

## *ortho*-Effects in the Acylation of Substituted Phenylureas with Isocyanates and Acetic Anhydride

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The reactions of *ortho*-chloro-, -bromo-, -iodo-, and -trifluoromethyl-aniline with nitrourea in aqueous acetone yield both the corresponding phenylurea and the phenylbiuret, in marked contrast to other *ortho*- and *para*-substituted anilines which yield only the urea. Biuret formation has been rationalised in terms of a mechanism involving electrophilic stabilisation of the conjugate base of the corresponding urea. *ortho*-Chloro-, -bromo-, and -iodo-substituents have also been shown to result in abnormal behaviour in the acylation of phenylureas with acetic anhydride in acetic acid. Here the effect has been attributed to electrophilic assistance in the departure of the leaving acetate group from the acetic anhydride. In contrast, no unusual *ortho*-effects were observed in the reactions of phenylureas with 3,4-dichlorophenyl isocyanate in acetonitrile, and the rate constants can be correlated accurately with the extended form of the Hammett equation.

DURING investigations of the synthesis of heterocyclic iodine compounds<sup>1</sup> we required 2-iodophenylurea. Nitrourea<sup>2</sup> has been used to convert primary and secondary amines into substituted ureas in high yield with formation of only a trace of the corresponding biuret. In our hands the reaction of 2-iodoaniline with an excess of nitrourea gave *ca.* 25% of 2-iodophenylbiuret in addition to the urea, whereas under the same conditions aniline gave only the urea. The attempted synthesis of 2-iodobenzohydrazide by the reaction of hydrazine hydrate with 2-iodobenzoyl chloride resulted in *NN'*-bis-(2-iodobenzoyl)hydrazine;<sup>3</sup> this represents another example of apparently anomalous reactivity in the presence of an *ortho*-iodo-substituent. The aim of the present investigation was to determine the nature of this reactivity by a further investigation of the reaction of anilines with nitrourea and by comparison with the reactions of substituted phenylureas (the intermediates in biuret formation) with 3,4-dichlorophenyl isocyanate and acetic anhydride.

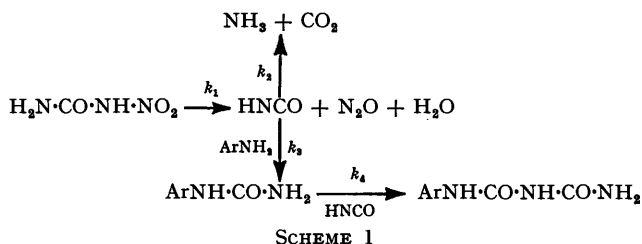
### RESULTS AND DISCUSSION

*Reaction between Nitrourea and Substituted Anilines.*—Nitrourea decomposes in aqueous solution (pH 1–11), to yield cyanic acid and nitrous oxide, *via* its conjugate base in a reaction which is not susceptible to general acid–base catalysis.<sup>4</sup> Cyanic acid is also unstable in aqueous solution.<sup>5</sup> In the formation of a biuret the aniline must react with cyanic acid to form the urea, which in turn reacts with a second molecule of cyanic acid (Scheme 1).

In view of the kinetic complexity of the system investigations were confined to preparative experiments under a standard set of conditions, *viz.* nitrourea (2.5 mol dm<sup>-3</sup>) and the aniline (0.8 mol dm<sup>-3</sup>) in refluxing aqueous 67% acetone. Except for some of the reactions where biuret was detected the products remained in

solution. No biuret was detected in the reactions of *meta*- and *para*-substituted anilines for the following range of substituents which cover the Hammett  $\sigma$  value range  $-0.4$  to  $+0.6$ : hydroxy-, methoxy-, methyl-, halogeno-, trifluoromethyl-, acetyl-, and 3,4-dichloro-. The yield of the phenylurea was  $>90\%$  in all cases except for that of 4-hydroxyphenylurea, which was more soluble in water than the others.

