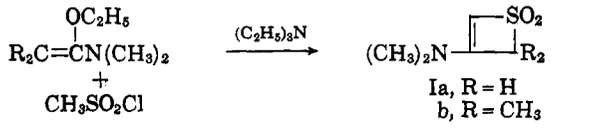
Communications TO THE EDITOR

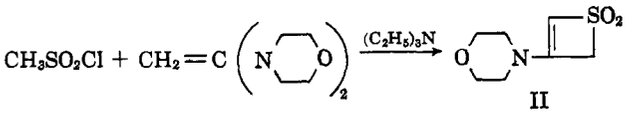
3-Thietanone 1,1-Dioxide

Sir:

The reaction of methanesulfonyl chloride with enamines[1,2] and with ketene acetals[3] in the presence of triethylamine leads to four-membered cyclic sulfones, namely, the 3-dialkylamino- and 3,3-dialkoxythietane 1,1-dioxides. Analogy with the cycloaddition reactions of ketenes suggests that "sulfene", $CH_2{=}SO_2$, is the intermediate in these reactions. We have noted that ketene O,N-acetals and aminals, treated with methanesulfonyl chloride in the presence of triethylamine, likewise yielded cycloadducts of "sulfene". In both reactions, however, spontaneous β-elimination occurred to produce the 3-dialkylaminothiete 1,1-dioxides.



Ia, R = H
b, R = CH_3



II

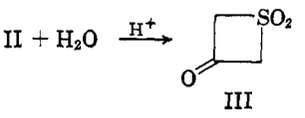
Methanesulfonyl chloride added to a solution of 1-ethoxy-N,N-dimethylvinylamine and triethylamine in tetrahydrofuran at 0° gave 3-dimethylaminothiete 1,1-dioxide (Ia), m.p. 121–123°, in 34% yield. *Anal.* Calcd. for $C_5H_9NO_2S$: C, 40.8; H, 6.2; N, 9.5; S, 21.8. Found: C, 40.8; H, 6.3; N, 9.4; S, 21.7. Infrared maximum was at 6.1 μ. N.m.r. spectrum (in chloroform) contained single peaks at 5.22 (C=CH), 4.45 (CH_2), and 2.80 p.p.m. [$N(CH_3)_2$].[4]

Under the same conditions, methanesulfonyl chloride and 1-ethoxy-N,N-dimethyl-isobutenylamine gave 4,4-dimethyl-3-dimethylaminothiete 1,1-dioxide (Ib), m.p. 135–136°, in 62% yield. *Anal.* Calcd. for $C_7H_{13}NO_2S$: C, 48.0; H, 7.5; N, 8.0; S, 18.3. Found: C, 48.2; H, 7.2; N, 7.8; S, 18.1. Infrared maximum was at 6.21 μ. N.m.r. spectrum (in chloroform) contained single peaks at 5.05 (C=CH), 2.92 [$N(CH_3)_2$], and 1.67 p.p.m. [$C(CH_3)_2$].

Methanesulfonyl chloride, 4,4′-vinylidenedimorpholine, and triethylamine reacted in tetrahydrofuran solution to afford crude 3-morpholinothiete 1,1-dioxide (II), in 84% yield. After one recrystallization from ethyl alcohol, II melted at 140–142°. *Anal.* Calcd. for $C_7H_{11}NO_3S$: C, 44.4; H, 5.9; N, 7.4; S, 16.9. Found: C, 44.2; H, 6.0; N, 7.2; S, 16.9. Infrared maximum was at 6.19 μ. N.m.r. spectrum (in chloroform) contained single peaks at 5.30 (C=CH) and 4.40 p.p.m. (CH_2), and two sets of triplets centered at 3.75 and 3.20 p.p.m. (morpholino group).

