Mononuclear Heterocyclic Rearrangements. Part 12.[1] Kinetic Study of Substituent Effects on the Rearrangement of the (*Z*)-Phenylhydrazones of Some 5-Aryl-3-benzoyl-1,2,4-oxadiazoles into 4-Aroylamino-2,5-diphenyl-1,2,3-triazoles in Dioxane–Water at Various pS^+ Values

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The kinetics of the title reaction have been studied in the pS^+ range 4.0—12.0, at various temperatures. The logarithmic kinetic constants show excellent linear free energy correlations with σ and σ^n for the pS^+-independent and pS^+-dependent ranges, respectively. The susceptibility constants obtained (ρ +0.85 and +1.75, at pS^+ 4.50 and 10.00, respectively) show that a larger negative charge is developed in the transition state of the base-catalysed reaction pathway than in that of the uncatalysed, pS^+-independent route.

The mononuclear heterocyclic rearrangement [2] of the (*Z*)-arylhydrazones of 3-benzoyl-1,2,4-oxadiazoles (Scheme) has been formulated as a kind of 'internal' nucleophilic substitution.[3]

The timing of formation of the N(α)–N(2) bond and of the rupture of the N(2)–O bond in the transition state depends on, *inter alia*, the nucleophilic character of N(α), as determined by the substituents present in the *N*-aryl moiety [4] and by the occurrence of base catalysis [catalysed loosening of the N(α)–H bond enhances the nucleophilicity of N(α)].[3,5] On the other hand, rupture of the N(2)–O bond should be influenced by the leaving group ability of the Ar–C(5)–O system.

Although the nature of the substituent at C(5) is expected to affect the rate of rearrangement, the only pertinent data collected hitherto come from our laboratory and show, indeed, that in the rearrangements of compounds bearing hydrogen, phenyl, and some alkyl groups at C(5), the reactivity depends on the electronic effects of these substituents.[1]

In order to obtain a deeper insight into this aspect of the mechanism, we have studied the kinetics of rearrangement of (*Z*)-phenylhydrazones of some 5-aryl-3-benzoyl-1,2,4-oxadiazoles (Ia—m).

Results and Discussion

The apparent first-order kinetic constants, k_A, for the rearrangement (Ia—m) ⟶ (IIa—m) have been measured in dioxane–water in the presence of buffers, in the pS^+ range 4.0—12.0, at various temperatures. The logarithmic kinetic constants, calculated at 313.15 K from activation parameters † (Table 1), are plotted *versus* pS^+ in Figure 1: the curves obtained are roughly parallel, thus showing that, independent of the substituent, the same mechanism operates at any pS^+.

As previously [3] observed for (Id), two different reaction pathways occur, depending on the pS^+ range: the one, uncatalysed, pS^+-independent (range 4.0—6.5), the other, base-catalysed, at higher pS^+ (>8.50).‡ At each pS^+ the rate depends on the nature of the substituent: thus, the reactivity is increased by electron-withdrawing substituents and decreased by electron-donating substituents.§

Hammett correlations of kinetic data with σ constants (Table 2) are excellent in the pS^+-independent range (at pS^+ 3.80—6.00; ρ 0.847 ± 0.028, *r* 0.9951, *n* 11) but less good in the pS^+-dependent range (*e.g.* at pS^+ 10.00; ρ +1.57 ± 0.08, *r* 0.9898, *n* 11). The plots relevant to the latter case (Figure 2) show that the electron-donating *para*-substituents deviate significantly from the straight line: the correlations are thus improved by exclusion of these points (*e.g.* at pS^+ 10.00; ρ +1.76 ± 0.04, *r* 0.9986, *n* 7; Figure 2, line *a*) or if σ^n values are used instead of σ (*e.g.* at pS^+ 10.00; ρ +1.72 ± 0.02, *r* 0.9996, *n* 11; Figure 2, line *b*). This allows us to infer that there is no through-conjugation between the electron-donating *para*-substituents present in the 5-aryl moiety and the C(5)—O(2) leaving group in the transition state.