The pattern of reactivity is different for *ortho*-substituted anilines (Table I) in that the biuret as well as



the urea is formed in certain cases. Except for the trifluoromethylanilines, yields, based on conversion of the aniline, are similar for corresponding *ortho*- and *para*-substituted anilines. When an electron-withdrawing group is introduced into an *ortho*-substituted aniline the yield is substantially reduced, whereas an electron-donating group has no appreciable effect. Evidently,  $k_2$  and  $k_3$  (Scheme 1) are of comparable magnitude, at least for the *ortho*-substituted anilines. *ortho*-Substitution leads to a decrease in basicity in comparison with the corresponding *para*-substituted anilines;<sup>6</sup> consequently reduced activity in nucleophilic reactions (*cf.*  $k_3$ ) might be expected.<sup>7</sup> (Reduced activity is shown in the reaction of anilines with phenyl isocyanate.<sup>8</sup>) Since the pH of the reaction solution will be dependent on the nitrourea ( $\text{p}K_a$  3.9) and ammonia and not on the reactant aniline,  $k_1$  and  $k_2$  will be independent of the

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<sup>1</sup> J. M. Briody and M. Pearse, *Chem. and Ind.*, 1971, 657.

<sup>2</sup> T. L. Davis and K. C. Blanchard, *J. Amer. Chem. Soc.*, 1929, 51, 1790.

<sup>3</sup> J. E. Leffler and A. F. Wilson, *J. Org. Chem.*, 1960, 25, 424.

<sup>4</sup> J. M. Briody and B. Boopsingh, *J.C.S. Perkin II*, 1972, 1487.

<sup>5</sup> G. D. Vogels, L. Uffink, and C. van der Drift, *Rec. Trav. chim.*, 1970, 89, 500.

<sup>6</sup> D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965.

<sup>7</sup> D. P. Evans, H. B. Watson, and R. Williams, *J. Chem. Soc.*, 1939, 1349; F. J. Stubbs and C. Hinshelwood, *ibid.*, 1949, S71.

<sup>8</sup> J. M. Briody and D. Narinesingh, unpublished observations.

reactant aniline and biuret formation must be a result of the enhancement of  $k_4$ .

The results for the 2-chloro-, 2-bromo-, and 2-iodo-anilines show that biuret formation ( $k_4$ ) is favoured by an electron-withdrawing group. This effect cannot be reconciled with nucleophilic attack of the urea on cyanic acid but would be consistent with nucleophilic attack

TABLE 1  
Biuret formation in the reactions of nitrourea with substituted anilines

Substituent	% Yield of urea + biuret	% Biuret in isolated product
2-Me	93	0
2-Et	97	0
2-OH	60	0
2-OMe	97	0
2-F	93	0
2-CF <sub>3</sub>	18	10
2,6-Me <sub>2</sub>	100	0
2-Cl	94	12
2,6-Cl <sub>2</sub>	46	30
2,4-Cl <sub>2</sub>	60	30
2,5-Cl <sub>2</sub>	15	7
2-Cl,4-Me	95	0
2-Br	94	7
2,4-Br <sub>2</sub>	46	18
2-Br,4-Me	97	5
2-I	95	25
2-I,4-Cl	72	60
2-I,4-Me	100	20

by the conjugate base of the urea. The observation<sup>9</sup> that the conjugate base is involved in the cyclisation of 2-carboxyphenylurea, in aqueous solution, to yield 2,4-dihydroxyquinazoline supports such a mechanism. Biuret formation is observed only for the 2-iodo-, 2-bromo-, 2-chloro-, and 2-trifluoromethyl substituents and these same substituents have been tentatively identified as having abnormal substituent effects in the <sup>1</sup>H n.m.r. spectra of phenylureas.<sup>10</sup> In the case of these large *ortho*-substituents, direct interaction with the carbonyl oxygen atom of the ureido-side-chain could lead to an electrophilic stabilisation of the conjugate base and hence an enhanced  $k_4$ . If size effects were unimportant the formation of biuret would have to be explained in terms of electronic effects [equation (i)].<sup>11</sup> The values<sup>12</sup> of  $\sigma_I$  (0.52, 0.47, 0.45, and 0.39) and

$$\log k_4 = \alpha\sigma_I + \beta\sigma_R + \text{constant} \quad (i)$$

$\sigma_R$  (−0.46, −0.24, −0.22, and −0.21) for the fluoro-, chloro-, bromo-, and iodo-substituents are such that to account for significantly different behaviour for the fluoro-substituent in comparison with the others the term involving  $\sigma_R$  must be similar to, or greater than, that involving  $\sigma_I$ . Since the resonance effect of halogeno-substituents is electron-donating and would tend to decrease  $k_4$ , the situation which will maximise  $k_4$  and

<sup>9</sup> A. F. Hegarty and T. C. Bruice, *J. Amer. Chem. Soc.*, 1969, **91**, 4924.

<sup>10</sup> J. M. Briody, in preparation.

<sup>11</sup> M. Charton, *Progr. Phys. Org. Chem.*, 1971, **8**, 235.