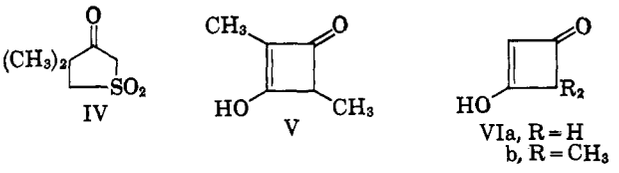
(1) G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.*, **84**, 313 (1962).
(2) G. Opitz and H. Adolph, *Angew. Chem.*, **74**, 77 (1962).
(3) W. E. Truce, J. J. Breiter, D. J. Abraham, and J. R. Norell, *J. Am. Chem. Soc.*, **84**, 3030 (1962).
(4) N.m.r. spectra were obtained with a Varian A-60 spectrometer at 60 Mc. Spectra are quoted in parts per million relative to tetramethylsilane as an internal standard.

The ease of hydrolysis of the enamine function in these cycloadducts permitted their selective hydrolysis to 3-thietanone 1,1-dioxides. II was stirred in aqueous solution with an acidic ion exchange resin (Amberlite IR-120) and 3-thietanone 1,1-dioxide (III) was recovered in 74% yield. After sublimation and recrystallization from tetrachloroethane, the compound melted at 216–221° with decomposition. *Anal.* Calcd. for $C_3H_4O_3S$: C, 30.0; H, 3.4; S, 26.7. Found: C, 29.8; H, 3.8; S, 26.3. Infrared maximum was at 5.62 μ. N.m.r. spectrum contained a single peak at 4.98 p.p.m. (CH_2 groups).



III

Infrared and n.m.r. spectra exhibited no evidence of an enol form of III in D_2O, tetrachloroethane, or dimethyl sulfoxide. In aqueous solution, III exhibited an acidity (pK_a 4.1) comparable to that of a carboxylic acid. It is appreciably stronger than an exceptionally acidic five-membered cyclic β-ketosulfone (IV, pK_a 5.8) described recently,[5] but less acidic than 1,3-cyclobutanedione and its homologs, the enolic ketene dimers V (pK_a 2.8)[6], VIa (pK_a ~3)[7], and VIb (pK_a 2.6).[8]



IV V VIa, R = H
b, R = CH_3

(5) W. E. Truce, W. W. Bannister, and R. H. Knospe, *J. Org. Chem.*, **27**, 2821 (1962).
(6) R. B. Woodward and G. Small, *J. Am. Chem. Soc.*, **72**, 1297 (1950).
(7) H. H. Wasserman and E. V. Dehmlow, *ibid.*, **84**, 3786 (1962).
(8) R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **27**, 3743 (1962).

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Steric Hindrance and Steric Assistance to Carbanion Formation in Elcb Elimination Reactions[1]

Sir:

Recently we described what appears to be the first example of an elimination reaction in a simple cyclohexane system where *cis* elimination is favored in rate over a comparable *trans* elimination.[2] We now wish to report experiments which establish that each of these reactions is proceeding by a carbanion (*i.e.*, E1cb)

(1) These results were presented in part at the Symposium on Bimolecular Elimination Reactions held at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1, 1963.
(2) F. G. Bordwell and E. W. Garbisch, Jr., *J. Org. Chem.*, **28**, 1765, (1963).

mechanism. As a by-product of this work we have been able to obtain clear-cut evidence for steric hindrance to carbanion formation and for steric assistance to carbanion formation.[3]

The following observations have been made relative to the rates of *cis* and *trans* elimination of acetic acid from the stereoisomeric 1-acetoxy-2-nitro-1-phenylcyclohexanes (I and II), as brought about by piperidine in chloroform–ethanol solution.

(1) Changes in temperature have a relatively small effect on the rate; the activation parameters are E_a = 6.9 kcal./mole and ΔS^* = −50 e.u. in each instance. (These values are comparable to certain other reactions in nonpolar media where ions are formed from neutral molecules.[7])

(2) An increase in solvent polarity causes an increase in reaction rate in each instance, as would be expected for reactions in which ions are formed from neutral molecules.