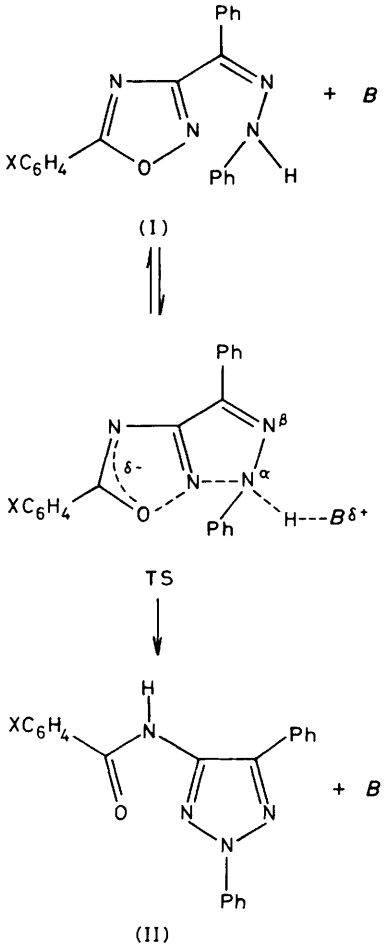
The calculated susceptibility constants and the kind of σ values used in the correlations deserve comment. First, the calculated ρ values are particularly high when one considers that the electronic effects are exerted by substituents far from the reaction centre and separated from the leaving group C(5)–O by the phenyl ring.[9] This behaviour could be accounted for by a mechanism where the two processes [the formation of the N(α)–N(2) bond and the rupture of the N(2)–O bond] are concerted, the breaking of N(2)–O bond has made some progress in the transition state, and a negative charge has developed in the 1,2,4-oxadiazole ring in the transition state (TS in the Scheme).

Comparison between the susceptibility constants calculated in the pS^+-dependent and the pS^+-independent ranges gives further information: in the base-catalysed reaction pathway, owing to the loosening of the N(α)–H bond by action of the base, the extent to which the N(α)–N(2) bond is formed is greater than in the uncatalysed reaction pathway. Thus, in the two cases there is a different degree of breaking of the N(2)–O bond, a different negative charge developing in the relevant

† Comments on the activation parameters have been given previously.[1,3]

‡ As previously shown [5] in this pS^+ range the mechanism of rearrangement implies a general base catalysis.

§ A similar trend in the electronic effects of 5-aryl substituents has been observed in other reactions involving ring fission through cleavage of the N(2)–O bond, such as the thermal rearrangement of 3-(2-phenylaminoethyl)-5-aryl-1,2,4-oxadiazoles into 1-phenyl-3-aroylamino-Δ^2-pyrazolines [6] or that of 3-(2-aminoaryl)-5-aryl-1,2,4-oxadiazoles into 3-acylaminoindazoles,[7] and the base-catalysed ring opening of 5-arylisoxazoles which gives 2-cyanoacetophenones.[8]



a; X = *p*-MeO
b; X = *p*-Me
c; X = *m*-Me
d; X = H
e; X = *p*-Cl
f; X = *p*-Br
g; X = *m*-Cl
h; X = *m*-Br
i; X = *m*-NO_2
l; X = *p*-CN
m; X = *p*-NO_2

Scheme.

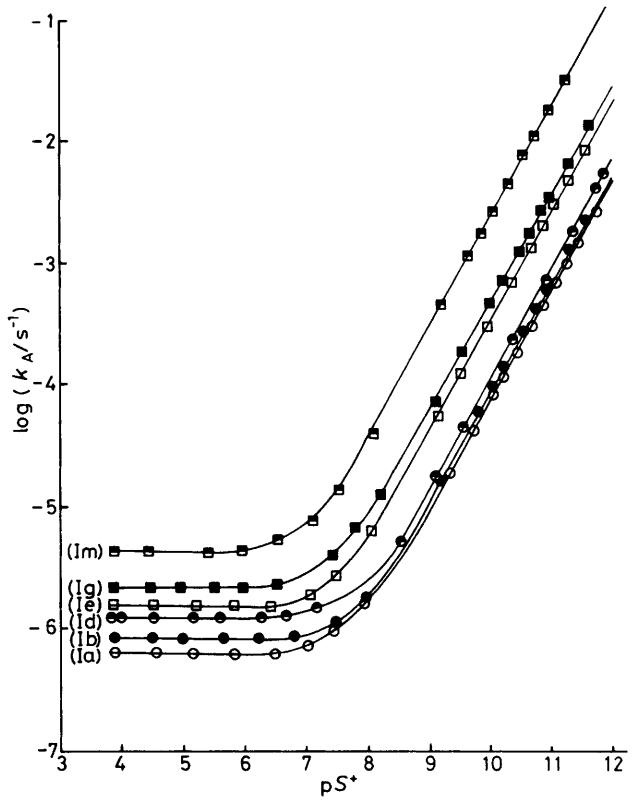


Figure 1. Plot of log k_A at 313.15 K in dioxane–water *versus* pS^+. Compounds (Ic), (If), (Ih), (Ii), and (Il) give plots similar to those for (Ib), (Ie), (Ig), and (Im), respectively (see Table 1)

transition state, and a consequent different sensitivity to the effects of the substituents in the aryl moiety at C(5).

