A Kinetic Study on the Base-catalysed $E \longrightarrow Z$ Isomerization of Some Arylhydrazones of 3-Benzoyl-5-phenyl-1,2,4-oxadiazole: Effect of the Substituents in the Arylhydrazone Moiety

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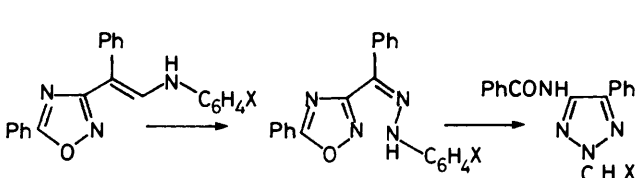
The kinetic data obtained in the study of the title reaction reveal unusual substituent effects. A logarithmic plot of reactivity data *versus* substituent constants (σ and/or σ^-) shows a 'zigzag' trend; it is suggested that this depends on a changeover of the mechanism and/or of the rate-determining step.

In the course of our studies on mononuclear heterocyclic rearrangements[1] of 1,2,4-oxadiazole derivatives[2] we have directed our attention to the synthesis and study of the reactivity of the *E*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1d**).[3,4] We have observed that 3-benzoyl-5-phenyl-1,2,4-oxadiazole reacts with phenylhydrazine in acetic acid, at room temperature, to give a mixture of *Z*-(**2d**) (57%) and the *E*-isomer (**1d**) (26%).[3] In the presence of base the *E*-isomer (**1d**) isomerizes to the *Z*-isomer (**2d**), which then rearranges into 3-benzoylamino-2,5-diphenyl-1,2,3-triazole (**3d**).[4] With reference to this isomerization–rearrangement process, the experimental data collected in benzene in the presence of piperidine at 313 K [instantaneous concentrations of the species present (**1d**), (**2d**), and (**3d**)] are consistent with the occurrence of two consecutive reactions according to Scheme 1, *i.e.*, irreversible isomerization of the *E*-isomer (**1d**) to the *Z*-isomer (**2d**), followed by the rearrangement of the *Z*-isomer (**2d**) into the triazole (**3d**). Both the reactions are piperidine-catalysed. It must be noted that a benzene solution (*ca.* 10^{-4} mol dm^{-3}) of (**1d**) in the presence of acetic acid (1 mol dm^{-3}) remains unchanged on being heated at 333 K for 48 h.



(**1**) (**2**) (**3**)

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

The study of the mechanism of the $E \longrightarrow Z$ isomerization has attracted the attention of many research workers: the course of both the thermal- and the acid-isomerization[5] has been widely studied and different mechanisms have been suggested. For example, for the $E \longrightarrow Z$ isomerization about the C=N double bond, the proposed mechanisms[5] include: (*i*) the rotation mechanism, involving a polarization or an unpairing of the π-electrons in the C=N double bond *via* a zwitterion or a biradical species; (*ii*) the imino-nitrogen inversion mechanism through a lateral shift of the substituent linked to the nitrogen; and (*iii*) the addition–elimination mechanism. The study of the influence of the substituents at the C=N double bond and of the solvents used on the reactivity rates can give information on the mechanism(s) of the isomerization.

In order to gain a deeper insight into the mechanism of the base-catalysed $E \longrightarrow Z$ isomerization of arylhydrazones of heteroaryl aryl ketones we have extended our study to the $E \longrightarrow Z$ isomerization of some *E*-arylhydrazones (**1a–k**) in different solvents [benzene (PhH), dioxane (D) and acetonitrile (AN)] in the presence of piperidine at 313 K.

A large variety of substituents in the arylhydrazone moiety, ranging from electron-repelling (alkyls) to strongly electron-withdrawing (cyano and nitro) groups are useful in investigating the isomerization mechanism. Moreover the solvents chosen, *i.e.* non-protic with very different relative permittivities (D, ε 2.21; PhH, 2.28; AN, 37.5) and nucleophilic constants[7] (PhH, B 48; AN, 160; D 237) should allow us to obtain information on the solvent effect, if any, on the mechanism.

Results and Discussion

As indicated in Scheme 1, the overall reaction (isomerization followed by rearrangement) consists of two consecutive reactions: this system is complicated by the fact that each reaction is a complex piperidine-catalysed reaction which can involve one and/or two molecules of piperidine. The study of this system can be much simplified by taking advantage of the independent knowledge of the rearrangement rates that we have recently determined.[2c,e,4] By measuring the variation of the optical density with time it is possible to calculate the values of the instantaneous concentrations of the three species present and the apparent rate coefficients of isomerization [$(k_A)_i$] of the *E*-isomers (see *Kinetic Measurements* in the Experimental section and Tables 1–3).*

* The $(k_A)_i$ values for the *E*-arylhydrazones (**1a–i**) and (**1j, k**) show a non-linear and a linear dependence on piperidine concentration, respectively, with curves crossing the origin in every case, (k_u which refers to the spontaneous, uncatalysed, pathway is 0), thus indicating that the reactions are wholly piperidine-catalysed. For compounds (**1a–i**) and (**1j, k**) the isomerization data fit equations (1) and (2), respectively.

$$(k_A)_i = k_2[\text{pip}] + k_3[\text{pip}]^2 \quad (1)$$

$$(k_A)_i = k_2[\text{pip}] \quad (2)$$

The second- (k_2) and the third-order (k_3) isomerization rate constants are collected in Tables 4–6.

