Substituent Effects on a Reversible Cycloaddition Reaction

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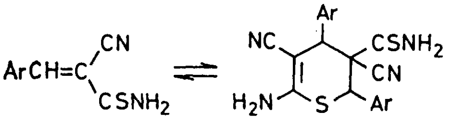
The effect of substituents in the aryl group on the reversible dimerisation of 3-aryl-2-cyanothioacrylamides (a $[2_s + 4_s]$ cycloaddition) has been determined from measurement of the equilibrium constants by ^{1}H n.m.r. spectroscopy. For a series of seven such compounds the free-energy change and enthalpy change show opposite linear correlation with the substituent Hammett σ values and these trends are rationalised in terms of the substituent perturbation to the frontier orbitals. The parameters ΔH° and ΔS° show a reverse correlation with ΔG° and a direct correlation with each other. The isokinetic temperature has been evaluated.

RECENTLY we reported[1] a novel cyclisation involving the self-condensation of an unsaturated thioamide (1) to form a substituted dihydrothiopyran (2). The regio- and stereo-control exhibited by this cyclisation were rationalised in terms of primary and secondary frontier-orbital interactions. Dimerisation of (1) to give (2) is unusual in three respects. It involves a heterodiene component, C=C–C=S, which has been studied very little, perhaps because compounds of sufficient reactivity have not been available. Dimerisations of the Diels–Alder type often require quite severe conditions but the present case proceeds at ambient temperature, albeit slowly, suggesting a relatively low activation energy for cyclisation. Retro-Diels–Alder reactions are known[2] but in most cases complete dissociation is observed. In contrast (1) and (2) are in equilibrium and the equilibrium constant is close to 1.0 at room temperature; hence this reaction is ideal for studying the effect of structural modifications on the energetics of such a cyclisation. We report here an evaluation of the thermodynamics of the reversible dissociation of (2) (dimer) to (1) (monomer) for a range of compounds in which the aryl group is phenyl with different *para*- and *meta*-substituents.



(1) (2)

EXPERIMENTAL

The dihydrothiopyrans (2) were prepared as previously described.[1] The solutions (c 0.2M) in $(CD_3)_2SO$ were equilibrated in n.m.r. tubes for two days in a thermostatted block and the n.m.r. spectrum obtained immediately on a JEOL PMX-60 spectrometer. Equilibrium is achieved so slowly in this reaction that negligible change in the spectrum was observed over a period of 15 min even in the cases where the equilibration temperature and the probe temperature differed by 15 °C. The validity of this method was confirmed by the linear plots of log k against T^{-1}.

Proportions of dimer and monomer were measured by careful integration or triangulation of appropriate peaks in each spectrum, the mean of several determinations being taken.* If the ratio of dimer to monomer is x for a simple equilibrium of the type $D \rightleftharpoons 2M$, then the fractional dissociation, α, is given by $\alpha = 1/(1 + 2x)$ and the equilibrium constant, K, by $K = \alpha^2 c/(1 - \alpha)$ where c is the concentration in mol l^{-1}. Values of K were obtained for at least three temperatures in the range 22—43 °C. Standard dissociation enthalpies (ΔH°) and entropies (ΔS°) were evaluated from least-square plots in the usual way. The major source of uncertainty in ΔG°, ΔH°, and ΔS° lies in the determination of x from the spectra. Individual values of K (or ΔG) have an uncertainty of *ca.* 10% and ΔH° and ΔS° an uncertainty of 5%.

RESULTS AND DISCUSSION

Only a limited temperature range was accessible for the measurement of K. The solvent is too viscous below 22 °C for good spectra and in most cases the concentration of dimeric form was too low for accurate estimation above 45 °C. The dissociation process was completely reversible but for the system with Ar = 4-$NO_2C_6H_4$, a slow degradation to unknown products became noticeable after two weeks. The equilibrium constants [for (2) $\rightleftharpoons$ (1)] and the derived ΔH° and ΔS° values are given in Table 1, together with the calculated standard free energies, ΔG°.

