STEREOCHEMISTRY OF THE (2 + 2) CYCLOADDITION BETWEEN ARYL ISOTHIOCYANATES AND DICYCLOHEXYLCARBODIIMIDE: A DIPOLE MOMENT STUDY

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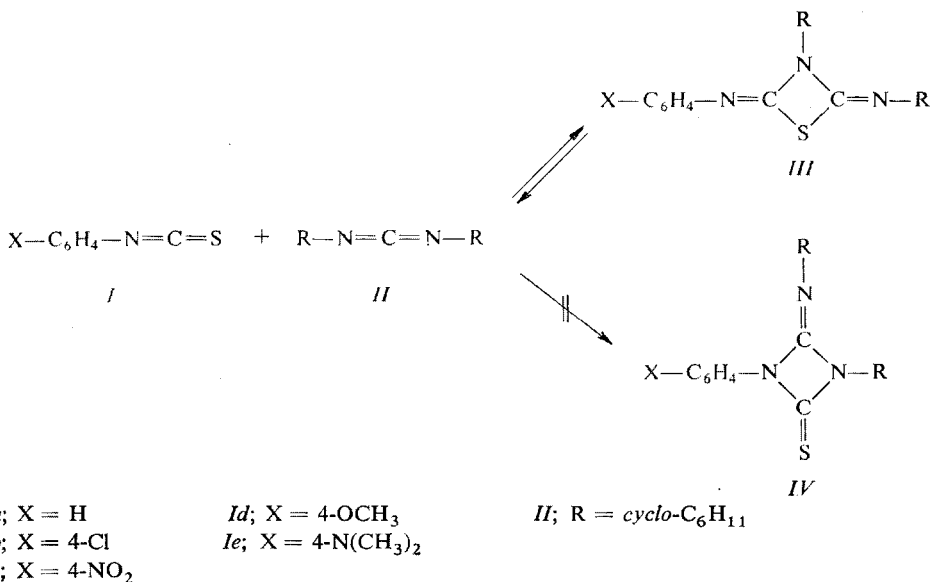*and C. N. R., Laboratory Ozzano E., Italy*

Dipole moment data confirm the 1,3-thiazetidine structure (*III*) of the 1 : 1 cycloadducts between aryl isothiocyanates and dicyclohexylcarbodiimide and allow to assigne the *Z*, *E* configuration on the two exocyclic C=N bonds. This result gives some insight on the stereochemistry of the cycloaddition and supports the mechanism previously advanced. The formation of the *Z*, *E* isomer (*D*) is consistent with a pericyclic process whose stereochemistry is kinetically controlled by steric factors in the transition state.

The (2 + 2) thermal cycloadditions of aryl isothiocyanates *I* and dicyclohexylcarbodiimide (*II*) have been reported[1,2] to occur head-to-tail and across the C=S bond of (*I*) to give four-membered 1 : 1 adducts having the 1,3-thiazetidine structure *III* instead of the 1,3-diazetidine *IV* previously assumed.[3] The cycloadditions are reversible, the equilibrium being shifted more towards the reactants by electron-releasing substituents in *I*. Kinetic evidence and the failure to evidentiate open-chain intermediates by trapping experiments, lead[2] to formulate the forward and reverse reactions as concerted processes occurring *via* a common four-centre transition state. A two-step mechanism *via* dipolar or diradical intermediates, however, could not be definitively ruled out.

This paper deals with the stereochemistry of adducts *III* and with related problems such as the regiochemistry and the steric course of the cycloaddition. In fact, each cycloadduct *III* can be a mixture of the four stereoisomers *A − D* or be entirely formed by one of these depending on whether there is or not a stereochemical control on the reaction. This problem, whose existence was already pointed out[2], is now examined through the analysis of dipole moments of the series of cycloadducts *III* where the

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para-substitution in Ar allows to use a well tried procedure[4] for obtaining a reliable configurational assignment.

$$X—C_6H_4—N=C=S \quad + \quad R—N=C=N—R$$

$$I \hspace{4.5cm} II$$

Ia; X = H   *Id*; X = 4-OCH$_3$ *II*; R = *cyclo*-C$_6$H$_{11}$
Ib; X = 4-Cl   *Ie*; X = 4-N(CH$_3$)$_2$
Ic; X = 4-NO$_2$

EXPERIMENTAL AND RESULTS

Materials: The preparation and characteristics of arylimino-2-3-cyclohexyl-4-cyclohexyl-imino-1,3-thiazetidines (*III*) have been described.[2] Dicyclohexylcarbodiimide (*II*) was distilled before measurements (b.p. 115°C/0·6 Torr.) and handled in a dry box.

Physical measurements: Determination of dipole moments was as previously reported[4,5]. Molar refractions were calculated from atom increments[6]. The experimental results are listed in Table I.

