Degradation of *O*-Arylisoureas in Alkali: a Low-temperature Chapman-type Rearrangement

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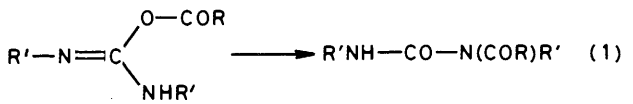
NN'-Di-isopropyl-*O*-arylisoureas are demonstrated to rearrange intramolecularly to the corresponding *NN'*-di-isopropyl-*N'*-arylurea in alkaline solution. The large negative Brønsted-type β_L value (−2.3) for the reaction measured against the p*K* of the corresponding phenol and a modest entropy of activation are consistent with a 1,3-aryl migration. The high efficiency of the migration compared with that of the Chapman rearrangement of *O*-aryl imidoethers is attributed to the greater internal nucleophilicity of the imino nitrogen, which in the present case bears a negative charge.

Isoureas play an important role in dehydration reactions mediated by carbodi-imides.[1] The 1,3-acyl migration reaction [equation (1)] is a complicating factor in peptide synthesis and is part of a general phenomenon [equation (2)] observed in imidate chemistry exemplified by the Chapman [2] and Curtin–Miller [3] rearrangements. The reaction occurs readily for *O*-acylisoureas [4] and *S*-acylisothioureas [5] and for *O*-acylisoimides [3] where an acyl group migrates, but temperatures of about 250 °C are required for *O*-arylisoimides.[2b,6]



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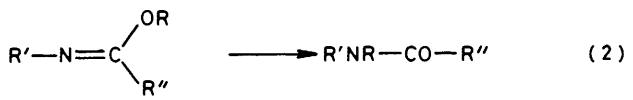

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Whereas the intramolecular 1,3-shift is possible on stereoelectronic grounds for the *O*-acyl- and *O*-aryl-isoureas it is not for the *O*-alkylisoureas and these species have been shown to rearrange intermolecularly.[2a] *O*-Alkylisoureas are also prepared from carbodi-imides, to act as alkylating agents in synthesis.[7]

N-Arylureas occur as by-products [7a-e] in coupling reactions of phenols with carbodi-imides to obtain *O*-arylisoureas. The easy isolation of *O*-arylisoureas from the reaction of carbodi-imides with phenols [4b,7f] gives us an opportunity to study the rearrangement reaction.

Experimental

Materials.—*NN'*-Di-isopropyl-*O*-phenylisoureas were prepared by the following general method. *NN'*-Di-isopropylcarbodi-imide (0.1 mol) was heated with the appropriate phenol (0.2 mol) on an oil-bath at 100 °C for 20 h. The mixture was then taken up in dichloromethane (100 ml) and washed with dilute NaOH solution (0.2M, 3 × 25 ml). Glacial acetic acid (2 ml) was added to precipitate any unchanged carbodi-imide. The solvent layer was filtered, washed again with dilute NaOH solution (0.2M, 2 × 25 ml), dried over $MgSO_4$, and evaporated *in vacuo*. The crude isourea was isolated as the picrate salt by recrystallisation from a cold *unsaturated* solution of picric acid in isopropyl alcohol. Recrystallisation was repeated until a constant m.p. was achieved. Product yields were of the order of 30—60% of the crystalline material and the melting points and analytical data are recorded in Table 1. ^{1}H N.m.r. and i.r. spectroscopy were carried out with a Jeol 100 MHz instrument (we thank Dr. D. O. Smith for this service) and a Perkin-Elmer 297 machine, respectively. The spectra are consistent with the proposed structures.

NN'-Di-isopropyl-*N'*-phenylurea was prepared by adding equimolar amounts (40 mmol) of isopropyl isocyanate and *N*-isopropylaniline to diethyl ether (25 ml), stirring on an ice-bath, and allowing to come to room temperature over 24 h. The product was evaporated and the material recrystallised from light petroleum (b.p. 60—80 °C) to yield white *plates* (51% yield of material), m.p. 62—63 °C (Found: C, 70.7; H, 9.0; N, 13.0%. $C_{13}H_{20}N_2O$ requires C, 70.9; H, 9.1; N, 12.8%); i.r. spectrum (Nujol mull) $\nu_{max.}$ 1 660 (C=O) and 3 420 cm^{-1} (N–H); ^{1}H n.m.r. spectrum δ ($CDCl_3$) 0.08—1.12 [12 H, dd, $(CH_3)_2C$], 3.48—3.72 (1 H, s, NH), 3.72—4.04 (1 H, m, –CH–), 4.72—5.00 (1 H, m, –CH–), and 7.08—7.52 (5 H, m, C_6H_5–).