<sup>12</sup> C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 1964, **2**, 323.

<sup>13</sup> J. M. Briody and D. Narinesingh, *Tetrahedron Letters*, 1971, 4143.

maintain the reactivity difference between fluorine and the other halogens is one in which  $\alpha \approx \beta$ . If this condition is met then the four most electron-withdrawing groups of all those considered in Table 1 are 2-chloro-, 2-bromo-, 2-iodo-, and 2-trifluoromethyl, *i.e.* those for which biuret formation was observed.

In any situation where the net effect of a halogen is electron withdrawal the effect will be more powerful for chlorine than for iodine and hence a greater tendency for biuret formation would be expected for the 2-chloro-substituent. However, biuret formation is greater for the 2-iodo-substituent; thus polar effects (as measured by  $\sigma_I$  and  $\sigma_R$ ) cannot afford a complete explanation of the substituent effects in the reactions of phenylureas with cyanic acid.

*Reaction between 3,4-Dichlorophenyl Isocyanate and Substituted Phenylureas.*—In view of the anticipated difficulties in a formal kinetic investigation of reactions involving cyanic acid, we chose to investigate the reaction of a phenyl isocyanate with substituted phenylureas in an attempt to define more closely the nature of the *ortho*-effects' noted above. Acetonitrile was chosen as solvent because the mechanism of the reaction between isocyanates and amines is known for this solvent, and 3,4-dichlorophenyl isocyanate was used because it gave convenient reaction rates.

To simplify the kinetic form the phenylurea was kept in at least ten-fold excess over the isocyanate. The observed rate of formation of product always showed accurate first-order behaviour. The reaction is also first-order in urea (see Table 2) and at constant urea

TABLE 2

Concentration effects in the reactions between phenylurea and 3,4-dichlorophenyl isocyanate in acetonitrile at 65 °C

10[Urea]/mol dm <sup>-3</sup>	10 <sup>3</sup> [ArNCO] <sub>initial</sub> /mol dm <sup>-3</sup>	10 <sup>4</sup> k <sub>obs</sub> /s <sup>-1</sup>
0.20	1.60	0.50
0.40	4.20	1.01
0.80	4.20	2.01
1.50	4.20	3.55
2.00	4.20	4.94
0.80	2.10	2.00
0.80	6.30	2.08

concentration the observed rate constant is independent of the initial isocyanate concentration. This simple kinetic form contrasts markedly with the complexity of that reported<sup>13,14</sup> for the reaction between amines and isocyanates in that the order in nucleophile is not greater than unity and there is no catalysis by the product. Substituent effects for *meta*- and *para*-substituted phenylureas (Table 3) show that the rate constant increases with increasing electron-donating power of the substituent. The data give a linear Hammett plot

<sup>14</sup> J. W. Baker and D. N. Bailey, *J. Chem. Soc.*, 1957, 4649, 4663; R. L. Craven, Amer. Chem. Soc., Div. Paint, Plastics and Printing Ink Chem., paper No. 35, Amer. Chem. Soc. meeting, Atlantic City, Sept. 1956; K. Sauer and M. N. Kasparian, *J. Org. Chem.*, 1961, **26**, 3498; I. de Guirre and J. C. Jungers, *Bull. Soc. chim. France*, 1965, 1316.

with slope ( $\rho$ )  $-0.66$ . A mechanism (Scheme 2) involving rate-determining bond formation ( $k_1$ ) between the nitrogen and the carbonyl carbon atom followed by

TABLE 3

Reactions between substituted phenylureas and 3,4-dichlorophenyl isocyanate in acetonitrile at 65 °C

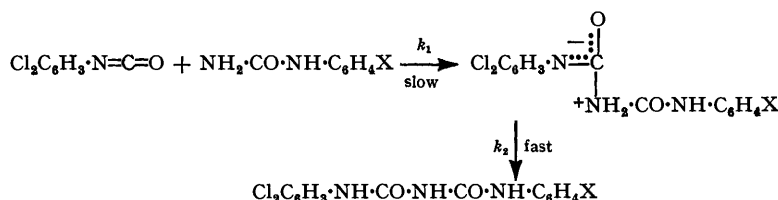
[ArNCO] <sub>initial</sub> = $1.60 \times 10^{-3}$ mol dm <sup>-3</sup>		[Urea] = $2.0 \times 10^{-2}$ mol dm <sup>-3</sup>	
Substituent	$10^5 k_{\text{obs}}/\text{s}^{-1}$	Substituent	$10^5 k_{\text{obs}}/\text{s}^{-1}$
4-OMe	8.54	3-CF <sub>3</sub>	2.60
4-Me	5.80	2-F	2.12
3-Me	5.48	2-Cl	1.60
H	4.98	2-Br	1.70
4-F	4.70	2-I	1.95
2-OMe	4.10	2-I,4-Me	2.35
4-I	3.82	2-Me	3.42
4-Br	3.73	2-Et	3.64
4-Cl	3.67	2-OMe	4.02
3-Cl	2.95	2-CF <sub>3</sub>	1.20
3-Br	2.90		