Calculations: The dipole moments for each configuration $A—D$ were calculated by assuming a planar arrangement of the 1,3-thiazetidine ring* and the following bond lengths (Å) and angles: C—S 1·76, C—N 1·43, ∢ C—S—C 74°, ∢ C—N—C 99°. Other bond angles were: ∢ S—C=N 132°, ∢ C=N—C 114°, ∢ C—N—C (exocyclic) 108°. The bond moments were those previously reported[4,5]: C=N 1·8 D, C—N 0·45 D, C—S 0·9 D, H$_{al}$—C 0·3 D, H$_{ar}$—C 0·0 D, C$_{ar}$—Cl 1·60 D. Reduction of the C$_{ar}$—N= moment to account for a possible conjugation was not considered since it is likely that the phenyl ring is twisted out from the C=N plane. However, for the nitro group an enhanced moment of 4·2 D was used; for the dimethylamino group the moment[7] was 1·58 D with an angle of 34° to the N—C$_{ar}$ bond (the direction of the moment is from N to C$_{ar}$) and for the methoxy group the values were 1·0 D and 74°, respectively. A free

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*   Owing to the C=N bonds the only possible distorsion of the ring from planarity would derive from a refolding along the S—N axis. However, this is expected to increase the angular strain without compensation by a decrease of the conformational strain as it occurs, for instance, in cyclobutanes.

rotation of the two substituents around the C_{ar}—X axis was assumed; in the case of the methoxy group this gives the same result as the presence of two planar conformations in equal amounts.

For the alternative 1,3-diazetidine structure *IV*, the values of the ring angles do not affect the final result as far as the ring is planar; other angles were ⪤ C—N=C 114°, ⪤ C—N—C(exocyclic) 108° and the C=S bond moment was 2·95 D. The two conformations with the N-aryl and N--cyclohexyl groups *cis* and *trans*, respectively, were assumed equally populated.

The vector addition was carried out graphically with a precision of 0·03 D. The graphical comparison[4] between calculated and experimental values is shown in Figure 1 while in Table I are reported only the calculated values for the Z, E configuration D.

DISCUSSION

Fig. 1 shows the lack of agreement between the experimental dipole moments and the calculated values for any configurational isomer with the 1,3-diazetidine structure *IV*. By contrast, the dipole moments calculated for the 1,3-thiazetidines *III* with the Z, E configuration on the C=N bonds (isomer *D*), match the experimental values, this providing a further support to the assigned[1,2] regiochemistry of the cycloaddition.

These conclusions appear quite reliable since they can be hardly reversed by assuming somewhat different bond moments and angles from those adopted. In addition, the fundamental premise of the graphical treatment employed appears fulfilled since the agreement between calculated and experimental points in Figure 1 gives

TABLE I

Dipole Moment Data of Substituted 1,3-Thiazetidines *IIIa—IIIe* (Benzene, 25°C)

Compound	Substituent	P_2^0 cm^3	$R_D{}^a$ cm^3	$\mu(5)^b$ D	$\mu(15)^b$ D	μ calc^c D
IIIa	H	177·1^d	104·5	1·81^d	1·67^d	1·42
IIIb	4-Cl	265·4	109·3	2·71	2·61	2·86
IIIc	4-NO$_2$	724	110·8	5·45	5·40	5·39
IIId	4-OCH$_3$	223·0	111·4	2·27	2·15	1·48^e
IIIe	4-N(CH$_3$)$_2$	199·5	119·1	1·90	1·75	1·26^e
II		155·9	64·0	2·08	2·01	—

^{a} Calculated from Vogel's increments[6] valid for 20°C; ^{b} correction for the atomic polarization 5%, or 15% of the R_D value, respectively; ^{c} calculated for the Z, E configuration (D); ^{d} the plot of ε_{12} vs w_2 seems to be slightly curved and the low solubility prevents its extension to higher concentrations; hence the values found may be somewhat low; ^{e} free rotation of the substituent vector assumed.

confidence for the identical configuration for all compounds *IIIa—IIIc*. For *IIId* and *IIIe* the results (Table I) are slightly inaccurate owing to the positional uncertainties of the "angular" substituents OCH_3 and $N(CH_3)_2$, but it seems unlikely that the configuration of these adducts differs from that of *IIIa—IIIc*. The experimental dipole moments of *IIId* and *IIIe*, higher than the calculated values by assuming a free rotation* about the C_{ar}—O and C_{ar}—N bonds, are explained by the preference of certain conformations.