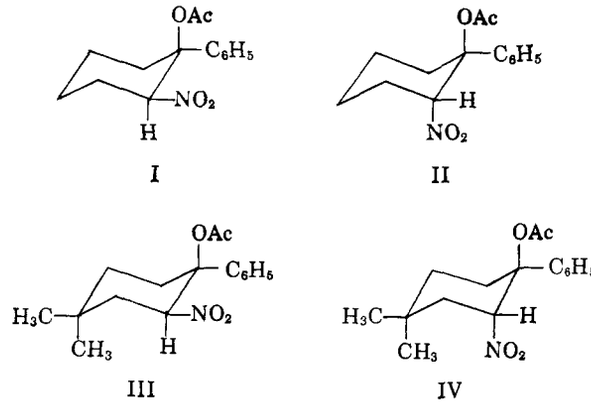
(3) Addition of 0.1 *M* lithium bromide or tetrabutylammonium iodide causes the rate in each instance to be approximately doubled.[8]

(4) An appreciable deuterium isotope effect is observed in each instance (K_H/K_D = 4.9 ± 0.3).

(5) Hammett plots for the rates of elimination of *m*- and *p*-substituted 1-acetoxy-1-aryl-2-nitrocyclohexanes in each instance gave an identical ρ-value of +1.45. This is of the order of magnitude expected for carbanion formation.

The fact that *cis* elimination is faster than *trans* elimination, together with the observations concerning temperature, medium, and substituent effects on the rates, provide compelling evidence for a carbanion mechanism. Since the response of both *cis* and *trans* eliminations to these effects is identical in every instance, *each* must involve a carbanion process.

An identical response to the rate of carbanion formation for I and II with changes in the nature of the aryl group is expected, since the aryl group has essentially the same spatial relationship to either an axial or equatorial hydrogen atom alpha to nitro.[9] It is conceivable, however, that the faster rate for II is caused by a difference in the spatial electronic influence of the acetoxy group on the axial and equatorial hydrogen atoms, since the field effect could be greater for the equatorial hydrogen atom. There does, in fact, appear to be a small difference of this kind, since the ratio of *cis*/*trans* elimination rates increases slightly (from 3.5 to 4.3) when $OCOCH_3$ (OAc) is replaced by $OCOCH_2Br$, and decreases slightly (from 3.5 to 2.8) when $OCOCH_3$ is replaced by $OCOCH_2CH_3$. The primary effect appears, however, to be steric hindrance to carbanion formation, as originally suggested.[2] This view is supported by the fact that the *cis*/*trans* rate ratio is increased sharply (from 3.5 to 78) by introduction of an axial methyl group (compare III and IV).



I Rel. rate, 1.0 II Rel. rate, 3.5 III Rel. rate, 0.23 IV Rel. rate, 18

As indicated, the rate of elimination (carbanion formation) for III is only about one-fourth that of I. This is attributed to *steric hindrance to carbanion formation*. On the other hand, the rate for IV was found to be about five times that of II. Conversion of IV to the planar carbanion ($\diagdown C^- — NO_2 \leftrightarrow \diagdown C{=}NO_2^-$) serves to relieve the steric involvement of the axial nitro group and the axial methyl group, and is an example of *steric assistance to carbanion formation*. The effect of the 4,4-*gem*-dimethyl pair cannot be accounted for as an electronic effect, since it was found that the presence of a single (equatorial) methyl group at the 4-position had a negligible effect on the rate. A conformational effect also appears to be ruled out, since the n.m.r. spectra of II, IV, and 1-acetoxy-*cis*-4-*t*-butyl-*trans*-2-nitro-1-phenylcyclohexane show that the hydrogen atoms alpha to the nitro group are similarly situated in each (indicating a similar environment), and the presence of the 4-*t*-butyl group was found to have a negligible effect on the rate of elimination.

Examination of the effect of ring size on the rate of elimination (rate of carbanion formation) revealed some marked differences which also are attributable to steric hindrance and assistance effects. The relative rates of elimination for various 1-acetoxy-2-nitro-1-phenylcycloalkanes relative to an open-chain analog are shown in Table I.