Kinetics.—The reactions of *NN*-di-isopropyl-*O*-arylisoureas were initially followed at constant high pH by scanning the u.v. spectrum repetitively using a Pye Unicam SP-800 spectrophotometer. Kinetics were measured using the wavelength for maximum absorbance change for each isourea (Table 2) with the SP-800 or Perkin-Elmer 124 spectrophotometers equipped with continuous potentiometric recorders. A typical experiment involved adding a solution of the isourea (as a stock solution in ethanol) on the flattened tip of a glass rod to the reactant solution (2.5 ml KOH buffer in 30% ethanol–water maintained at an ionic strength of 1.0M with KCl) in a silica cell in the thermostatted cell compartment (25 °C) of the spectrophotometer. The change in optical density was recorded with time and pseudo-first-order rate constants calculated from plots of $A_t - A_\infty$ *versus* time on semi-logarithmic graph paper. The pH of the solution in the silica cell was measured after each reaction using a Radiometer (Copenhagen) PHM-26 pH-meter calibrated with E.I.L. buffers to ±0.01 pH unit.

Product Analysis.—The reaction products of the alkaline reaction of *NN'*-di-isopropyl-*O*-phenylisourea were determined by h.p.l.c. analysis. The column packing was Lichrosorb RP 8 with particle size 5 μm. Injection of the sample was by a 10 μl calibrated Hamilton syringe. The mobile phase was a 50% (v/v) solution of sodium pentane-1-sulphonate (0.005M) in aqueous glacial acetic acid (0.3% v/v) and AnalaR methanol; the pump rate was 2 ml min^{-1} and the peaks were detected at 250 nm.

Standard solutions in methanol were prepared from samples of *NN'*-di-isopropyl-*O*-phenylisourea picrate, *NN'*-di-isopropyl-*N'*-phenylurea, picric acid, and phenol. The isourea was treated with KOH solution under the conditions of the kinetic experiments (at a concentration of *ca.* 10^{-7}M) and after the reaction was complete the product was acidified with a few

Table 1. Analytical and physical properties of *NN'*-di-isopropyl-*O*-arylisourea picrates

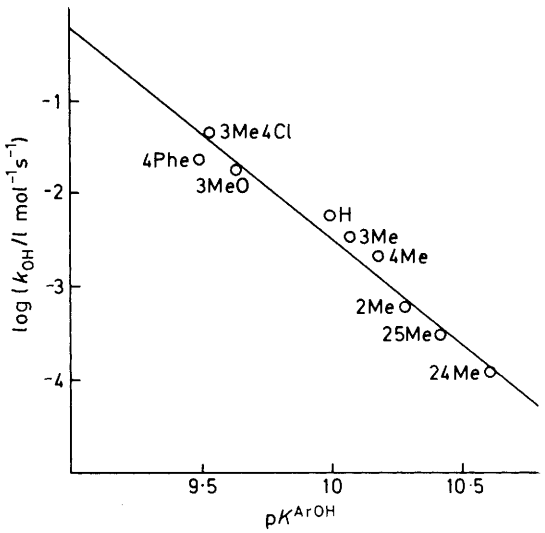
Substituent	M.p. (°C) [a]	Found (%) [b]			Formula	Requires (%)		
		C	H	N		C	H	N
4-Phenyl	124—126	57.4	5.1	13.1	$C_{25}H_{26}N_5O_8$	57.3	5.0	13.4
3-Methoxy	137—138.5	50.8	5.3	14.5	$C_{20}H_{25}N_5O_9$	50.6	5.2	14.6
Parent	196—197	50.7	5.3	15.3	$C_{19}H_{23}N_5O_8$	50.8	5.1	15.6
3-Methyl	156—158	51.6	5.3	15.0	$C_{20}H_{25}N_5O_8$	51.8	5.4	15.1
4-Methyl	159—160	51.8	5.2	15.0	$C_{20}H_{25}N_5O_8$	51.8	5.4	15.1
2-Methyl	155—156	51.7	5.2	14.8	$C_{20}H_{25}N_5O_8$	51.8	5.4	15.1
2,5-Dimethyl	161—163	52.7	5.3	14.5	$C_{21}H_{27}N_5O_8$	52.8	5.6	14.7
2,4-Dimethyl	166—168	52.7	5.5	14.5	$C_{21}H_{27}N_5O_8$	52.8	5.6	14.7
4-Chloro-3-methyl [c]	147—149	48.4	4.6	14.4	$C_{20}H_{23}ClN_5O_8$	48.3	4.6	14.1