Table 1. Apparent first-order rate constants, k_A,[a] for the isomerization (**1a–k**) into (**2a–k**) in dioxane at 313 K in the presence of piperidine (pip).

					(**1a**)[b]					
[pip]/mol dm^{-3}	0.100	0.200	0.300	0.400	0.510	0.600	0.700	0.800	0.880	
k_A/10^{-5} s^{-1}	0.118	0.251	0.401	0.567	0.769	0.949	1.16	1.41	1.60	
					(**1b**)[c]					
[pip]/mol dm^{-3}	0.128	0.240	0.375	0.470	0.600	0.720	0.840	0.940	1.00	
k_A/10^{-5} s^{-1}	0.142	0.282	0.472	0.618	0.837	1.06	1.29	1.50	1.64	
					(**1c**)[d]					
[pip]/mol dm^{-3}	0.121	0.250	0.408	0.500	0.650	0.760	0.889	1.00		
k_A/10^{-6} s^{-1}	0.970	2.10	3.61	4.59	6.25	7.56	9.12	10.6		
					(**1d**)[e]					
[pip]/mol dm^{-3}	0.130	0.230	0.367	0.470	0.580	0.734	0.857	0.938	1.00	
k_A/10^{-5} s^{-1}	0.111	0.203	0.339	0.450	0.573	0.760	0.919	1.03	1.12	
					(**1e**)[f]					
[pip]/mol dm^{-3}	0.101	0.202	0.300	0.408	0.505	0.606	0.707	0.808	0.900	1.01
k_A/10^{-5} s^{-1}	0.158	0.332	0.510	0.722	0.923	1.16	1.39	1.65	1.88	2.19
					(**1f**)[g]					
[pip]/mol dm^{-3}	0.120	0.235	0.360	0.505	0.606	0.725	0.830	0.940	1.01	
k_A/10^{-5} s^{-1}	0.180	0.367	0.581	0.848	1.04	1.28	1.51	1.76	1.92	
					(**1g**)[h]					
[pip]/mol dm^{-3}	0.120	0.240	0.360	0.480	0.600	0.720	0.840	0.920	1.00	
k_A/10^{-5} s^{-1}	0.149	0.308	0.480	0.658	0.850	1.05	1.26	1.41	1.56	
					(**1h**)[i]					
[pip]/mol dm^{-3}	0.120	0.240	0.350	0.470	0.600	0.730	0.840	0.910	1.00	
k_A/10^{-5} s^{-1}	0.152	0.315	0.473	0.655	0.864	1.08	1.28	1.41	1.58	
					(**1i**)[j]					
[pip]/mol dm^{-3}	0.122	0.245	0.367	0.490	0.612	0.775	0.898	1.02		
k_A/10^{-6} s^{-1}	0.980	2.05	3.18	4.40	5.72	7.60	9.07	10.6		
					(**1j**)[k]					
[pip]/mol dm^{-3}	0.120	0.240	0.400	0.540	0.700	0.830	0.910	1.00		
k_A/10^{-6} s^{-1}	0.675	1.34	2.22	2.99	3.90	4.62	5.06	5.59		
					(**1k**)[l]					
[pip]/mol dm^{-3}	0.178	0.347	0.465	0.614	0.713	0.792	0.891	0.990		
k_A/10^{-6} s^{-1}	0.648	1.31	1.74	2.34	2.73	3.02	3.37	3.76		

[a] The rate constants are accurate to within ±3%. [b] [**1a**] 3.79 × 10^{-4} mol dm^{-3}, λ 340–375 nm. [c] [**1b**] 5.43 × 10^{-4} mol dm^{-3}, λ 340–375 nm. [d] [**1c**] 2.79 × 10^{-4} mol dm^{-3}, λ 340–375 nm. [e] [**1d**] 3.92 × 10^{-4} mol dm^{-3}, λ 340–375 nm. [f] [**1e**] 3.65 × 10^{-4}mol dm^{-3}, λ 340–375 nm. [g] [**1f**] 3.61 × 10^{-4} mol dm^{-3}, λ 340–375 nm. [h] [**1g**] 3.64 × 10^{-4} mol dm^{-3}, λ 340–375 nm. [i] [**1h**] 3.57 × 10^{-4} mol dm^{-3}, λ 340–375 nm. [j] [**1i**] 4.18 × 10^{-4} mol dm^{-3}, λ 325–400 nm. [k] [**1j**] 3.44 × 10^{-4} mol dm^{-3}, λ 354–380 nm. [l] [**1k**] 2.49 × 10^{-4} mol dm^{-3}, λ 340–375 nm.

An examination of the kinetic data reveals the following points.