TABLE I

EFFECT OF RING SIZE ON THE ELIMINATION OF ACETIC ACID FROM 1-ACETOXY-2-NITRO-1-PHENYLCYCLOALKANES BY AMINE BASES IN CHLOROFORM–ETHANOL

Ring size	Elimination rate[a]
4	1150[b]
5	97[c]
6	0.45[c]; 0.13[b]
7	0.72[c]; 0.23[b]

[a] Relative to *erythro*-2-acetoxy-3-nitro-2-phenylbutane as 1.0. [b] *trans* elimination. [c] *cis* elimination.

(3) Although the importance of steric hindrance and assistance in determining the rates of SN1 and certain other types of reactions has long been recognized,[4] and is now well documented,[5] clear-cut examples of steric effects in carbanion formation are rare. The influence of steric effects in carbanion reactions has been recognized and considered,[6] but the presence of large concomitant electronic effects usually makes it difficult to decide what, if any, role steric factors are assuming.

(4) H. C. Brown, *Science*, **103**, 385 (1946).

(5) See, for example, E. L. Eliel, "Stereochemistry of Carbon Compounds" McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 222–224.

(6) See, for example, the discussion by J. Hine, N. W. Burske, M. Hine, and P. B. Langford, *J. Am. Chem. Soc.*, **79**, 1409 (1957).

(7) Compare, for example, the values of E_a = 10.8 kcal. and ΔS^* = −46 for the reaction of aniline with phenacyl bromide in chloroform solution; H. E. Cox, *J. Chem. Soc.*, **119**, 142 (1921).

(8) For the ionization of *t*-butyl bromide in 90% acetone–water, addition of 0.1 *M* lithium bromide or lithium chloride causes a 1.4-fold increase in rate; L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *J. Chem. Soc.*, 979 (1940).

(9) N.m.r. spectra support the conformational assignments made to I and II and show that these compounds are conformationally homogeneous.

The enhanced rate of carbanion formation for the four- and five-membered ring nitro acetates, as compared to the open-chain nitro acetate, is believed to be a consequence of relatively low steric hindrance to the approaching base and greater crowding of groups due to eclipsing effects. In other words, steric hindrance to carbanion formation is less, and steric assistance to carbanion formation is greater. With the six- and seven-membered ring nitro acetates, steric hindrance is greater and steric assistance is less than in the smaller rings.

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Acceleration of *p*-Nitrophenyl Ester Peptide Synthesis by Imidazole

Sir:

The *p*-nitrophenyl ester procedure is among the most useful for the synthesis of peptides.[1] Yields are good, side reactions seem not to be present, and racemization is virtually absent.[2] The reaction usually is carried out by allowing the components to react in a suitable solvent for some indefinite period of time, often days. A long reaction time increases the probability of side reactions, particularly racemization. We have found that addition of imidazole can decrease the reaction time by a large factor.

N-Carbobenzoxy-L-proline *p*-nitrophenyl ester[3] (44 mg., 0.12 mmole) and L-tyrosine methyl ester[4] (20 mg., 0.10 mmole) in 1.0 ml. of ethyl acetate were allowed to stand at room temperature. Under these conditions, there was a substantial amount of unreacted tyrosine methyl ester (perhaps 20%) after twenty-four hours, but the reaction was complete after forty-eight hours. The reaction was followed by thin-layer chromatography on silica gel using 10% methanol–chloroform as developing solvent with detection of spots by the *t*-butyl hypochlorite method.[5] In separate experiments, imidazole (7 mg., 0.10 mmole; 14 mg., 0.20 mmole; 68 mg., 1.0 mmole) was added at zero time. Each amount exerted a pronounced catalytic effect approximately in proportion to the quantity of imidazole added. One equivalent (0.10 mmole) resulted in somewhat less than 50% tyrosine methyl ester reacted in two hours; two equivalents caused about 50% reaction in one hour; while ten equivalents caused the reaction to be nearly complete at one-half hour and complete at one hour. There was no evidence of the presence of O-acylated materials as has been observed with N-carbobenzoxy-L-valine *p*-nitrophenyl ester and L-tyrosine methyl ester in the presence of triethylamine.[6]