[a] M.p.s were determined using a Kofler block. [b] Analyses were by Mr. A. J. Fassam of this laboratory using a Carlo Erba CHN analyser. [c] Found: Cl, 7.3%. $C_{20}H_{23}ClN_5O_8$ requires Cl, 7.2%.

Table 2. Rate constants for the reaction of *NN'*-di-isopropyl-*O*-arylisourea picrates with hydroxide ion [a,b]

Substituent	λ_{kln}/nm [c]	10^3k_{OH}/ l mol^{-1} s^{-1} [d]	pK^{ArOH} [e]
4-Phenyl	300	24	9.51
3-Methoxy	290	17	9.65
Parent	290	5.7	10.00
3-Methyl	290	3.4	10.08
4-Methyl	300	2.2	10.19
2-Methyl	290	0.56	10.28
2,5-Dimethyl	295	0.29	10.41
2,4-Dimethyl	300	0.12	10.60
4-Chloro-3-methyl	285	51	9.56

[a] Temperature 25 °C, 30% ethanol–water (v/v), ionic strength maintained at 1M with KCl. Typically, substrate concentrations were between 10^{-6} and 10^{-7}M in the reaction cell. [b] The rate constants obey the equation: log k_{OH} = 20.3 − 2.3 pK^{ArOH} (r 0.955). [c] Wavelength for kinetic study. [d] The tolerance on the rate constants is ±5%. [e] Values of pK from G. B. Barlin and D. D. Perrin, *Quart. Rev. Chem. Soc.*, 1966, **20**, 75 and W. P. Jencks and J. Regenstein in 'Handbook of Biochemistry,' ed. H. A. Sober, Chemical Rubber Publishing Co., Cleveland, Ohio, 1970.



Brønsted-type relationship for the hydroxide-ion-catalysed rearrangement of *N,N'*-di-isopropyl-*O*-arylisoureas as a function of the pK of the corresponding phenol (30% EtOH–H_2O, 25 °C, 1M ionic strength); the line is theoretical from the equation given in Table 2

drops of concentrated H_2SO_4, diluted with AnalaR methanol, and filtered through a Millipore membrane. The retention times and areas of the product peaks were compared with those of standard samples of phenol, picric acid, and urea. The u.v. spectrum of the products of alkaline reaction of the phenylisourea was also compared with those of picric acid and the urea at the same molar concentration.

Results

Product analysis of the reaction of the phenylisourea in alkaline solution indicated that 90.1% of the original substrate had been converted into the urea (*NN'*-di-isopropyl-*N'*-phenylurea) and that a small proportion (2.7%) was phenol. The method indicates that some phenol is produced and we believe that the error in the measurements encompasses the discrepancy in the stoicheiometry observed above. Since the observation of a linear Brønsted relationship (see later) indicates a single mechanism there is no reason to suspect that the more reactive isoureas are producing the corresponding phenol; therefore we did not carry out product analyses for these substrates. No correction is made in the kinetics as the proportion of phenol product is negligible. The product u.v. spectrum for the reaction of the phenylisourea is similar to that expected for an equivalent mixture of the urea and picric acid, in qualitative agreement with the above conclusions.

The reactions were accurately first order over *ca.* 90% of the total reaction (substrates at 10^{-6}—10^{-7}M) and the pseudo-first-order rate constants are proportional to the hydroxide ion concentration. The intercepts at zero hydroxide ion concentration are commensurate with the errors in the rate constants. The derived second-order rate constants are collected in Table 2 and fit a Brønsted-type equation against the pK of the corresponding phenol (Figure). A temperature dependence of the second-order rate constant for reaction of hydroxide with the phenylisourea was carried out and the data are presented in Table 3.