(*a*) The rate constants for each *E*-arylhydrazone are little affected by the nature of the solvent (*e.g.* the rate ratios between k_2 values in AN and PhH range from 2.1 to 8.5, and those in D and in PhH from 1.8 to 0.9, respectively).

(*b*) The effect on the reactivity of the substituent in the arylhydrazonic moiety is very low [in D the highest rate ratio (k_2)(**1e**)/(k_2)(**1k**) is *ca.* 4] in spite of the occurrence of base catalysis, which indicates the relevance of N_α–H bond breaking, surely largely affected by the substituent effect.[2e] The low reactivity range observed can therefore be viewed as a piece of evidence in favour of a change of mechanism and/or of the rate-determining step in a multi-step mechanism on changing the substituent.

(*c*) In each solvent the same reactivity trend on changing the substituent is observed; *i.e.*, a decrease in reactivity on going from *p*-Me (**1a**) to *m*-Me (**1c**) or H (**1d**); an increase to *p*-Cl (**1e**); and then a further decrease to *p*-NO_2 (**1k**).

The difference in the reactivities observed in the range of compounds (**1a–e**) (substituents from *p*-Me to *p*-Cl) are surely out of the range of uncertainties connected with the kinetic measurements; on the other hand the purity of the substrates used has been accurately checked. Moreover it must be remarked that any attempts to fit the kinetic data to a unique one-parameter relationship furnish results with a poor statistical meaning (*e.g.*, using $\sigma_{m,p}$ and/or σ_p^- substituents constants, one calculates ρ −0.255 ± 0.098, r 0.658, n 11, confidence level 95%). In conclusion, the Hammett-type plot shows a true 'zigzag' trend which cannot be considered an artifact: in contrast, it seems to indicate a change of mechanism and/or of the rate-determining step as a function of the substituents present,[8] which cover a sufficiently wide σ-range (*ca.* 1.4 units). Our plans to extend this range to more

Table 2. Apparent first-order rate constants, k_A,[a] for the isomerization of (**1a**), (**1c**), (**1e**), (**1g**), (**1i**), (**1j**), and (**1k**) into (**2a**), (**2c**), (**2e**), (**2g**), (**2i**), (**2j**), and (**2k**) in benzene at 313 K in the presence of piperidine.

				(**1a**)[b]					
[pip]/mol dm^{-3}	0.100	0.200	0.328	0.495	0.618	0.783	0.910	1.02	
$k_A/10^{-6}$ s^{-1}	0.740	1.72	3.28	5.89	8.17	11.8	14.9	18.0	
				(**1c**)[c]					
[pip]/mol dm^{-3}	0.101	0.202	0.303	0.404	0.525	0.646	0.758	0.882	1.01
$k_A/10^{-6}$ s^{-1}	0.525	1.17	1.94	2.80	4.03	5.40	6.82	8.71	10.7
				(**1e**)[d]					
[pip]/mol dm^{-3}	0.0960	0.190	0.325	0.470	0.620	0.746	0.910	1.01	
$k_A/10^{-6}$ s^{-1}	0.980	2.13	4.30	7.04	10.6	13.9	19.0	22.6	
				(**1g**)[e]					
[pip]/mol dm^{-3}	0.090	0.190	0.320	0.490	0.610	0.760	0.880	1.00	
$k_A/10^{-6}$ s^{-1}	0.790	1.86	3.45	6.04	8.11	11.0	13.8	16.7	
				(**1i**)[f]					
[pip]/mol dm^{-3}	0.121	0.242	0.364	0.485	0.606	0.768	0.889	1.01	
$k_A/10^{-6}$ s^{-1}	0.810	1.73	2.75	3.88	5.12	6.92	8.37	9.95	
				(**1j**)[g]					
[pip]/mol dm^{-3}	0.122	0.245	0.367	0.490	0.612	0.775	0.898	1.02	
$k_A/10^{-6}$ s^{-1}	0.612	1.23	1.84	2.45	3.07	3.88	4.49	5.11	
				(**1k**)[h]					
[pip]/mol dm^{-3}	0.195	0.310	0.450	0.637	0.753	0.885	1.04		
$k_A/10^{-6}$ s^{-1}	0.806	1.31	1.86	2.71	3.15	3.74	4.39		

[a] The rate constants are accurate to within ±3%. [b] [**1a**] 2.00 × 10^{-4} mol dm^{-3}, λ 340–380 nm. [c] [**1c**] 2.24 × 10^{-4} mol dm^{-3}, λ 340–380 nm. [d] [**1e**] 2.02 × 10^{-4} mol dm^{-3}, λ 340–380 nm. [e] [**1g**] 1.88 × 10^{-4} mol dm^{-3}, λ 340–380 nm. [f] [**1i**] 2.24 × 10^{-4} mol dm^{-3}, λ 325–400 nm. [g] [**1j**] 2.45 × 10^{-4} mol dm^{-3}, λ 354–380 nm. [h] [**1k**] 1.35 × 10^{-4} mol dm^{-3}, λ 340–380 nm.

