in n-hexane for insertion into: A, THF; B, THP

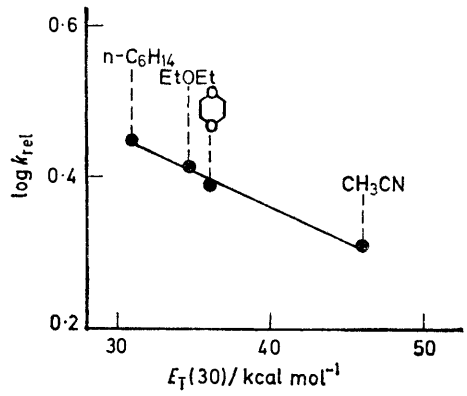


FIGURE 4 Plot of log k_{rel} for insertion into THF against $E_T(30)$ in the presence of piperylene (0.25M) as a measure of the solvent polarity effect. E_T Values for solvent–substrate 9 : 1 (v/v) were used

Quenching Experiments with Piperylene.—The formation of the triplet nitrene product,[6] ethyl carbamate (III), is inhibited in the presence of piperylene (>0.25M)

$$^3(N_3CO_2Et) \longrightarrow {}^3(NCO_2Et) \xrightarrow{\text{H abstraction}} \underset{\text{(III)}}{H_2NCO_2Et} \quad (3)$$

(Table 1). This indicates that piperylene acts as a good quencher for the triplet nitrene or triplet ethyl azidoformate.

The k_{rel} values of THF in the absence of piperylene is larger than that in its presence as shown in Figures 1, 2, and 4 and in Table 1. This can reasonably be interpreted by assuming that THF is reactive to both the singlet (S) and triplet nitrene (T) to give carbamate (IIa).

$$\text{THF} + \underset{\text{S}}{^1(NCO_2Et)} \xrightarrow{k_{TS}} \text{(IIa)} \quad (4)$$

$$\text{THF} + \underset{\text{T}}{^3(NCO_2Et)} \xrightarrow{k_{TT}} \text{(IIa)} \quad (5)$$

Since cyclohexane reacts with only the singlet nitrene[9] to give urethane (I), we obtain equation (6) where k_C, k_{TS}, and k_{TT} are the rate constants in equations (1), (4), and (5) respectively. From equations (2) and (6),

$$d[(IIa)]/d[(I)] = \{(k_{TS}[THF]_0[S] + k_{TT}[THF]_0[T])/(k_C[Cyclohexane]_0[S])\}(4/12) \quad (6)$$

equation (7) is obtained. Therefore the k_{rel} value in the

$$k_{rel} = (k_{TS} + k_{TT}[T]/[S])/k_C \quad (7)$$

absence of piperylene is low by comparison with that in the presence of piperylene, because [T]/[S] decreases in the latter case. k_{TS}/k_C Is constant in the presence of piperylene (>0.25M) since [T] is zero (Table 1).

TABLE 1

Quenching experiments with piperylene in THF–cyclohexane (THF : cyclohexane : ethyl azidoformate 1 : 1 : 25; total volume 10.0 ml)

[Piperylene]/M	k_{re}	Carbamate (III) : Urethane (I)
0	5.2	1.5
0.023	4.7	1.5
0.10	3.2	0.4
0.25	3.4	0
0.45	3.4	0
0.55	3.2	0

The low k_{rel} values of THF and THP in 1,4-dioxan by comparison with the other solvents (Figures 1—3) can be explained by the stabilization of the singlet nitrene state in 1,4-dioxan, as demonstrated in equation (7).

Effect of 1,4-*Dioxan on the Formation of Ethyl Carbamate* (III).—The relative yield of carbamate (III) to urethane (I) was used as a measure of the relative concentrations of [T] and [S]. This relative yield decreases when 1,4-dioxan is used as solvent or added to the system, with a few exceptions (Table 2). Similarly the relative yield diminishes when 1,4-dioxan is increased in the n-hexane–1,4-dioxan mixture (Table 3). These

TABLE 2

Relative yield of ethyl carbamate compared with that of cyclohexylurethane

Solvent (22.5 ml)	1 : 1 Substrate (2.5 ml)		
	THF–Cyclohexane	THP–Cyclohexane	1,4-Dioxan–cyclohexane
n-Hexane	7.8	9.6	2.1
1,4-Dioxan	3.8	5.4	
Ethyl ether	22.4	16.7	16.0
THF			14.0
THP		26.2	20.8
n-Butyronitrile	3.2	1.3	0.4
Acetonitrile	13.9	20.3	13.0

results also indicate that the singlet nitrene concentration is increased in 1,4-dioxan.