It is evident that ΔG° closely follows the electron-withdrawing capacity of the substituent in the phenyl ring and a plot of ΔG° against the appropriate Hammett σ-parameter, σ_p or σ_m, gives an excellent correlation [equation (1)].

$$\Delta G^\circ = 11.3\sigma + 3.2 \; (n = 7, r = 0.97) \qquad (1)$$

However the enthalpy changes ΔH° show exactly the opposite trend [equation (2)], but the points for the two

$$\Delta H^\circ = -158\sigma + 81 \qquad (2)$$

nitro-substituents deviate enormously (Figure 1). A similar correlation exists for the values of ΔS°, which are typically large and positive for such reactions. It appears that although the effect of acceptor substituents is such as to increasingly favour the monomer relative to the dimer in terms of intrinsic molecular energies (ΔH°) the actual reaction energetics are controlled by the significant change in the entropy term. Furthermore, acceptor substituents which are also π-acceptors appear to behave differently from π-donor substituents. A strong correlation also exists between ΔH° and ΔS° and the evaluation of this correlation is discussed below.

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* Measurements are difficult for the 4′-chloro-compound and the results are less accurate in this case.

TABLE 1

Equilibrium constants and thermodynamic parameters for the equilibrium (2) $\rightleftharpoons$ (1)

Substituent[a]	Temp. (° C)	$\frac{k}{\text{mol l}^{-1}}$	$\frac{\Delta G^\circ}{\text{kJ mol}^{-1}}$	$\frac{\Delta H^\circ}{\text{kJ mol}^{-1}}$	$\frac{\Delta S^\circ}{\text{J mol}^{-1}\text{ K}^{-1}}$
4-H	22.0	0.244			
4-H	27.0	0.355			
4-H	30.5	0.637	2.72	80.5	261
4-H	37.0	1.15			
4-F	23.0	0.113			
4-F	30.5	0.207	5.12	52.2	158
4-F	37.0	0.291			
4-Cl	23.0	0.078			
4-Cl	39.0	0.186	6.68	49.0	142
4-Cl	43.0	0.202			
4-Br	23.0	0.089			
4-Br	29.0	0.115	6.07	31.4	86
4-Br	39.0	0.171			
4-Br	43.0	0.199			
4-NO_2	24.0	0.0071			
4-NO_2	31.8	0.0146	12.11	58.5	156
4-NO_2	38.0	0.0200			
4-NO_2	41.5	0.0307			
4-NO_2	47.8	0.0408			
3-OMe	24.0	0.265			
3-OMe	29.8	0.314	3.51	64.0	203
3-OMe	31.8	0.461			
3-OMe	38.0	0.780			
3-NO_2	24.0	0.0101			
3-NO_2	29.8	0.0211	10.82	73.4	210
3-NO_2	31.8	0.0235			
3-NO_2	34.3	0.0342			
3-NO_2	38.0	0.0480			
3-NO_2	41.5	0.0489			

[a] The aryl groups in (1) and (2) are XC_6H_4.

In order to understand the differential effect of the phenyl substituent on the energies of the monomeric and dimeric forms of these substituted thioacrylamides, we can examine this reaction in terms of the frontier orbitals of the interacting species.

Whilst it is reasonable to apply frontier orbital (FO) theory to the monomeric species to rationalise the regiocontrol exhibited by this reaction,[1] substituent effects should influence the energies of both monomer and dimer. However the phenyl groups in the dimer are attached to saturated carbon atoms, and the substituent effect is effectively isolated from the heterocyclic ring. Hence there can be only a very limited dependence of the dimer molecular energy on the electron-accepting properties of the substituents. Accordingly the major, and controlling effect of a substituent can be expressed in terms of FO interactions between monomers. This represents a reaction profile in which only the reactant enthalpy and the activation enthalpy are sensitive to substituent effects (Figure 2).

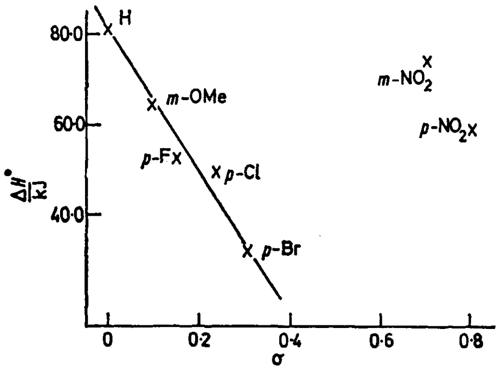


FIGURE 1 Plot of ΔH° for the equilibrium (2) $\rightleftharpoons$ (1) against Hammett σ values