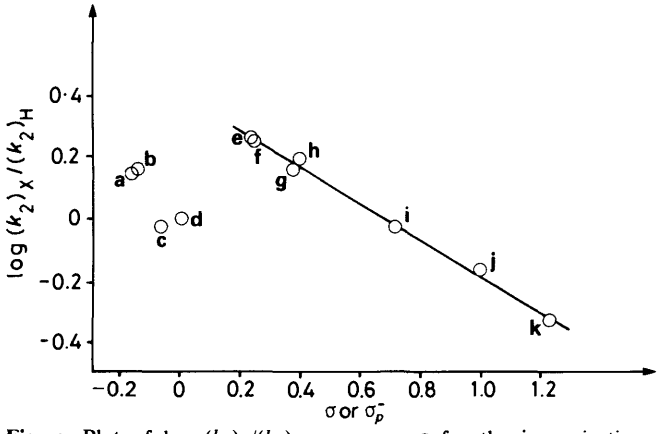
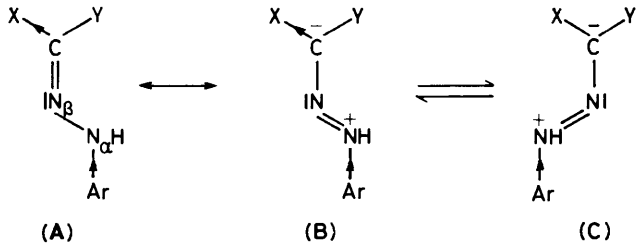


Figure. Plot of log $(k_2)_X/(k_2)_H$ *vs.* σ or σ_p^- for the isomerization (**1**) ⟶ (**2**) at 313 K in dioxane.



Scheme 2.

electron-donating substituents (σ <0) have been discouraged by the results of the synthesis of the (*E*)-*p*-methoxyphenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole, which has typically furnished (see the Experimental), both *E*- and *Z*-isomers, as indicated by TLC analysis. We have not been able to separate the two isomers, even by flash chromatography, and obtained the *E*-isomer impure from the *Z*-isomer (formed during the separation process). Looking at the trend in the free energy relationships (see the Figure) one can expect that the *p*-MeO substituent, owing to its strong electron-donating ability, would be very effective in promoting the isomerization reaction (see also below the discussion on the effect of alkyl groups on the isomerization rates).

An analysis of the kinetic data (Tables 4–6) shows that the k_2 term contributes to the kinetic pattern for all the substituents; it is thus possible to establish a structure–reactivity relationship. For a better understanding of the substituent effects we can try to dissect the structure–reactivity diagram. Let us consider the reactions in D, for which the largest range of substituents has been studied. Starting from the left side of the plot (see Figure) a decrease has been observed on going from *p*-alkyl-substituted arylhydrazones (**1a**, **b**) to the *m*-Me and the unsubstituted phenylhydrazones (**1c**, **d**) and this agrees with a rotation mechanism [5,6] of the isomerization reaction. In this mechanism, in fact, an electron-donating substituent in the arylhydrazone moiety increases the nucleophilicity of the N_α-atom, the lone pair of which can conjugate with the C=N double bond of the imine system (α-effect). As a consequence the double-bond character decreases and the rotation mechanism for the isomerization reaction is favoured. The unusual inverted polarization of the C=N double bond is favoured by the strong electron-withdrawing effect of the 1,2,4-oxadiazole residue, which delocalizes the negative charge appearing on the carbon atom (see Scheme 2). The base piperidine catalyses the process by interacting with the hydrogen linked to N_α through different

Table 3. Apparent first-order rate constants, k_A,[a] for the isomerization of (**1a**), (**1c–e**), and (**1i–k**) into (**2a**), (**2c–e**), and (**2i–k**) in acetonitrile at 313 K in the presence of piperidine.

				[**1a**[b]]				
[pip]/mol dm^{-3}	0.124	0.243	0.367	0.498	0.618	0.783	0.883	0.960
$k_A/10^{-5}$ s^{-1}	0.697	1.41	2.21	3.11	3.99	5.28	6.14	6.79
				[**1c**[c]]				
[pip]/mol dm^{-3}	0.122	0.245	0.367	0.490	0.612	0.775	0.899	1.02
$k_A/10^{-5}$ s^{-1}	0.408	0.844	1.30	1.78	2.29	3.00	3.57	4.15
				[**1d**[d]]				
[pip]/mol dm^{-3}	0.124	0.237	0.371	0.505	0.623	0.783	0.906	1.02
$k_A/10^{-5}$ s^{-1}	0.417	0.823	1.34	1.88	2.39	3.12	3.71	4.30
				[**1e**[e]]				
[pip]/mol dm^{-3}	0.124	0.247	0.371	0.502	0.608	0.780	0.880	1.03
$k_A/10^{-5}$ s^{-1}	0.645	1.31	2.00	2.76	3.39	4.47	5.12	6.12
				[**1g**[f]]				
[pip]/mol dm^{-3}	0.110	0.240	0.360	0.480	0.610	0.750	0.880	0.970
$k_A/10^{-5}$ s^{-1}	0.428	0.958	1.47	2.00	2.61	3.29	3.93	4.41
				[**1i**[g]]				
[pip]/mol dm^{-3}	0.100	0.175	0.320	0.465	0.630	0.760	0.880	1.00
$k_A/10^{-5}$ s^{-1}	0.236	0.422	0.806	1.22	1.72	2.15	2.57	3.00
				[**1j**[h]]				
[pip]/mol dm^{-3}	0.120	0.240	0.350	0.480	0.600	0.760	0.880	1.00
$k_A/10^{-5}$ s^{-1}	0.159	0.324	0.443	0.607	0.765	0.977	1.12	1.30
				[**1k**[i]]				
[pip]/mol dm^{-3}	0.122	0.245	0.367	0.490	0.612	0.775	0.898	1.02
$k_A/10^{-6}$ s^{-1}	1.10	2.16	3.27	4.39	5.45	6.89	8.00	9.10