On a preparative scale, L-tyrosine methyl ester (2.34 g., 0.012 mole) and imidazole (6.80 g., 0.10 mole) were dissolved in ethyl acetate (125 ml.); N-carbobenzoxy-L-proline *p*-nitrophenyl ester (3.70 g., 0.010 mole) was added. After one hour at room temperature, the neutral material (4.47 g.) was isolated and crystallized from 30 ml. of 1:1 ethyl acetate–cyclohexane to yield 3.88 g. (91%) of N-carbobenzoxy-L-prolyl-L-tyrosine methyl ester as irregular prisms, m.p. 82–85°; $[\alpha]^{26}D$ −26° (*c* 1, methanol). Calcd. for $C_{23}H_{26}N_2O_6$: C, 64.77; H, 6.15; N, 6.57. Found: C, 64.69; H, 6.34; N, 6.46. Similar results were obtained in the absence of imidazole by heating the reaction solution twenty-four hours at 55°.

Imidazole has been used to facilitate peptide synthesis from a methyl ester[7] and a thiophenyl ester and has been found to promote acetylation with acetyl phenyl phosphate[9] and α-glucose pentaacetate.[10] The mechanism of these reactions probably involves an acylimidazole intermediate. The latter has been demonstrated in the imidazole-catalyzed hydrolysis of *p*-nitrophenyl acetate.[11] Acylimidazoles themselves are effective acylating agents[12] and have been used for peptide synthesis.[13]

The catalytic effect of the imidazole ring also was strikingly shown by the reaction of N-carbobenzoxy-L-proline *p*-nitrophenyl ester (44 mg., 0.12 mmole) with L-histidine methyl ester[14] (17 mg., 0.10 mmole) in 1.0 ml. of ethyl acetate at room temperature. Formation of N-carbobenzoxy-L-prolyl-L-histidine methyl ester was complete in two hours as shown by thin-layer chromatography (30% methanol–chloroform). The rate was thus comparable to the addition of between two and ten equivalents of imidazole to the tyrosine methyl ester reaction. The enhanced effect of the imidazole ring in histidine may be ascribed to the initially formed (*im*)-acyl-histidine ester being able to transfer the acyl group to an α-amino group within the same molecule. We are investigating the possible utility of imidazole in other syntheses.

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(2) M. W. Williams and G. T. Young, *J. Chem. Soc.*, **881** (1963).
(3) M. Bodanszky and V. du Vigneaud, *J. Am. Chem. Soc.*, **81**, 5688 (1959).
(4) E. Fischer, *Ber.*, **41**, 850 (1908).
(5) R. H. Mazur, B. W. Ellis, and P. S. Cammarata, *J. Biol. Chem.*, **237**, 1619 (1962). For thin-layer plates, J. M. Schlatter found that exposure to a *t*-butyl hypochlorite atmosphere for 10 min. and aeration for 10 min. before spraying with starch–iodide gave excellent results.
(6) J. Ramachandran and C. H. Li, *J. Org. Chem.*, **28**, 173 (1963).
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(8) T. Wieland, H. Determann, and W. Kahle, *ibid.*, **2**, 154 (1963).
(9) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272 (1959).
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(11) (a) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1652, 1656 (1957); (b) T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957).
(12) (a) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**,1280 (1959); (b) H. A. Staab, M. Lüking, and F. H. Dürr, *Chem. Ber.*, **95**, 1275 (1962); (c) H. A. Staab and A. Mannschreck, *ibid.*, **95**, 1284 (1962); (d) H. A. Staab and W. Rohr, *ibid.*, **95**, 1298 (1962).
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(14) R. B. Merrifield and D. W. Woolley, *J. Am. Chem. Soc.*, **78**, 4646 (1958).

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