Any uncatalysed rearrangement of the neutral isourea was completely obscured by the alkaline reaction, which took more than 99% of the total reaction flux. We estimate that in the case of the phenyl derivative any neutral reaction will have a rate constant less than 10^{-4} s^{-1}, which represents the error on the intercept at zero hydroxide ion concentration.

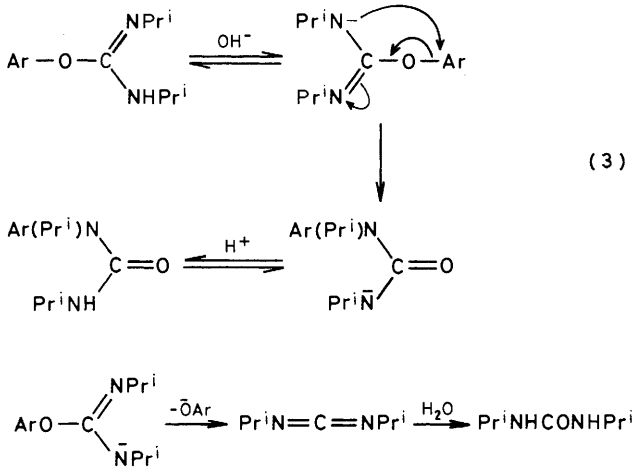
Discussion

Product analysis indicates conclusively that the major reaction occurring in the reaction of hydroxide ion with *NN'*-di-isopropyl-*O*-phenylisourea is the rearrangement to *N*-phenylurea; this is confirmed by the product spectra. The low molar

Table 3. Temperature dependence of the rate constant for hydroxide ion attack on *NN'*-di-isopropyl-*O*-phenylisourea picrate [a]

Temperature (°C)	$10^3 k_{OH}$/l mol^{-1} s^{-1} [b]
26.90	0.91
31.90	1.44
38.10	2.74
42.80	4.17
48.30	7.58

[a] Ethanol–water (30%, v/v), ionic strength maintained at 1M with KCl. [b] The second-order rate constants obey an Arrhenius equation with the following parameters (for 26.9 °C): $\Delta H^{\ddagger}$, 17.6 ± 0.5 kcal mol^{-1}; $\Delta S^{\ddagger}$, −13.5 ± 0.8 cal K^{-1} mol^{-1}.



(3)

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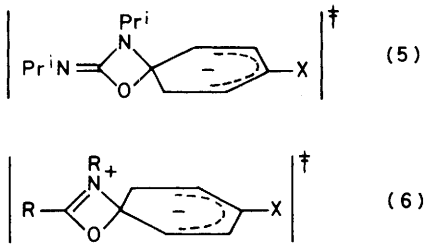
concentration of the *O*-phenylisourea used in the product analysis studies (~10^{-7}M) excludes the possibility that the rearrangement reaction is intermolecular. The rearrangement is catalysed by hydroxide ion and the simplest mechanism for this reaction involves ionisation of the NH group followed by 1,3-migration of the aryl species [equation (3)]. The unimolecular pathway is consistent with a relatively small entropy of activation. We can exclude the possible route in equation (4) as not providing significant reaction flux for the observed reaction although the presence of a small amount (3%) of phenol in the product analysis indicates that this reaction [equation (4)] might play a minor role.

The extraordinarily large β_L (−2.3) for the variation of the hydroxide ion rate constant with the aryl substituent is consistent with an S_NAr type of mechanism where attack of a nucleophile, in this case the nitrogen anion, is much more important than cleavage of the Ar–O bond. It is possible that a concerted migration occurs but if this were the case the bonding would necessarily be required to be strong for the Ar–O and Ar–N because the very high β indicates destruction of the aromaticity with charge being forced close to the substituent. The transition-state of the rate-controlling step is indicated by the Brønsted selectivity to be as in equation (5), whether or not a discrete intermediate exists; the N–C and O–C bonds to the spiro-carbon must be almost fully formed to give such a very large Brønsted β value.