[a] The rate constants are accurate to within ±3%. [b] [**1a**] 3.59 × 10^{-4} mol dm^{-3}, λ 340 nm, log ε 4.30. [c] [**1c**] 3.61 × 10^{-4} mol dm^{-3}, λ 340 nm, log ε 4.31. [d] [**1d**] 3.65 × 10^{-4} mol dm^{-3}, λ 340 nm, log ε 4.28. [e] [**1e**] 3.31 × 10^{-4} mol dm^{-3}, λ 340 nm, log ε 4.34. [f] [**1g**] 3.60 × 10^{-4} mol dm^{-3}, λ 340 nm, log ε 4.29. [g] [**1i**] 3.05 × 10^{-4} mol dm^{-3}, λ 325–360 nm. [h] [**1j**] 3.01 × 10^{-4} mol dm^{-3}, λ 340–375 nm. [i] [**1k**] 3.00 × 10^{-4} mol dm^{-3}, λ 340–375 nm.

Table 4. Linear regression analysis[a] of apparent first-order kinetic constants for the isomerization of (**1a–m**) into (**2a–m**) in dioxane at 313 K in the presence of piperidine according to equations $k_A = k_2[\text{pip}] + k_3[\text{pip}]^2$ or $k_A = k_2[\text{pip}]$.

Compound	$(k_2 \pm s_2)$/ 10^{-5} dm^3 mol^{-1} s^{-1}	$(k_3 \pm s_3)/10^{-5}$ dm^6 mol^{-2} s^{-1}	r	n
(**1a**)	1.09 ± 0.00	0.821 ± 0.008	0.9997	9
(**1b**)	1.03 ± 0.00	0.606 ± 0.004	0.9998	8
(**1c**)	0.767 ± 0.002	0.297 ± 0.003	0.9996	8
(**1d**)	0.813 ± 0.002	0.305 ± 0.003	0.9997	9
(**1e**)	1.50 ± 0.00	0.658 ± 0.005	0.9998	10
(**1f**)	1.45 ± 0.00	0.445 ± 0.004	0.9998	9
(**1g**)	1.20 ± 0.00	0.364 ± 0.002	0.9997	9
(**1h**)	1.23 ± 0.00	0.353 ± 0.003	0.9998	9
(**1i**)	0.770 ± 0.002	0.267 ± 0.003	0.9996	8
(**1j**)	0.557 ± 0.001		0.9999	8
(**1k**)	0.383 ± 0.002		0.9999	8

[a] s_2 and s_3 are the standard deviations of the regression parameters k_2 and k_3, respectively; r is the correlation coefficient; n is the number of experimental points. The confidence level values for significance of regression parameters are all better than 99.9%.

Table 5. Linear regression analysis[a] of apparent first-order kinetic constants for the isomerization of (**1a**), (**1c–e**), (**1g**), (**1i**), and (**1k**) into (**2a**), (**2c–e**), (**2g**), (**2i**), and (**2k**) in benzene at 313 K in the presence of piperidine according to equations $k_A = k_2[\text{pip}] + k_3[\text{pip}]^2$ or $k_A = k_2[\text{pip}]$.

Compound	$(k_2 \pm s_2)/10^{-5}$ dm^3 mol^{-1} s^{-1}	$(k_3 \pm s_3)/10^{-5}$ dm^6 mol^{-2} s^{-1}	r	n
(**1a**)	0.634 ± 0.003	1.11 ± 0.01	0.9999	8
(**1c**)	0.460 ± 0.002	0.584 ± 0.004	0.9999	9
(**1d**)[b]	0.442 ± 0.003	0.563 ± 0.005	0.9998	6
(**1e**)	0.879 ± 0.007	1.34 ± 0.01	0.9998	8
(**1g**)	0.806 ± 0.005	0.862 ± 0.008	0.9997	8
(**1i**)	0.628 ± 0.001	0.355 ± 0.002	0.9999	8
(**1j**)	0.500 ± 0.005		0.9999	8
(**1k**)	0.424 ± 0.003		0.9999	7

[a] As in Table 4. [b] See ref. 4.

base-catalysed pathways.[2d,9] The decrease in reactivity with decreasing electron-repelling effect in the substituent (σ < 0) in the arylhydrazone moiety is therefore well accounted for.