a fast prototropic rearrangement ( $k_2$ ) is consistent with the experimental observations. In the reaction between phenyl isocyanate and aniline the term corresponding to  $k_2$  is rate-limiting. Since aniline is more basic than

of the experimental value. Thus the *ortho*-effect for the reaction between 3,4-dichlorophenyl isocyanate and substituted phenylureas is electronic in nature and steric effects are negligible, as might be expected for a reaction

$$\log k_{\text{obs}} = -0.767\sigma_I - 0.608\sigma_R - 4.550 \quad (\text{ii})$$

centre remote from the benzene ring and the *ortho*-substituent. Since the composition of the electronic effect, as determined by  $\beta/\alpha = 0.8$ , is similar to that for the Hammett correlation for *para*-substituents ( $\beta/\alpha = 1.0$ ) and magnitudes of  $\alpha$  and  $\beta$  are similar to that of the Hammett reaction constant ( $\rho = -0.66$ ) for the reaction of the *para*-substituted phenylureas, we may equate the electrical effects of a substituent at the *ortho*- and *para*-positions. The reactivity difference (*ca.* two-fold) between an *ortho*- and the corresponding *para*-substituted phenylurea is independent of the size of the substituent and may be attributed to a change in conformation<sup>10</sup> of the ureido-side chain with respect to the benzene ring on the introduction of an *ortho*-substituent, *i.e.* from a position roughly co-planar with the benzene ring to a position perpendicular to the ring.



SCHEME 2

phenylurea it would be expected to form the more stable addition intermediate and a change in rate-determining step could result.

Substituent effects for the *ortho*-substituted phenylureas were analysed by a least-squares procedure by

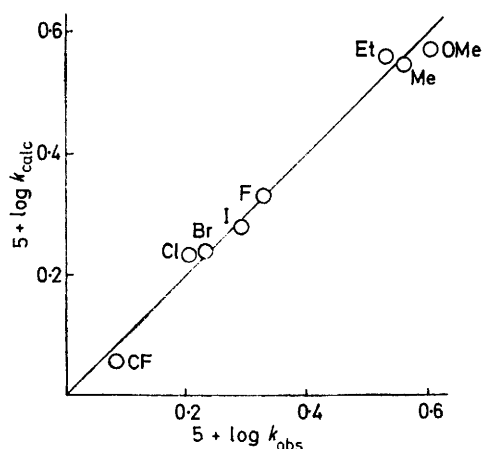


FIGURE 1 Comparison of observed and calculated [equation (ii)] rate constants for the reactions of *ortho*-substituted phenylureas with 3,4-dichlorophenyl isocyanate

using equation (i). An excellent correlation [equation (ii); multiple correlation coefficient 0.993] was obtained which predicts  $\log k_{\text{obs}}$  (Figure 1) to within 0.03 of a unit

*Reaction between Acetic Anhydride and Substituted Phenylureas.*—The reactions considered so far have involved acylation by addition. In order to make a comparison with the more widely studied acylation by substitution we investigated the reaction between acetic anhydride and phenylureas. Acetic acid was used as

TABLE 4

Concentration effects in the reactions between substituted phenylureas and acetic anhydride in acetic acid at 94 °C

$10^3[\text{Urea}]_{\text{initial}}/\text{mol dm}^{-3}$	$[\text{Ac}_2\text{O}]/\text{mol dm}^{-3}$	Phenylurea $10^4 k_{\text{obs}}/\text{s}^{-1}$	2-Iodo-phenylurea $10^4 k_{\text{obs}}/\text{s}^{-1}$
2.00	1.40	2.30	3.00
2.00	1.00	1.58	2.10
2.00	0.60	0.95	1.36
1.00	1.00	1.55	w.06
3.00	1.00	1.60	2.12

solvent because of the necessity to work at temperatures above the b.p. of acetonitrile if unduly slow reactions were to be avoided. For the same reason, the concentration of acetic anhydride was much greater than that required to maintain first-order kinetics. The rate of formation of phenylacylurea was always accurately first-order and the reaction is also first-order in acetic anhydride (see Table 4). At constant acetic anhydride concentration the observed rate constant was shown to

be independent of the urea concentration for the reactions with phenyl- and 2-iodophenyl-urea.