TABLE 3

Relative yield of ethyl carbamate compared with that of cyclohexylurethane in n-hexane–1,4-dioxan

Solvent (22.5 ml) mol % 1,4-dioxan in n -hexane	Substrate (2.5 ml) 1 : 1 THF–cyclohexane (13.1 mmol)	1 : 1 THP–cyclohexane (12.2 mmol)
0	7.8	9.6
10	9.8	
25	7.9	7.4
50	5.8	
75	5.5	5.1
100	3.8	5.4

Activation Parameters for the Insertions in the Presence and Absence of Piperylene.—The activation parameters for the insertion of the nitrene into THF, THP, and 1,4-dioxan compared with cyclohexane were evaluated to provide information of the effect of 1,4-dioxan on the kinetics of reaction. The data are summarized in Table 4. The effect of added piperylene (0.25M) on the activation parameters ΔE_a and $\Delta\Delta S^‡$ for insertion into 1,4-dioxan is much smaller than that for insertion into THF or THP. This indicates that the nitrene is almost entirely in the singlet state in 1,4-dioxan even if piperylene is not present.

TABLE 4

Activation parameters for insertion in the presence and absence of piperylene (0.25M) (15—50°; THF, THP, or 1,4-dioxan : cyclohexane : ethyl carbamate 1 : 1 : 25; total volume 10.0 ml)

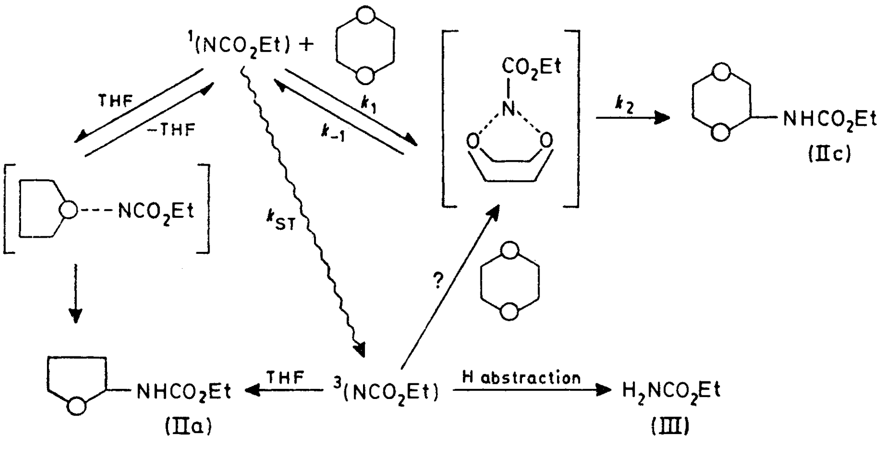
	Absence of piperylene		Presence of piperylene	
Ethereal substrate	$\Delta\Delta S^‡$/cal mol $^{-1}$ K^{-1}	ΔE_a/kcal mol^{-1}	$\Delta\Delta S^‡$/cal mol^{-1} K^{-1}	ΔE_a/kcal mol^{-1}
THF	7.8	1.4	−2.5	−1.5
THP	8.0	1.9	1.6	0.0
1,4-Dioxan	3.5	1.3	2.1	0.9

Effect of Addition of 15-*Crown*-5 *Ether.*—The effect of the addition of the crown ether to the system is nearly the same as that of 1,4-dioxan (Table 5). Therefore singlet stabilization in 1,4-dioxan seems to be caused by the interaction of the nitrene with two lone pairs of electrons of the boat or skew-boat forms of 1,4-dioxan (Scheme 2). In order to explain the stabilization of the singlet nitrene by 1,4-dioxan, we postulate the interaction of the vacant *p* orbital of the singlet nitrene with the two lone pairs of 1,4-dioxan (Scheme 2). This interaction competes sufficiently with the intersystem crossing rate (k_1[1,4-Dioxan] $\gg k_{ST}$) to reduce the yield of carbamate (III). Furthermore, the formation of carbamate (IIc) after singlet stabilization needs high energy for steric reasons since the ΔE_a and $\Delta\Delta S^‡$ values for insertion into 1,4-dioxan in the presence of piperylene are fairly high compared with those for insertion into THF or THP. Thus the relation $k_{-1} \gg k_2$, holds for 1,4-dioxan. In an ether such as THF, singlet stabilization would not occur since the insertion product (IIa) is probably preferentially formed after interaction of the singlet nitrene with THF with little return to singlet nitrene and THF. The low k_{rel} value of 1,4-dioxan by comparison with those for THF or THP, *ca.* 1/10 or 1/5, supports this assumption.

TABLE 5

Effect of 15-crown-5 ether on insertion into THF

Cyclo-hexane (g)	THF (g)	1,4-Dioxan (g)	Crown ether (g)	Ethyl azido-formate (mg)	k_{re}
1.102	0.551	0	0	48	5.10
0.633	0.553	0.477	0	48	3.97
0.642	0.557	0	0.474	48	3.78



SCHEME 2

Alternatively interaction between two *p* orbitals of the triplet nitrene and two lone pairs of 1,4-dioxan might exclusively quench the triplet nitrene to give the singlet nitrene. This type of interaction which involves a bent three-centre bond has been postulated by Gleiter and Hoffmann.[5] If this process is much more stronger than a two-centre interaction of the triplet nitrene with ethers such as THF, we cannot neglect this possibility. In this case, the interaction may correspond to the interaction of the singlet nitrene with **1,4-dioxan** as shown in Scheme 2.