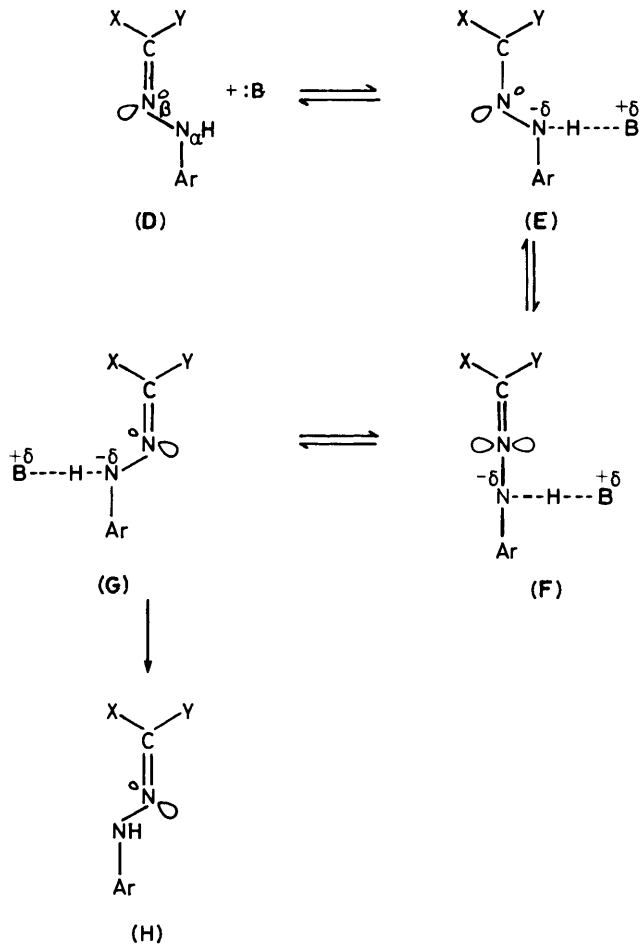
Moving towards the right-hand side of the structure–reactivity plot, *i.e.* on introduction of a weak electron-withdrawing substituent (σ-range 0–0.2) an increase in reactivity is observed which appears to be characteristic of a changeover in mechanism. The further shift towards the right in the plot, *i.e.* on introduction of strong electron-withdrawing substituents (σ > 0.2) causes a decrease in reactivity, which can indicate a changeover of the rate-determining step in a multi-step mechanism.

We think that the behaviour observed in the range of substituents from H to *p*-NO_2 (**1d–k**) can be accounted for by a unique multi-step piperidine-catalysed inversion mechanism. We can outline the situation as follows (Scheme 3). With weak

Table 6. Linear regression analysis[a] of apparent first-order kinetic constants for the isomerization of (**1a**), (**1c–e**), (**1g**), and (**1i–k**) into (**2a**), (**2c–e**), (**2g**), and (**2i–k**) in acetonitrile at 313 K in the presence of piperidine according to equations $k_A = k_2[pip] + k_3[pip]^2$ or $k_A = k_2[pip]$.

Compound	$(k_2 \pm s_2)/10^{-5}$ dm^3 mol^{-1} s^{-1}	$(k_3 \pm s_3)/10^{-5}$ dm^6 mol^{-2} s^{-1}	r	n
(**1a**)	5.38 ± 0.01	1.76 ± 0.02	0.9997	8
(**1c**)	3.24 ± 0.00	0.813 ± 0.004	0.9999	8
(**1d**)	3.25 ± 0.01	0.943 ± 0.011	0.9996	8
(**1e**)	5.09 ± 0.01	0.820 ± 0.008	0.9997	8
(**1g**)	3.81 ± 0.00	0.766 ± 0.008	0.9997	8
(**1i**)	2.29 ± 0.00	0.713 ± 0.003	0.9999	8
(**1j**)	1.28 ± 0.01		0.9997	8
(**1k**)	0.891 ± 0.002		0.9999	8

[a] As in Table 4.



Scheme 3.

electron-withdrawing substituents the rate-determining step is ion-pair formation, therefore on going from (**1d**) to (**1e**) or (**1f**) an increase in reactivity is observed. A further increase in the electron-withdrawing character of the substituent makes the inversion step around the sp-hybridized imino nitrogen atom (N_β) rate-determining; the present substituent therefore causes a decrease in the reactivity. In fact, these substituents (*a*) favour ion-pair formation (with a 'late' character for the corresponding transition state), (*b*) increase the electron density on N_α (which will assume a partial anionic character), and consequently (*c*) increase the stereoelectronic interactions between the lone-pairs of the two adjacent nitrogen atoms. They also disfavour the inversion process.* Accordingly, the kinetic data for the substituted *E*-arylhydrazones (**1e–k**) give excellent linear free-energy relationships (ρ −0.58 ± 0.01, *i* 0.39 ± 0.01, *n* 7, *r* 0.999) using σ and σ_p^- values† (these last substituent constants are required for X = *p*-CN and *p*-NO_2 because of the strong electronic interactions between N_α and aryl that occur in these instances), with a susceptibility constant which consists of two partial processes dominated by the negative ρ value of the second one.[8]