Accepting the finding that the *Z, E* stereoisomer *D* is the major product of the reaction, attempts can be made to rationalize its formation. A kinetic study[2] of the reaction has provided results consistent with a one-step mechanism and it was suggested that the two interacting double bonds approach orthogonally in the transition state to allow the orbital overlap in a *supra-antara*-facial way $\left(_\pi 2_s + _\pi 2_a\right)$, similarly to that proposed by Woodward and Hoffmann for concerted reactions of other
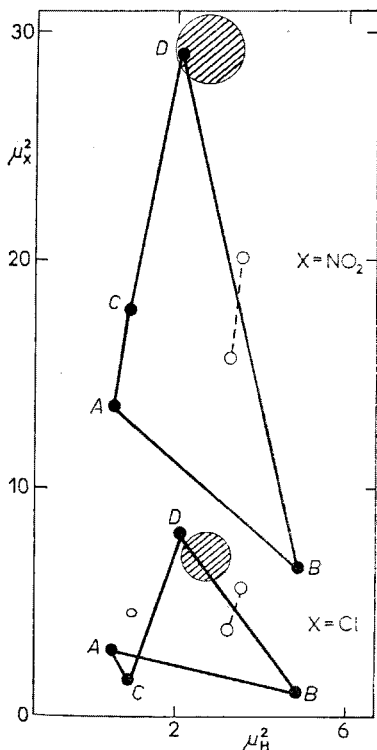

FIG. 1

Comparison of Squared Dipole Moments of *III*, Experimental (hatched circles) and Calculated for the Configurations *A—D* (full points)

x-Axis the unsubstituted derivative *IIIa*; *y* axis 4-chloro and 4-nitro derivatives *IIIb*, *IIIc*; empty points calculated for the alternative structure *IV* in two configurations.

* In dipole moment calculations, the term "free rotation" indicates a mathematical simplification rather than a physical reality. The agreement between calculated and experimental values does not imply that the rotation is actually free, but indicates the presence of two or more conformers in comparable amounts.

cumulens[8]. However, since it remained undefined which of the two reactants is the 2_s and which the 2_a component,* both these possibilities will be considered.

With isothiocyanate acting *antara*-facially and carbodiimide *supra*-facially, the reactants can approach in the transition state in four different arrangements** $E - H$ and give the isomers $A - D$ which differ for the configuration of the two C=N double bonds (Scheme 1). Adducts $A - D$ are obtained in their stable geometry from the corresponding transition state by simultaneous twisting motions of the reacting centres as indicated by the arrows, in concert with the completion of the two new bonds. Hence, the stereochemistry in the adduct is fixed by the initial approach of the two interacting double bonds and by the spatial arrangement of the rest of the molecules in that moment. In a similar way, with carbodiimide *antara*-facial and isothiocyanate *supra*-facial, the possible transition states would be $I - L$, each leading to one of the isomers $A - D$ (Scheme 1).

The formation of isomer D may be explained by steric hindrance factors controlling the stereochemistry of the pericyclic process. In fact, among the transition states $E - H$, the more favourable steric situation occurs in F and H since isothiocyanate approaches the reacting double bond of carbodiimide on the face *trans* to the right--hand R group. Moreover, the transition state H appears sterically less hindered than F since the group Ar of isothiocyanate and the left-hand group R of carbodiimide are situated on the opposite sides of a plane bisecting the NCS group. By contrast, when the transition states $I - L$ are examined in the light of the same arguments, one would expect the formation of isomer C owing to the favourable steric situation in the transition state K. In conclusion, the stereochemistry of the cycloaddition is consistent with a concerted mechanism and a kinetic control by steric factors in the transition state where isothiocyanate plays *antara*-facial and carbodiimide *supra*-facial roles. If the reaction were thermodynamically controlled, the product expected on steric grounds would be C whose molecule itself is least sterically hindered.

While the unique stereochemical course of the cycloaddition constitutes another evidence in favour of the concerted mechanism, it appears hardly compatible with the alternative two-step pathways involving open-chain diradical or dipolar species[2].

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* The difficulties for the unfavourable orthogonal approach of the reactants in concerted cycloadditions of heterocumulenes are overcome by a donor-acceptor interaction between an orthogonal vacant p orbital of the antarafacial component (pseudovinylium ion) and the p orbitals of the other reactant[8]. As perturbation calculations on the isothiocyanate-carbodiimide system are not yet available, we may advance that in view of the electrophilic behaviour of the NCS group,[2,9] the isothiocyanate ground-state can have a pseudovinylium ion character which makes this reactant a better candidate to act antarafacially in this cycloaddition.