EXPERIMENTAL

I.r. spectra were obtained on a Hitachi model EPI-G3 spectrometer. N.m.r. spectra were taken with Nippon Denshi high resolution JNM 4H 100 spectrometer with tetramethylsilane as internal standard. G.l.c. for quantitative analyses was performed with a Hitachi model 063-0012 g.l.c. unit on an aluminium column (2 m × 2 mm ext. diam.), packed with polyethylene glycol 20 M (10%) in Uniport KS (60—80 mesh). Helium was used as carrier gas. Photolyses were performed with an external 300 W high pressure Hg lamp (Eikosha model PIH-300).

Cyclohexane, THF, THP, 1,4-dioxan, 1,3-dioxolan, n-hexane, ethyl ether, n-butyronitrile, and acetonitrile were purified by standard methods. Piperylene was purified by distillation, b.p. 42°, of commercial material. Ethyl azidoformate,[12] b.p. 45—46° at 35 mmHg, cyclohexylurethane (I),[12] m.p. 54.5—55.5°, and 15-crown-5 ether,[13] b.p. 106—110° at 0.2 mmHg, were obtained by methods described in the literature.

Ethyl Tetrahydrofuran-2-carbamate (IIa).—A solution of THF (308 mmol) and ethyl azidoformate (7.4 mmol) was heated in a Pyrex pressure vessel at 110° for 21 h. The reaction mixture was distilled under reduced pressure and the product (IIa) was collected, b.p. 93—96° at 3 mmHg (lit.,[6] 84—86° at 0.07 mmHg), $\nu_{max.}$ (CCl_4) 3 430 (NH), 1 720 (C=O), 1 500 (NH), and 1 220 cm^{-1} (C–O–C).

Ethyl Tetrahydropyran-2-carbamate (IIb).—A solution of THP (143 mmol) and ethyl azidoformate (48 mmol) in a quartz tube was irradiated at 25° for 35 h. The mixture was distilled under reduced pressure, and the desired product was purified by g.l.c. on an aluminium column (2 m × 6 mm ext. diam.), b.p. 83—86° at 1 mmHg (lit.,[6] 108° at 0.15 mmHg), τ (CCl_4) 8.7—8.9 (3 H, t, CH_3), 8.1—8.8 (6 H, m, 3-, 4-, 5-H_2), 6.5 (2 H, t, 6-H_2), 6.2 (1 H, t, CH), 6.0 (2 H, q, OCH_2), and 5.4br (1 H, NH).

Ethyl 1,4-Dioxan-2-carbamate (IIc).—A solution of 1,4-dioxan (235 mmol) and ethyl azidoformate (35 mmol) was heated at 110° for 34 h. The mixture was distilled under reduced pressure and the product was separated, b.p. 103—105° at 1 mmHg (lit.,[6] 102—103° at 0.15 mmHg), $\nu_{max.}$ (CCl_4) 3 450 (NH), 1 740 (C=O), 1 510 (NH), and 1 215 cm^{-1} (C–O–C).

Ethyl carbamate (III) was purified by recrystallization, m.p. 48—50°, of commercial material from toluene.

Photochemical Reactions and Analyses.—Ethyl azidoformate, cyclohexane, and THF, THP, or 1,4-dioxan (total 2.5 ml) in the molar ratio 1 : 30 : 30, were placed in a quartz vessel, and to this solvent (22.5 ml) was added. After purging with dry nitrogen, the mixture was irradiated at 25° under nitrogen for 1 h, resulting in *ca.* 50% decomposition of azide. The solvent and azide were removed under reduced pressure at room temperature. The residue was dissolved in benzene (*ca.* 0.5 ml), and analysed by g.l.c. under conditions which gave satisfactory separation: injector 210, detector 200, and column 150°. Non-photolysed mixtures did not produce carbamate under the g.l.c. conditions. The insertion products (I) and (II) and carbamate (III) were identified by comparison of their i.r. and n.m.r. spectra with those of authentic materials. Quantitative analyses were performed by calibrating the detector response with a weighed amount of the known material, and then comparing the peak areas of unknown samples with the standard. The k_{rel} values were derived from the quantitative data thus obtained. The yield of carbamate (III) compared with that of urethane (I) was obtained by a similar procedure.

The solvent polarity effect in the presence of piperylene (0.25M) was determined by the method mentioned above. Quenching experiments with piperylene and experiments to find the activation parameters and using crown ether (Tables 1, 4, and 5) were performed under conditions similar to those above.

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