The results obtained in the other solvents studied (PhH and AN) are similar to those observed in D: in fact, a 'zigzag' trend is observed as a function of the present substituent and moreover an excellent linear free-energy relationship with low negative susceptibility constants for arylhydrazones containing strong electron-withdrawing substituents (**1e, g, i–k**) is observed, which is reminiscent of the situation observed in other isomerizations which occur through the inversion mechanism.[6a,d,f] The variations observed in the measured ρ-values are consistent with the proposed mechanism. In fact the highest and the lowest negative susceptibility constants have been measured in AN (ρ_{AN} −0.76 ± 0.02, *i* 0.36 ± 0.02, *n* 5, *r* 0.9987) and in PhH (ρ_{PhH} −0.32 ± 0.01, *i* 0.38 ± 0.01, *n* 5, *r* 0.9994), respectively, whereas an intermediate value in D has been observed in accord with expectations based on the different polar and basic characteristics of the three solvents studied [$\varepsilon_{AN} > \varepsilon_{PhH} = \varepsilon_D$; $B_D > B_{AN} > B_{PhH}$] that affect the ion-pair formation and consequently the stereoelectronic interactions between the lone pairs at N_α and N_β in the transition state.

We have also attempted a treatment of our kinetic data by using multiparameter relationships. In this way we have used the Young and Jencks modification[12] of the Yukawa–Tsuno equation and the DSP treatment.[13] In both cases we have observed a simplification of the free energy relationships (a concave downward curve and a straight line, respectively) but the susceptibility constants calculated, also due to their inherent statistical uncertainty, do not allow a better insight into the reaction mechanism.

On the other hand, we think it is not always correct to constrain the data into a linear correlation: indeed, the non-linearity of a free-energy relationship can well help the understanding of the reaction mechanism.[8] Moreover the use of multiparameter approaches (Yukawa–Tsuno–Jencks or DSP treatment, which with *meta*- and *para*-substituents imply the introduction of four susceptibility parameters) makes sense only if it allows a deeper insight into the chemical data. A non-linear log *k versus* σ plot clearly indicates that the mechanism or the rate-determining step of the reaction does not remain the same when the substituent is changed. Therefore the occurrence of concave upward or downward curves can give useful information on the mechanism.

We will now make a few comments on the solvent effects that, we think, agree with the mechanisms proposed. The rate ratios observed on going from one solvent to another are quite small, indicating that a relatively low variation of the charge separation occurs on going from the reagents to the transition state as also indicated by the low substituent effect. For this reason we shall discuss only the variations from benzene to acetonitrile. It is noticeable that the highest rate ratio was observed in the case of an electron-repelling substituent [for (**1a**), rate ratio 8.5], confirming the effect expected for a polar solvent, which is better than an apolar one in allowing the charge separation required by the rotation mechanism.

* It is well known that oximes are stable in the presence of base and that oximate anions are not able to isomerize [ref. 6(*e*)].

† Refs. 10 and 11, respectively.

Table 7. Physical data of compounds (**1a–k**).

Compound	M.p./°C	ν_{NH}/cm^{-1}	$\lambda_{max.}$/nm	log ε	δ(CDCl$_3$)	δ(DMSO)
(**1a**)	98–100	3 300	340	4.30		2.25 (s, 3 H, CH_3), 6.80–8.20 (m, 14 H, ArH), 9.65 (s, 1 H, NH)
(**1b**)	110–112	3 270	340	4.28	1.20 (t, 3 H, CH_2CH_3), 2.60 (q, 2 H, CH_2CH_3), 6.90–7.65 (m, 12 H, ArH), 8.05–8.35 (m, 3 H, *ortho* H, NH)	
(**1c**)	143–144	3 210	336	4.31	2.30 (s, 3 H, CH_3), 6.90–7.90 (m, 12 H, ArH), 8.00–8.35 (m, 3 H, *ortho* H, NH)	2.40 (s, 3 H, CH_3), 7.20–8.10 (m, 14 H, ArH), 10.90 (s, 1 H, NH)
(**1d**)[b]	138–140	3 290	335	4.31	6.80–7.70 (m, 13 H, ArH), 8.10–8.40 (m, 3 H, *ortho* H, NH)	6.70–8.40 (m, 15 H, ArH), 9.45 (s, 1 H, NH)
(**1e**)	165–166	3 320	337	4.35		7.30–8.20 (m, 14 H, ArH), 9.80 (s, 1 H, NH)
(**1f**)	180–181	3 320	337	4.37		7.30–8.20 (m, 14 H, ArH), 9.80 (s, 1 H, NH)
(**1g**)	129–130	3 320	331	4.34	6.65–7.70 (m, 12 H, ArH), 8.00–8.30 (m, 3 H, *ortho* H, NH)	7.20–8.30 (m, 14 H, ArH), 9.90 (s, 1 H, NH)
(**1h**)	144–145	3 230	332	4.35	6.90–7.70 (m, 12 H, ArH), 7.95–8.30 (m, 3 H, *ortho* H, NH)	7.00–8.20 (m, 14 H, ArH), 9.90 (s, 1 H, NH)
(**1i**)	198–199	3 290	318	4.40	7.30–8.00 (m, 12 H, ArH), 8.05–8.30 (m, 3 H, *ortho* H, NH)	7.40–8.30 (m, 14 H, ArH), 10.30 (s, 1 H, NH)
(**1j**)	204–205	3 230	340	4.47	6.90–7.75 (m, 12 H, ArH), 8.00–8.35 (m, 3 H, *ortho* H, NH)	7.20–8.20 (m, 14 H, ArH), 10.40 (s, 1 H, NH)
(**1k**)	206–207	3 290	376	4.54	7.00–7.85 (m, 12 H, ArH), 8.00–8.35 (m, 3 H, *ortho* H, NH)	7.10–8.40 (m, 14 H, ArH), 9.80 (s, 1 H, NH)