** If the two positions of the (left-hand) cyclohexyl group R linked to the reacting double bond were considered, the number of transition states will rise to eight. Actually, each adduct $A - D$ represents a pair of enantiomers.
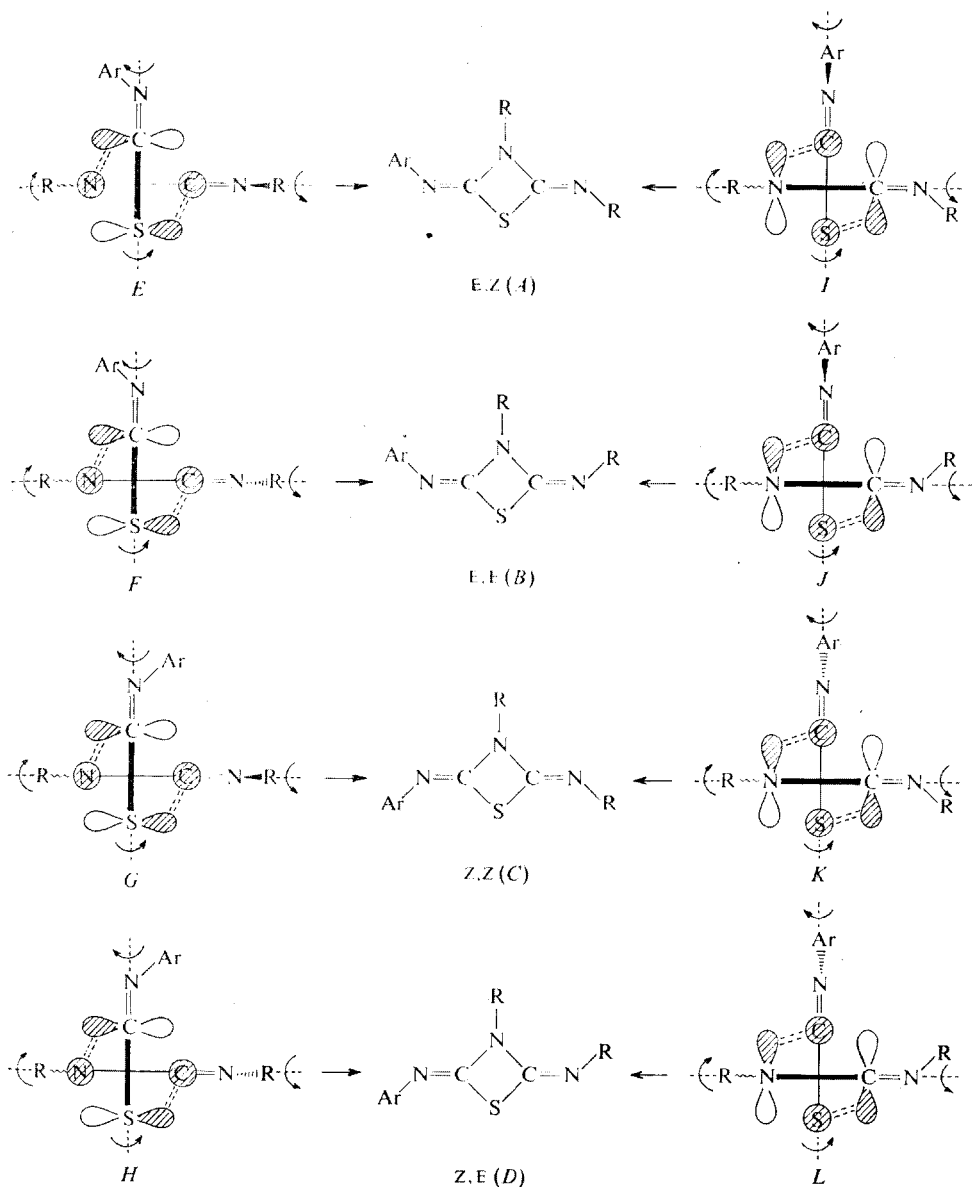
SCHEME 1

In fact, since the most favourable steric arrangements of the postulated intermediate appear to be *Va* and *Vb*, one would expect at least the formation of a mixture of the

Z, Z isomer C (from Va) and Z, E isomer D (from Vb), the former prevailing on the latter.
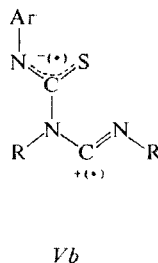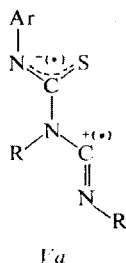
On the hypothesis that the geometry of the transition state may be affected also by electrostatic factors, attempts were made to evaluate its dipole moment $\mu_{\neq}$. From simple vector addition of dipole moments of the reactants (Table I), the estimated values of $\mu_{\neq}$ were 2·2 or 4·5 D, depending only on the position of the (left-hand) group R of carbodiimide in $E - H$; this prevents the choice of one of these transition states on electrostatic grounds. Attempt to evaluate $\mu_{\neq}$ from solvent dependence of reaction rates[2,10] was also unsuccessful since the plot of log k against $(\varepsilon - 1)/(2\varepsilon + 1)$ was not linear. The rough value of $\mu_{\neq}$ ranging between 8 and 9 D is only indicative of a considerable charge transfer in the transition state.

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