Observed rate constants for a series of substituted phenylureas, obtained under standard conditions at two different temperatures, are collected in Table 5. The data for the *meta*- and *para*-substituted phenylureas at 94 °C yield an excellent Hammett plot of slope ( $\rho$ )

TABLE 5

Reactions between substituted phenylureas and acetic anhydride in acetic acid

Substituent	At 94.2 °C 10 <sup>4</sup> k <sub>obs</sub> /s <sup>-1</sup>	At 79.5 °C 10 <sup>5</sup> k <sub>obs</sub> /s <sup>-1</sup>
4-OMe	2.43	
4-Me	2.09	
3-Me	1.70	
H	1.58	5.03
3-OMe	1.41	4.40
4-I	1.27	3.90
4-F	1.14	
4-Cl	1.10	
4-Br	1.09	
3-COMe	0.89	2.72
3-Cl	0.85	
3-Br	0.83	2.47
3-CF <sub>3</sub>	0.84	
4-COMe	0.71	
4-CF <sub>3</sub>	0.70	
2-OMe	2.68	8.57
2-Me	1.02	3.12
2-Et	0.95	3.12
2-F	0.91	2.83
2-Cl	1.24	4.37
2,4-Cl <sub>2</sub>	0.78	
2,5-Cl <sub>2</sub>	0.77	
2-Br	1.68	6.12
2-I	2.10	8.33
2-I,4-Cl	1.50	
2-I,4-Me	2.79	
2-CF <sub>3</sub>	0.77	2.25

−0.67; the more limited set at 79 °C yields a plot of slope −0.79.

A correlation of the data at 94 °C for the *ortho*-substituted ureas with equation (i) gives equation (iii),

$$\log k_{\text{obs}} = -0.009\sigma_I - 0.550\sigma_R - 4.005 \quad (\text{iii})$$

with standard deviations in  $\alpha$  and  $\beta$  of 0.315 and 0.356, respectively, and a multiple correlation coefficient of 0.568. This correlation is insignificant and it appears that the *ortho*-effect for this reaction series cannot be explained solely in terms of inductive and resonance effects. Nevertheless, a shift in the rate-limiting step of a multi-stage reaction (*cf.* semicarbazone formation),<sup>15</sup> where the response to the electrical effect of a substituent is markedly different from one stage to the next, could lead to an insignificant correlation with equation (i).

The introduction of substituents at the 4- and 5-positions in 2-iodo- and 2-chloro-phenylurea shows that the reaction is facilitated by electron-donating substituents. A Hammett plot of the effect of the extra substituent gives a slope ( $\rho$ ) of  $-0.68 \pm 0.04$  for the 2-iodo- and  $-0.71 \pm 0.2$  for the 2-chloro-phenylureas. The values are close to that obtained ( $-0.67$ ) for the *meta*- and *para*-substituted phenylureas. Further, if

<sup>15</sup> B. M. Anderson and W. P. Jencks, *J. Amer. Chem. Soc.*, 1960, **82**, 1773.

we defer consideration of the chloro-, bromo-, and iodo-substituents, the rate constants for the remaining *ortho*-substituents (OMe, Me, Et, F, and CF<sub>3</sub>) follow the trend of the corresponding Hammett substituent constants and also cover approximately the same range of values as for the corresponding *para*-substituents. In view of the qualitatively similar substituent effects at the *ortho*-, and *meta*- and *para*-positions, and the

TABLE 6

Activation parameters for the reactions between substituted phenylureas and acetic anhydride

Substituent	$\Delta H/\text{kJ mol}^{-1}$	$\Delta S/\text{J mol}^{-1} \text{K}^{-1}$
H	80.7	−99.5
3-OMe	82.3	−96.1
4-I	83.6	−94.0
3-COMe	83.6	−96.6
3-Br	85.7	−90.7
2-F	82.3	−99.5
2-Cl	74.0	−120.4
2-Br	71.1	−125.4
2-I	64.8	−140.9
2-OMe	80.3	−95.7
2-Me	83.6	−95.3
2-Et	86.5	−87.8
2-CF <sub>3</sub>	87.4	−87.4

evidence (linear Hammett plot) against a change in mechanism for *meta*- and *para*-substituents we conclude that there is no change in rate-determining step amongst these *ortho*-substituents.

