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AMBIDENT NEIGHBOURING GROUPS, VI (1), THE MOST POWERFUL NEUTRAL NEIGHBOURING GROUP - THE N-ARYLTHIOUREIDO GROUP.

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One of the simplest ways of assessing the potency of a neighbouring group system (G) is to examine the effect such a group has upon a leaving group (X) in a beta-position, i.e. by comparison of the rates of loss of X^- from G-C-C-X and H-C-C-X. In reality the function G exercises a dual effect on X, inductively influencing the loss of X^- along the carbon chain and anchimerically assisting the loss of X^- by operating through space from the beta position. The simple approach ignores the detailed mechanism of the effect and instead examines its power - an approach which has some merit as a guide to synthetic principles. We published an array of neighbouring group potencies (defined in that simple way) some time ago (2) and in that array the most powerful neighbouring group (under neutral or acidic conditions) was the arylamido system, ArCONH-. We now report data concerning an even more potent system - the N-aryl-thioureido group, (ArNHCSNH). While stereochemical work using the parent thioureido (NH_2CSNH) group has been reported (3) there have been no previous kinetic studies recorded on such systems.

The model compounds we choose for our study were the trans - (N-p-substituted phenyl) thioureido cyclohexyl chlorides (I). These were readily prepared by reacting trans-2-chlorocyclohexylamine (4) with a range of p-substituted phenyl isothiocyanates in ethereal solution. When the compounds (I) were heated in 80% aqueous ethanol at 75° for periods varying from 6-9 hours (depending upon the compounds' reactivity), they formed the fused-cis-4,5-tetramethylenethiazolines (II) in very high ($>$ 93%) yields (Table 1). The nature of this cyclisation process was probed further using the parent phenyl compound (IIA, X = H). First the cis character of the thiazoline (II) was confirmed when it was cleaved to cis-2-aminocyclohexyl thiol (and aniline). This ring cleavage was achieved when the material (IIA) was heated in a sealed ampoule with an excess of concentrated hydrochloric acid (5) for 48 hours. Workup

yielded 20% recovered starting material, 60% of aniline hydrochloride and 60% of cis-2-aminocyclohexyl thiol (III), m.p. 238-241°. This material was identified (i.r. spectra, mixed m.p.) with an authentic sample synthesised unambiguously (6). The formation of the thiazoline would indicate the operation of an S-5 ring-closure but there remained the possibility of an initial N-3 closure followed by a rearrangement of the resulting thiocarbamoylimine to the thiazoline (7). In any event we prepared N-(phenylthiocarbamoyl) cyclohexane (1,2) imine (IV),

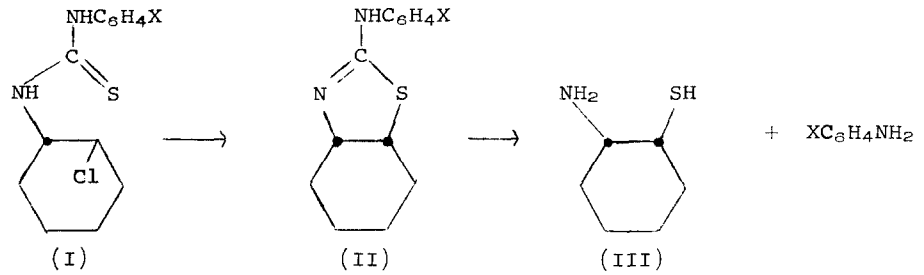

Figure 1

m.p. 148-150° (from cyclohexane (1,2) imine and phenylisothiocyanate) and subjected it to identical solvolysis conditions as the starting material (IA, X=H). Compound (IV) was recovered unchanged (in 96% yield) and hence the N-3 process does not precede the S-5 cyclisation under our conditions. Baker and coworkers (3) also found the S-5 process to be the major reaction of the thioureido system under neutral conditions.