In conclusion, the higher ρ values in the pS^+-dependent range (ρ +1.71—1.78) than in the pS^+-independent range (ρ +0.847) suggest a later transition state for the base-catalysed than for the uncatalysed reaction. In this respect the necessity for using σ^n constants to correlate the kinetic data in the base-catalysed range is easily understood, in that the large negative charge present in the 1,2,4-oxadiazole ring ' induces ' the electron-donating substituents to behave as having the less unfavourable electronic effect, *i.e.* only the inductive effect. The behaviour of the phenylhydrazones (Ia, b, e, and f) represents a further example of the ability of substituents to exert different electronic effects as a function of the electronic demand of the reaction centre in the transition state.[10]

An alternative interpretation * of the correlations observed could be that in the base-catalysed range the two processes [the formation of the N(α)–N(2) bond and the rupture of the N(2)–O bond] are concerted, but not necessarily synchronous, so that formation of the new bond could have made more progress than rupture of the old. This situation implies a late

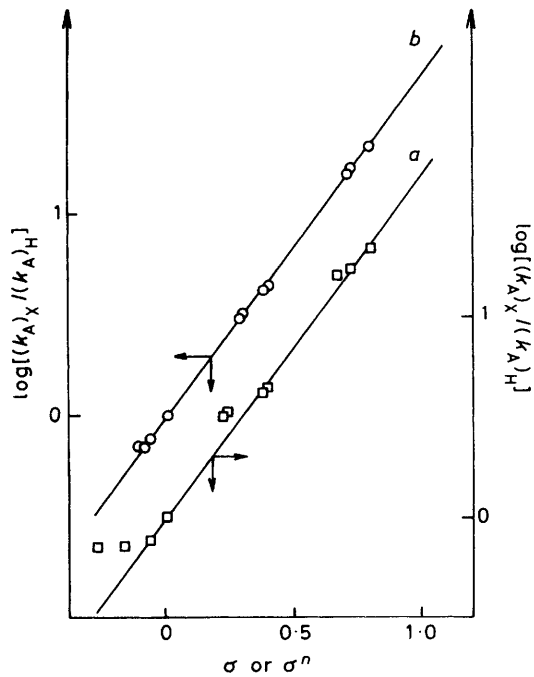


Figure 2. Plot of log $[(k_A)_X/(k_A)_H]$ *versus* σ (line *a*) or σ^n (line *b*). The straight line *a* has been calculated by excluding electron-donating *para*-substituents (Ia, b, e, and f)

* We thank a referee for his suggestions on this point.

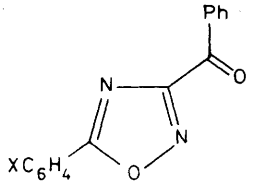
Table 1. $-\log k_A$ values calculated at 313.15 K from activation parameters at various pS^+ values

	pS^+	3.80	4.50	5.00	6.00	7.00	7.50	8.00	8.50	9.00	9.50	10.00	10.50	11.00	11.50	12.00
p-OMe		6.200	6.200	6.200	6.200	6.160	6.000	5.760	5.460	5.011	4.560	4.110	3.660	3.209	2.759	2.309
p-Me		6.125	6.125	6.125	6.125	6.100	6.010	5.778	5.450	5.007	4.554	4.101	3.648	3.195	2.742	2.289
m-Me		6.074	6.074	6.074	6.074	6.050	5.930	5.720	5.390	4.976	4.519	4.062	3.605	3.148	2.691	2.234
H		5.905	5.905	5.905	5.905	5.860	5.750	5.570	5.290	4.853	4.403	3.952	3.502	3.051	2.601	2.150
p-Cl		5.798	5.798	5.798	5.798	5.725	5.525	5.230	4.815	4.356	3.902	3.447	2.993	2.538	2.084	1.629
p-Br		5.763	5.763	5.763	5.763	5.630	5.440	5.155	4.780	4.360	3.901	3.443	2.985	2.526	2.068	1.609
m-Cl		5.660	5.660	5.660	5.660	5.520	5.310	5.035	4.670	4.223	3.771	3.319	2.867	2.415	1.963	1.511
m-Br		5.642	5.642	5.642	5.642	5.480	5.280	5.000	4.650	4.221	3.768	3.314	2.860	2.407	1.954	1.500
m-NO_2		5.333	5.333	5.333	5.333	5.080	4.830	4.490	4.079	3.622	3.165	2.708	2.251	1.794	1.337	0.880
p-CN		5.424	5.424	5.424	5.424	5.255	4.980	4.570	4.120	3.643	3.192	2.740	2.289	1.837	1.386	0.935
p-NO_2		5.340	5.340	5.340	5.340	5.150	4.880	4.490	4.020	3.531	3.067	2.604	2.140	1.677	1.213	0.750