Consideration of the effect of temperature on the rate of reaction supports this conclusion. A plot (Figure 2) of the type recommended by Exner<sup>16</sup> shows an isokinetic relationship for all substituents with the exception of the *ortho*-chloro-, -bromo-, and -iodo-. Detailed statistical

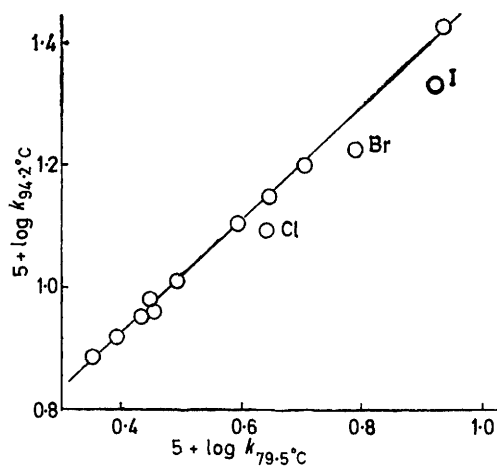


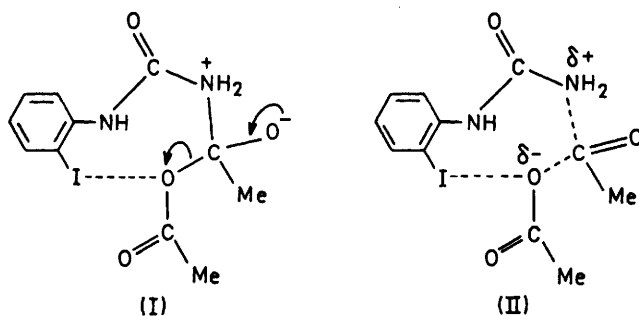
FIGURE 2 Isokinetic relationship for the reactions of substituted phenylureas with acetic anhydride, showing the deviations of the *ortho*-chloro-, -bromo-, and -iodo-substituents.

treatment<sup>16</sup> of the data confirms that these halogeno-substituents deviate from the isokinetic relationship, since the standard deviation  $S_0$  is reduced from 0.02 to 0.005 log units (*i.e.* from a value greater to a value less than the experimental error or *ca.* 0.01) when these substituents are omitted from the data set.

<sup>16</sup> O. Exner, *Coll. Czech. Chem. Comm.*, 1964, **29**, 1094; *Progr. Phys. Org. Chem.*, 1973, **10**, 411.

Transition state enthalpies and entropies of activation, calculated from the data in Table 5, are recorded in Table 6. With the exception of the 2-Cl, 2-Br, and 2-I substituents the values for both  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  lie within relatively narrow limits,  $84.0 \pm 3.8$  kJ mol<sup>-1</sup> and  $-93.6 \pm 6.2$  J K<sup>-1</sup> mol<sup>-1</sup>, respectively. The anomalous halogeno-substituents have considerably reduced enthalpies compensated to a large extent by reduced entropies of activation. This behaviour cannot be reconciled either by electronic effects (as determined by  $\sigma_I$  and  $\sigma_R$ ) or by steric effects (as determined by van der Waals radii) since the other *ortho*-substituents cover the same possible range of electronic and steric effects. Since the reaction centre is remote from the ring, steric effects should not be apparent except on the conformation of the ureido-side-chain and we have already concluded<sup>10</sup> that the conformation is the same for all the *ortho*-substituents considered here. Further, since the *ortho*-effect in the reactions of phenylureas with 3,4-dichlorophenyl isocyanate is dominated by predictable electronic factors, the complexity of the *ortho*-effect in the reactions with acetic anhydride is all the more remarkable.

The mechanism of acylation by substitution<sup>17</sup> may



involve either a tetrahedral intermediate or a synchronous displacement, but the results presented here do not demand either. We propose that the rate enhancements observed for the larger halogeno-substituents are due to electrophilic assistance in the departure of the acetate group as in (I) or (II). Of these possibilities (I) (or a prototropically rearranged form) appears the more probable since it does not involve such a specific conformation for nucleophilic attack of the urea on acetic anhydride.