The decreased degrees of freedom of this transition-state over the ground-state anion would explain the low but negative entropy of activation (−13.5 cal K^{-1} mol^{-1}). In a fragmentation reaction, for example the hydroxide-catalysed decomposition of aryl carbamate to isocyanate and aryl oxide,[8]



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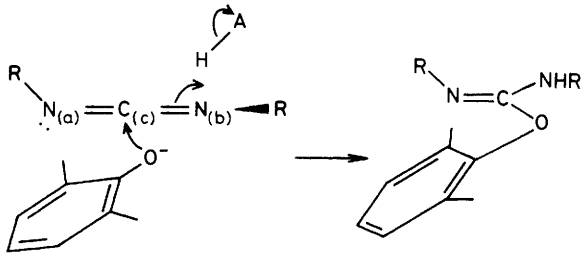
the entropy of activation is slightly positive (*ca.* 5 cal K^{-1} mol^{-1} for phenyl *N*-phenylcarbamate). In both the above example and the present reaction there is the complicating feature of the ionisation of the NH group; nevertheless this might be expected to give similar entropy contributions in each case. The more negative entropy of activation for the rearrangement is attributed to the loss of freedom from reactants to transition-state (requiring rotations *etc.*) which do not occur in the fragmentation reaction.

The sensitivity of the rearrangement to aryl substituent is very much greater than that found by Wiberg and Rowland [6] for the 1,3-aryl migration [equation (2), R = Ar, R″ = Ar]. The low value obtained by these workers (β_L = −0.78) [6] might be explained by the zwitterionic nature of the transition-state derived from the neutral reactants [equation (6)]. Possibly the substituent on the migrating aryl group ' sees ' less negative charge owing to the effect of the positive charge residing on the nitrogen. The isourea case has a fully negatively charged transition-state [equation (5)]. A further explanation for a lower selectivity is that the Chapman rearrangement [6] is carried out at much higher temperatures (260 °C) than the present (25 °C) and it is established that temperature has an effect on the magnitude of selectivities.[9]

The high reactivity of the isourea rearrangement compared with that of the Chapman rearrangement [6] is easily attributed to the high internal nucleophilicity of the imino nitrogen, which bears a negative charge in the former case. The ease of rearrangement of the *O*-acylisoureas and *S*-acylisothioureas (half-lives of the order of 60 [4b] and 1 s,[5] respectively) is explained on the greater electrophilicity of the acyl function compared with that of the aryl function. It is probable that the *N*-substituent has a significant effect in both imidate and isourea rearrangements where electron-releasing substituents should favour the reaction. Previous authors have indicated that *ortho*-substituents on the aryl group of *O*-arylisoureas tend to retard the O ⟶ N migration in the neutral species.[10] Model building using Corey–Pauling–Koltun (CPK) precision space-filling models indicates that there is *no* steric requirement to formation of the transition-state for the 1,3-migration of the *O*-(2,6-dichlorophenyl)-*NN'*-di-isopropylisourea starting from the conformation illustrated in equation (7). There exists, however, a high barrier to conformational changes in the ground-state of this molecule, which are not seen in the parent or 2-chloro species. Inspection of CPK models of carbodi-imido and phenolate attacking group indicates that the conformation of the phenol in the transition-state relative to the carbodi-imide atoms must be as shown in the diagram [equation (7)] because of unfavourable interactions imposed by the substituents on $N_{(b)}$ and the phenyl ring if a different torsional angle about $C_{(c)}$–O is taken. Recent studies indicate that the reaction of carboxylic acids with carbodi-imides involve concerted general acid-catalysed attack of the carboxylate anion [equation (8)] [4b] and it is probable that a similar mechanism holds for attack of the phenols.[11] The lone pair of the imino nitrogen $N_{(a)}$ in equation (7) produced in the addition of phenolate ion is hindered strongly by the phenyl ring and it seems inconceivable that



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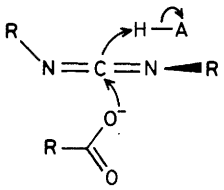

(8)

this could be the site of the protonation by a general acid. This argument indicates that the product *O*-arylisourea is formed in the best conformation for the neutral species to rearrange to the *N*-arylurea. Even if the formation of the *O*-arylisourea is stepwise from carbodi-imide and phenol, the intermediate anion will still possess a hindered $N_{(a)}$ and a freely available $N_{(b)}$. These arguments are reasonable and they dispose of the possibility suggested previously [10] that the *O*-(2,6-disubstituted aryl)isourea resists rearrangement through steric retardation. In any case, the observation that picric acid and dicyclohexylcarbodi-imide gives *N*-2,4,6-trinitrophenyl-*NN'*-dicyclohexylurea [11b] seems to be contrary to the steric argument.[10]

Acknowledgements

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