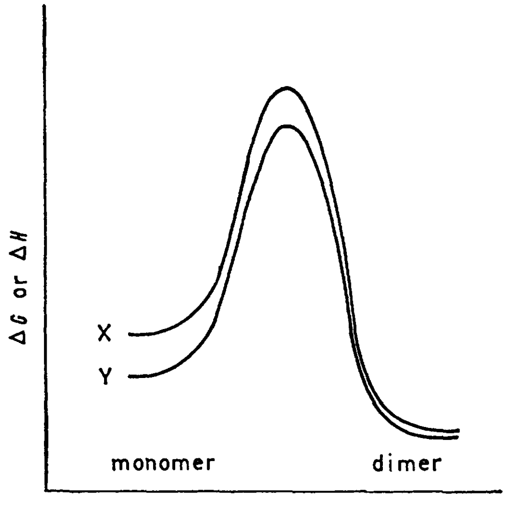
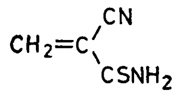


FIGURE 2 Reaction profile for the monomer $\rightleftharpoons$ dimer equilibrium for different aryl substituents. For ΔG, X = Br and Y = H and for ΔH, X = H and Y = Br

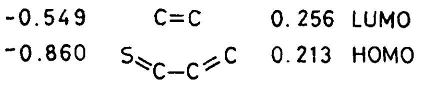
Since a dimerisation involves only one type of molecular species (rather than two) the energies of HOMO (E_H) and LUMO (E_L) are the same for both diene and dienophile and the energy separation, $E_L - E_H$, is the same for either interaction, HOMO-LUMO or LUMO-HOMO, of the diene and dienophile, and the reaction pathway is controlled by the magnitude of the orbital coefficients at the interacting sites. Previous calculations[1] on a model compound (3) have shown that the



$CH_2{=}C(CN)CSNH_2$

(3)

major contribution to the interaction energy is due to overlap of the diene HOMO with the dienophile LUMO. The appropriate orbital coefficients are shown in (4) and



(4)

the interacting energy levels are shown in Figure 3. The dominance of this interaction means that the diene can be regarded as nucleophilic and the dienophile as electrophilic.

Fleming[3] has shown by qualitative arguments that an acceptor substituent (*a*) lowers the HOMO and LUMO of benzene, (*b*) lowers the HOMO and LUMO of a diene or a dienophile and brings these levels closer together, and that (*c*) phenyl conjugation with a diene or dienophile raises the HOMO and lowers the LUMO. Application of these qualitative rules to the model compound suggests that the presence of a phenyl group would increase reactivity by (*c*) and that a further increase in reactivity would be expected for an acceptor substituent in the phenyl ring [by a combination of (*a*) and (*b*)].

To substantiate this qualitative reasoning selected calculations have been carried out at the CNDO/2 level to determine the effect of representative substituents on the HOMO and LUMO energies of styrene. This model compound was used since computing limitations rule out calculations on (1). Orbital energies for the HOMO and LUMO of styrene and its 4-fluoro-, 4-chloro-, and 4-cyano-derivatives are given in Table 2. As expected from the qualitative reasoning outlined above, E(LUMO) decreases with increasing acceptor strength supporting the idea that the dienophile is interacting *via* its LUMO, and hence that reactivity should be increased by acceptor substituents. It should be noted that the HOMO energy is much less sensitive to the substituent effect, but it does increase. Hence the HOMO energy of the diene (1) will increase through the series of substituents investigated (Table 1), assuming that (1) responds in the same way as styrene. These substituent effects are summarised in Figure 3.

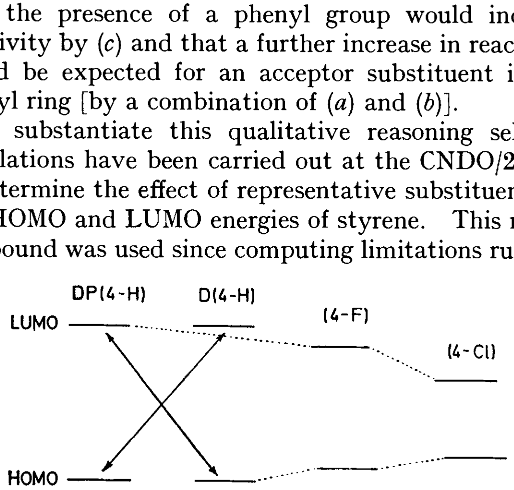


FIGURE 3 Interacting energy levels for diene (D) and dienophile (DP), showing the effect of the 4-substituent (4-H, 4-F, 4-Cl) on the dominant interaction (DP-HOMO with D-LUMO)

Thus these qualitative and quantitative arguments based on orbital energies of the frontier orbitals suggest that the substituent effect should be opposite to that determined experimentally from the measured enthalpy changes. However application of FO theory properly requires consideration not only of the energies of the interacting orbitals but also of the magnitude of the overlap between the participating orbitals at the positions of incipient bond formation. Accordingly we have estimated the interaction energy E_{int} as described previously.[1] The only suitable model interaction within our computational limitations was that between (3) as diene and styrene as dienophile using for (3) the orbital coefficients evaluated previously and shown in (4). The dominant orbital interaction for the 4-H compound is shown in Figure 4.