#### EXPERIMENTAL

U.v. and i.r. spectra were obtained with a Zeiss PMQ11 and a Perkin-Elmer 257 spectrometer, respectively. N.m.r. spectra were recorded with a Varian A60 or Perkin-Elmer R10 spectrometer, with tetramethylsilane as internal standard and dimethyl sulphoxide or hexadeuteriodimethyl sulphoxide as solvent.

**Materials.**—Nitrourea was prepared by the method of Davies and Blanchard<sup>2</sup> and was recrystallised from methanol. Commercial anilines were used without further

purification, except if markedly discoloured, in which case they were either recrystallised or redistilled. Pure specimens of the ureas were obtained by recrystallisation from aqueous methanol of the product from the reaction of the corresponding aniline with either nitrourea or potassium cyanate.<sup>18</sup> 3,4-Dichlorophenyl isocyanate was purified by Soxhlet extraction with sodium-dried petroleum (b.p. 40–60 °C) and had m.p. 43 °C. Acetic anhydride was refluxed over magnesium powder and distilled; b.p. 138 °C. Acetic acid was dried by azeotropic distillation with benzene, a fraction of m.p. >16.5 °C being collected. Acetonitrile was purified by a modification of the method of O'Donnell, Ayres, and Mann.<sup>19</sup> Before the final distillation the acetonitrile was dried over calcium hydride for 24 h and then distilled from anhydrous rhodium carbonate, the fraction of b.p. 81.5 °C being collected. Various batches of the solvent gave kinetic data reproducible to within  $\pm 10\%$ . (If phosphorus pentoxide was used as drying agent kinetic data were reproducible to within ca.  $\pm 30\%$  amongst various batches of solvent.)

**Reaction of Anilines with Nitrourea.**—The aniline (0.05 mol) and nitrourea (0.15 mol) were added to 2 : 1 acetone-water (60 cm<sup>3</sup>), and m-sodium hydrogen carbonate (2 ml) was added to adjust the pH of the solution to allow ready decomposition of the nitrourea.<sup>4</sup> The mixture was refluxed on a water-bath for 2 h, evaporated almost to dryness, filtered, washed with water, and allowed to dry. A <sup>1</sup>H n.m.r. spectrum of this crude product was used to determine the relative amounts of urea, biuret, and unchanged aniline (in the case of the least basic, solid amines). Biurets were isolated by fractional crystallisation, e.g. 2-iodophenylbiuret,  $\lambda_{\text{max}}$  (Nujol) 750s, 1 012w, 1 236m, 1 258m, 1 290m, 1 350m, 1 435s, 1 500s, 1 550m, 1 575s, 1 590s, 1 615m, 1 640m, 1 665m, 1 680m, 1 700s, 1 730sh, 3 190m, 3 260m, and 3 405 cm<sup>-1</sup>;  $\delta$  10.3 (1 H, s), 9.2 (1 H, s), 6.8–8.0 (4 H, m), and 6.7 (2 H, s) (Found: C, 31.8; H, 2.8; I, 41.3; N, 13.8. C<sub>8</sub>H<sub>8</sub>INO<sub>2</sub> requires C, 31.5; H, 2.6; I, 41.6; N, 13.8%). The most useful spectroscopic features for determining the presence of biuret are the singlet absorptions at  $\delta$  ca. 9 and 10, which are well removed from any resonance in the spectrum of the corresponding urea,<sup>10</sup> and the carbonyl stretching band at ca. 1 700 cm<sup>-1</sup> (cf. 1 650 cm<sup>-1</sup> for the urea).

**Reaction of Phenylureas with 3,4-Dichlorophenyl Isocyanate.**—Kinetic data were obtained from reactions performed in volumetric flasks. Solutions of the urea in acetonitrile were equilibrated at the reaction temperature (65 °C) before addition of an appropriate volume of a stock solution of the isocyanate to initiate the reaction. The isocyanate was always in at least ten-fold deficiency in comparison with the urea. Samples (1 cm<sup>3</sup>) were quenched in acetonitrile (to 10 cm<sup>3</sup>) and the reaction was followed by measuring the increase in absorbance in the wavelength range 295–305 nm. Infinity values were taken after at least ten half-lives and first-order rate constants (reproducible to within  $\pm 3\%$ ) were obtained from the slope of a plot of  $\log(O.D._\infty - O.D._t)$  versus time (*t*).

Products were isolated by the following procedure for the reactions of 4-methylphenylurea and phenylurea with 3,4-dichlorophenyl isocyanate. A solution of the urea (0.02 mol dm<sup>-3</sup>) and the isocyanate (0.004 mol dm<sup>-3</sup>) in acetonitrile was maintained at 65 °C until the reaction was

<sup>17</sup> D. P. N. Satchell and R. S. Satchell, in 'The Chemistry of Carboxylic Acids and Esters,' ed. S. Patai, Wiley, New York, 1969.