Table 2. Linear free energy relationships [a] for the mononuclear heterocyclic rearrangement (I) ⟶ (II) in dioxane–water (1 : 1 v/v) at 313.15 K and at various pS^+ values

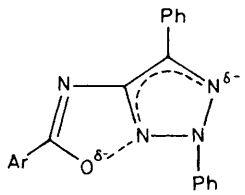
Relationship	$\rho \pm s_\rho$	R	$i \pm s_i$	Hydrazones (I)
		at pS^+ 3.80—6.00		
$\log[(k_A)_X/(k_A)_H] = \rho\sigma$	0.847 ± 0.028	0.9951	−0.07 ± 0.01	(Ia—m)
		at pS^+ 7.00		
$\log[(k_A)_X/(k_A)_H] = \rho\sigma$	1.05 ± 0.05	0.9915	−0.05 ± 0.02	(Ia—m)
		at pS^+ 7.50		
$\log[(k_A)_X/(k_A)_H] = \rho\sigma$	1.21 ± 0.05	0.9925	−0.01 ± 0.02	(Ia—m)
		at pS^+ 8.00		
$\log[(k_A)_X/(k_A)_H] = \rho\sigma$	1.38 ± 0.06	0.9919	0.05 ± 0.03	(Ia—m)
$\log[(k_A)_X/(k_A)_H] = \rho\sigma$	1.50 ± 0.05	0.9975	−0.02 ± 0.02	(Ic, d, g—m)
$\log[(k_A)_X/(k_A)_H] = \rho\sigma^n$	1.50 ± 0.03	0.9977	−0.04 ± 0.01	(Ia—m)
		at pS^* 9.00		
$\log[(k_A)_X/(k_A)_H] = \rho\sigma$	1.56 ± 0.08	0.9895	0.10 ± 0.03	(Ia—m)
$\log[(k_A)_X/(k_A)_H] = \rho\sigma$	1.75 ± 0.05	0.9983	−0.01 ± 0.02	(Ic, d, g—m)
$\log[(k_A)_X/(k_A)_H] = \rho\sigma^n$	1.71 ± 0.02	0.9996	0.00 ± 0.01	(Ia—m)
		at pS^+ 10.00		
$\log[(k_A)_X/(k_A)_H] = \rho\sigma$	1.57 ± 0.08	0.9898	0.11 ± 0.03	(Ia—m)
$\log[(k_A)_X/(k_A)_H] = \rho\sigma$	1.76 ± 0.04	0.9986	−0.01 ± 0.02	(Ic, d, g—m)
$\log[(k_A)_X/(k_A)_H] = \rho\sigma^n$	1.72 ± 0.02	0.9996	0.00 ± 0.01	(Ia—m)
		at pS^+ 11.00		
$\log[(k_A)_X/(k_A)_H] = \rho\sigma$	1.58 ± 0.08	0.9899	0.11 ± 0.03	(Ia—m)
$\log[(k_A)_X/(k_A)_H] = \rho\sigma$	1.77 ± 0.04	0.9987	0.00 ± 0.02	(Ic, d, g—m)
$\log[(k_A)_X/(k_A)_H] = \rho\sigma^n$	1.73 ± 0.02	0.9995	0.01 ± 0.01	(Ia—m)
		at pS^+ 12.00		
$\log[(k_A)_X/(k_A)_H] = \rho\sigma$	1.60 ± 0.08	0.9900	0.12 ± 0.03	(Ia—m)
$\log[(k_A)_X/(k_A)_H] = \rho\sigma$	1.78 ± 0.04	0.9986	0.00 ± 0.02	(Ic, d, g—m)
$\log[(k_A)_X/(k_A)_H] = \rho\sigma^n$	1.74 ± 0.02	0.9992	0.01 ± 0.01	(Ia—m)

[a] ρ, reaction constant; s_ρ, standard deviation of ρ; R, correlation coefficient; i, intercept of the regression line with the ordinate σ = 0; s_i, standard deviation of i; the substituents in the listed hydrazones (I) are those involved in the calculation of ρ. σ Values from D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 240; σ^n values from A. J. Hoefnagel and B. M. Wepster, *J. Am. Chem. Soc.*, 1973, **95**, 5357.