TABLE 2

HOMO and LUMO energies[a] of 4-substituted styrenes

4-Substituent	E(HOMO)	E(LUMO)
H	−0.4492	0.1023
F	−0.4402	0.0962
Cl	−0.4388	0.0728
CN	−0.4399	0.0728

[a] In atomic units, from CNDO/2 calculations.

Assuming that the exchange integral β is the same for formation of C–C and C–S bonds the calculated values of E_{int} (in eV) for the interactions between (3) and three of the substituted styrenes, expressed in terms of β, are 31.230 β^2 (4-H), 26.796 β^2 (4-F), and 22.035 β^2 (4-CN). In spite of the difference between the model and the real experimental interaction, the correct trend in molecular interaction energies is reproduced by these calculations of E_{int} in contrast to the conclusions reached on the basis of orbital energies. This emphasises the need for a full evaluation of FO interactions when subtle structural changes are under investigation. It can be noted that if $\Delta G°$ alone had been determined experimentally the trend in this parameter could have been rationalised in terms of frontier orbital energies, giving a completely erroneous interpretation of the effect of substituents on the energy of reaction.

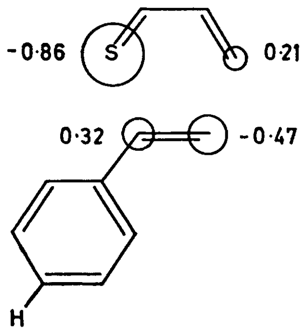


FIGURE 4 Orbital coefficients for the dominant interaction between diene ($CH_2{=}CHCSNH_2$) and dienophile ($PhCH{=}CH_2$), a model for the dimerisation of arylthioacrylamides

The calculation of E_{int} confirms that the influence of acceptor substituents on the equilibrium between (1) and (2) is principally due to changes in entropy. Substituent effects on molecular entropy are generally poorly understood and are usually implicitly ignored. In the present case, we make the assumption (similar to that noted above in the discussion of $\Delta H°$) that the substituent induced changes in $S°$ correspond to changes in the entropy of the monomer, dimer entropy remaining relatively constant. This means that the introduction of an acceptor substituent into the benzene ring reduces the molecular entropy ($S°$) of (1). Apart from a minor loss of translational freedom associated with the introduction of a large atom or group, it is difficult to account for this reduction in $S°$. Some measure of increased rigidity may come from increased conjugation between the phenyl group and the unsaturated side-chain involving π-donation by the substituent. This would account for the low $\Delta S°$ for the *p*-nitro-compound, this group being a π-acceptor. π-Donor interactions cannot be very important, however, because $\Delta S°$ does not follow the order of donor ability. Increased solvation of the more polarised π-system in the substituted cases will reduce $S°$ in the monomer, and although a similar interaction will occur in the dimer there may be a differential effect.

As noted above $\Delta H°$ is linearly related to $\Delta S°$ and this correlation is summarised by equation (3). Similar isokinetic relationships have often been noted for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for a wide range of reactions but are rarely reported for equilibria, although, in principle, for any equilibrium for which a linear free-energy relationship holds, a relation of type (3) should also hold.[4] Exner[4]

$$\Delta H^{\circ} = 278\Delta S^{\circ} + 7.5 \qquad (3)$$

has shown that proper determination of an isoequilibrium or isokinetic temperature cannot be obtained from a direct correlation such as equation (3), owing to the strong correlation intrinsic to parameters derived from the same experimental data. In unfavourable cases the observed linear relationship is entirely spurious. Exner[4] has given a rigorous treatment of this problem and the isoequilibrium temperature, β has been evaluated by his method. A value, $\beta = 269°$, was determined from the slope of the least-squares plot of ΔG_{298} against ΔG_{310} excluding the two points for NO_2 substituents which do not lie on the line. This deviation from a genuine isoequilibrium relationship for the compounds substituted with a NO_2 group is in agreement with the abnormally low values of ΔH° and ΔS° noted above. It suggests that the correlation of ΔG° with σ, equation (1), may only coincidentally include the NO_2-substituted members of the series and that a different mechanism may be operating in these cases. One possibility is a change from a concerted cycloaddition to a two-step reaction. Studies of solvent effect on the reaction rates may elucidate this point.

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