<sup>18</sup> F. Kurzer, *Org. Synth.*, 1951, **31**, 8.

<sup>19</sup> J. F. O'Donnell, J. T. Ayres, and C. K. Mann, *Analyt. Chem.*, 1965, **37**, 1161.

complete. The mixture was evaporated to dryness under reduced pressure at room temperature and the crude product was recrystallised three times from aqueous methanol in order to remove the excess of urea. 1-(3,4-Dichlorophenyl)-5-phenylbiuret, m.p. 218 °C (Found: C, 51.7; H, 3.3; Cl, 22.05; N, 12.9.  $C_{14}H_{11}Cl_2N_3O_2$  requires C, 51.85; H, 3.4; Cl, 22.05; N, 12.9%), and 1-(3,4-dichlorophenyl)-5-(4-methylphenyl)biuret (Found: C, 53.35; H, 3.5; Cl, 21.05; N, 12.4.  $C_{15}H_{13}Cl_2N_3O_2$  requires C, 52.35; H, 3.55; Cl, 21.0; N, 12.4%) were obtained in >70% yield. By using these products, solutions were prepared which were identical in composition with those expected at the completion of kinetic runs. Absorbance measurements on these solutions agreed closely with those obtained from kinetic runs and indicated that the reactions proceed in high yield.

Although no kinetic studies were performed under equimolar conditions or with isocyanate in excess, the absorbance of reaction mixtures in such cases was found to increase slowly at first and then more rapidly. Moreover, the absorbance of the reaction mixture at the completion of the reaction was greater than that obtained from the expected synthetic solution. Preparative experiments showed that the product was independent of the nature of the starting urea (3-trifluoromethyl-, 2-methyl-, 4-methyl-, or 2-iodo-phenylurea). This compound, identical with the product of the reaction of 3,4-dichlorophenyl isocyanate with 3,4-dichloroaniline, was NN'-bis-(3,4-dichlorophenyl)-urea, m.p. 281—282 °C (Found: C, 44.75; H, 2.35; Cl, 40.25; N, 8.4.  $C_{13}H_8Cl_4N_2O$  requires C, 44.6; H, 2.4; Cl, 40.0; N, 8.0%);  $\delta$  9.0 (2 H, s), and 7.4—7.8 (6 H, m). Presumably the biuret initially formed by the reaction of

the isocyanate with the urea disproportionates<sup>20</sup> to yield 3,4-dichloroaniline, which then reacts with the excess of isocyanate.

*Reaction of Phenylureas with Acetic Anhydride.*—Kinetic data were obtained from reactions performed in a manner similar to that for the reaction between ureas and the isocyanate. Acetic anhydride was in at least ten-fold excess. The reaction was initiated by addition of a weighed amount of urea, the mixtures were quenched by diluting 1 cm<sup>3</sup> samples to 25 cm<sup>3</sup> with acetic acid, and the increase in absorbance in the range 255—262 nm was measured.

Products for some of these reactions were obtained under the same conditions as for the kinetic runs except that equimolar concentrations (0.1 mol dm<sup>-3</sup>) of the urea and acetic anhydride were used. The solution was evaporated to dryness; the crude product corresponded to >90% yield in all cases. Recrystallisation from aqueous methanol yield gave compounds with identical i.r. spectra. For example, the following products were isolated: N-acetyl-N'-phenylurea, m.p. 184—185 °C (lit.,<sup>21</sup> 185—186 °C);  $\delta$  2.18 (3 H, s), 7.4 (5 H, m), and 10.7 (2 H, unresolved singlets), and N-acetyl-N'-2,3-dichlorophenylurea, m.p. 233—234 °C (Found: C, 43.75; H, 3.25; Cl, 28.8; N, 10.9.  $C_9H_8Cl_2N_2O_2$  requires C, 43.7; H, 3.25; Cl, 28.75; N, 11.3%);  $\delta$  2.20 (3 H, s), 7.4—8.4 (3 H, m), 10.02 (1 H, s), and 11.32 (1 H, s).

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<sup>21</sup> H. Aspelund and K. Mackelae, *Acta Acad. Aboensis, Math. Phys.*, 1963, **23**, 18 (*Chem. Abs.*, 1964, **61**, 5596).