Table 1, Product Data

	Starting Materials (I)		Cis-thiazolines (II)	
X=	m.p.	Yield	m.p.	Yield
CH_3O	130-131	85%	140-142	93%
CH_3	120-121	90%	145-147	94%
H	128-130	89%	132-134	98%
Cl	135	87%	180-182	97%
NO_2	134-135	92%	190-192	96%

Having established the character of the neighbouring group process we were studying, we next examined the rates and thermodynamic parameters, of the S-5 reactions (Table 2).

Table 2

Rates of S-5 closure of trans-p-substituted phenylthioureido cyclohexylchlorides (I).

Substrate (I, X =)	10^5k.sec.$^{-1}$(50°)	10^4k.sec.$^{-1}$(75°)	$\Delta H^{\ddagger}$, k.cal/mole	$\Delta S^{\ddagger}$, e.u.
CH_3O	3.31	5.50	24.31	-3.87
CH_3	3.23	5.36	24.31	-3.92
H	3.06	5.06	24.29	-4.07
Cl	2.67	4.43	24.30	-4.32
Br	2.62	4.36	24.30	-4.35
NO_2	1.36	2.25	24.26	-5.78

The first order rate constants remained constant during a run, thus being insensitive to the HCl generated - a fact confirmed when the kinetic measurements were rerun in the presence of sodium acetate as buffer and afforded the same rate constants. The data obtained correspond to a Hammett ρ of -0.26 (r =-0.997). Thus while the influence of the remote p-substituent in the phenyl ring on the S-5 reaction is small, the sign of ρ is consistent with electron-donation from this p-substituent increasing the nucleophilicity of the sulphur atom. The thermodynamic parameters similarly show little response to substituent variation, the reaction being apparently isoenthalpic and thus entropy controlled (8). In a comparison of the rates of solvolysis of compounds (I) with the corresponding arylamido (ArCONH) compounds (9) the thioureido system was ca. 30-60 times more potent a neighbouring group than the substituted amido system.

Finally, we decided to evaluate the arylthioureido neighbouring group's potency more quantitatively, using the driving force parameter (L) suggested by Winstein (10). For this purpose we needed as a starting material the cis isomer of (I), namely cis-phenylthioureidocyclohexyl chloride (V). We prepared compound (V), m.p. 126-128° by reacting cis-2-chlorocyclohexylamine (11) with phenylisothiocyanate. Table 3 contains the rates of solvolysis of this cis-compound (V) and cyclohexylchloride itself in 80% aqueous ethanol under buffered (NaAc) conditions. From these data, using k_h = rate of solvolysis of cyclohexyl-chloride, k_c = rate of compound (V), and k = rate of solvolysis of compound (I), then L can be calculated as 3.93 k. cal. mole^{-1}. This compares with an L value of 4.60 at 25° for the acetoxy group (10). These L values include both the

inductive and anchimeric influences of the neighbouring group. The acetoxy group is thus both more electron-withdrawing (inductively) and more electron releasing (anchimerically) than the arylthioureido system but the overall effect of the acetoxy group is still very much smaller as a rate-enhancing function than the thioureido system.

Table 3. Additional Rate Data.

Substrate	$k.sec.^{-1}$ 75°	$k.sec.^{-1}$ 95°	$k.sec.^{-1}$	$k.sec.^{-1}$	$\Delta H^{\ddagger}$ k.cal/mole	$\Delta S^{\ddagger}$ e.u.
VI[a]	7.31×10^{-6}[b]	5.93×10^{-7}[b]	2.65×10^{-6}[c] (111°)	4.25×10^{-6}[c] (116°)	25.8	-17.2
V	1.24×10^{-6}[b]	1.65×10^{-5}	5.44×10^{-5}[a] (105°)		35.5	16.2
I	5.06×10^{-4}	3.63×10^{-3}[b]			24.29	- 4.07

[a]Cyclohexylchloride; [b]calculated from rate data at other temperatures; [c]temperatures at which rate measurements were made.

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