(III)

(a—m as Scheme)



(IV)

transition state (IV), as regards the triazole ring (which is almost completely formed), but quite an early transition state with respect to N–O bond fission, with the component of charge in the oxadiazole ring rather localized and then largely inductive in nature.

Experimental

Synthesis and Purification of Compounds.—Compounds (Id) and (IId),[11] and dioxane [12] were prepared and/or purified

Table 3. Physical data of compounds (I)—(III)

Compound	M.p. (°C)	I.r. (Nujol) (cm^{-1}) ν_{NH}	I.r. (Nujol) (cm^{-1}) ν_{CO}	U.v. [a] $\lambda_{max.}$/nm	U.v. [a] log ε	N.m.r. ($CDCl_3$) δ_{NH}
(Ia) [b]	139	3 240		366	4.23	11.55
(Ib) [c]	150	3 240		366	4.25	11.50
(Ic) [c]	148	3 230		366	4.24	11.55
(Id) [d]				366	4.22	
(Ie) [c]	165	3 220		366	4.22	11.45
(If) [c]	164	3 220		366	4.20	11.45
(Ig) [c]	139	3 270		366	4.21	11.50
(Ih) [c]	150	3 260		366	4.20	11.40
(Ii) [c]	178	3 240		350	4.25	11.30
(Il) [b]	166	3 250 [e]		352	4.22	11.30
(Im) [b]	191	3 240		354	4.27	11.30
(IIa) [f]	213	3 280	1 660	285	4.44	
(IIb) [f]	200	3 240	1 650	295	4.40	
(IIc) [f]	179	3 260	1 650	290	4.38	
(IIe) [f]	228	3 270	1 660	295	4.39	
(IIf) [f]	215	3 260	1 660	295	4.38	
(IIg) [f]	200	3 300	1 660	290	4.39	
(IIh) [f]	212	3 300	1 660	290	4.35	
(IIi) [f]	235	3 250	1 650	290	4.42	
(III) [f]	245	3 240 [g]	1 650	285	4.45	
(IIm) [f]	229	3 240	1 650	290	4.46	
(IIIa) [f]	148		1 680			
(IIIb) [f]	107		1 670			
(IIIc) [f]	87		1 670			
(IIIe) [f]	131		1 680			
(IIIf) [f]	138		1 670			
(IIIg) [f]	112		1 675			
(IIIh) [f]	105		1 675			
(IIIi) [f,h]	174		1 675			
(IIIl) [f]	151		1 665 [i]			
(IIIm) [i]	188		1 660			

[a] Wavelengths and log ε at the maximum used for spectrophotometric determinations, in dioxane–water (1 : 1, v/v). [b] Crystallized from benzene–light petroleum. [c] Crystallized from benzene–ethanol. [d] See refs. 11 and 13. [e] ν_{CN} 2 230 cm^{-1}. [f] Crystallized from ethanol. [g] ν_{CN} 2 230 cm^{-1}. [h] Lit.[14] m.p. 174—175 °C. [i] ν_{CN} 2 230 cm^{-1}. [l] Crystallized from dioxane–ethanol.

according to methods reported previously. (Z)-*Phenylhydrazones* (Ia—c and e—m) were prepared from the corresponding 5-aryl-3-benzoyl-1,2,4-oxadiazoles (IIIa—c and e—m) with phenylhydrazine in ethanol and/or acetic acid, and purified by crystallization and/or chromatography. The *Z*-configuration of the phenylhydrazones was confirmed by u.v., i.r., and n.m.r. spectra, [*cf.* the reports for (Id) [13]]. Triazoles (IIa—c and e—m) were obtained almost quantitatively through thermal or base-induced rearrangement of phenylhydrazones (Ia—c and e—m) and purified by crystallization. The *oxadiazolyl ketones* (IIIa—c and e—m) were prepared by the reaction of phenylglyoxylyl chloride oxime with the corresponding aromatic aldehyde oximes in refluxing toluene, according to the procedure reported,[14] and purified by crystallization and/or chromatography (yields 30—50%, not optimized). All new compounds gave satisfactory elemental analytical data. Physical data are reported in Table 3.

pS^+ *and Kinetic Measurements.*—Details of the operational pH scale used (pS^+) have already been reported.[3,5] The kinetics were measured as previously described.[3] The wavelengths and log ε values at the maxima used for spectrophotometric determinations of kinetic constants are reported in Table 3. The kinetic constants and the activation parameters measured at each pS^+ value are in Supplementary Publication No. SUP 23814 (11 pages).*

* For details of Supplementary Publications see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, 1984, Issue 1.

Acknowledgements

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