[a] The observed m.p. values can be affected by thermal isomerization and rearrangement processes. [b] Data from ref. 3.

For electron-withdrawing substituents a completely different situation was observed: *e.g.* for (**1k**) a very low rate ratio (2:1) was measured. This fact is seemingly unexpected but in fact, the inversion mechanism occurs through two transition states and, as we have pointed out (see above), in the presence of a strongly electron-withdrawing substituent the second step is rate-determining. As the transformation (**E**) ⟶ (**F**) clearly indicates, it does not require a significant variation in the charge distribution.

Conclusions

The data we have collected on the *E* ⟶ *Z* isomerization of some arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole in various solvents have pointed out the very low influence of both the substituents present in the arylhydrazonic moiety and the solvent used, notwithstanding the large spread of substituents (from *para*-alkyls to *p*-NO_2 group) and of solvents (from apolar to largely polar, and from poorly nucleophilic to greatly nucleophilic) involved. The whole of the data obtained can be rationalised by considering a change both of mechanism (rotation and imino nitrogen inversion) and of the rate-determining step in the imino-nitrogen inversion mechanism.

Experimental

M.p.s were determined using a Kofler hot-stage apparatus. IR spectra were determined with a Perkin-Elmer 1310 instrument, UV spectra with a Beckman DU-6 spectrophotometer, and ^{1}H NMR (60 MHz) with a Varian EM 360 A spectrometer (tetramethylsilane was used as the internal standard). TLC was performed on Merck aluminium sheets with silica gel 60 F_{254}, using cyclohexane–ethyl acetate as the eluant. Dry-column chromatography was performed on Merck silica gel deactivated with water (15%).

Synthesis and Purification of Compounds.—Compounds (**1d**),[3] (**2a–k**),[2a,b] (**3a–k**),[2a,b] benzene,[14] dioxane,[14] acetonitrile,[15] and piperidine[14] were prepared and/or purified according to the methods previously reported. *E*-Arylhydrazones (**1a–c**) and (**1e–k**) were prepared from 3-benzoyl-5-phenyl-1,2,4-oxadiazole on treatment with the appropriate arylhydrazine hydrochloride in acetic acid in the presence of sodium acetate, following the procedure previously reported for (**1d**).[3]

To a solution of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (2 g, 8 mmol) in acetic acid (25–30 cm^3) was added the suitable arylhydrazine hydrochloride and sodium acetate (12 mmol), and the mixture was kept at room temperature in the dark. The *Z*-isomer slowly separated. When the reaction was finished (verification by TLC analysis; two or three days) the *Z*-arylhydrazone was filtered off and washed with acetic acid. The filtrate was diluted with water (400–500 cm^3) giving a mixture of both *Z*- and *E*-arylhydrazones which was filtered off and washed with water to remove acetic acid. The mixture was extracted with ether and the ethereal extracts were washed with aqueous sodium hydrogen carbonate to remove acetic acid and then with water, dried over sodium sulphate and evaporated. The dry mixture was rapidly chromatographed on a column of silica gel using cyclohexane–ethyl acetate in various ratios as the eluant, yielding, at first, additional amounts of the *Z*-isomer, some fractions containing both isomers and impurities (discarded) and then fractions containing the pure *E*-isomer (**1**). Evaporation of these fractions at reduced pressure left a residue which was taken up with light petroleum and filtered off to give the pure *E*-isomer (**1**) (TLC). The *E*-configuration was confirmed on the basis of spectroscopic data (IR, UV, NMR) following the procedure reported for (**1d**).[3]

All new compounds gave satisfactory analytical data; physical data are reported in Table 7.

Kinetic Measurements.—The kinetics of the isomerization reaction (**1a–k**) ⟶ (**2a–k**) in D, PhH, and AN, at various piperidine concentrations, were studied spectrophotometrically using solutions with an initial [(**1a–k**)] of 1.88–5.43 × 10^{-4} mol dm^{-3}. In order to obtain the concentrations of (**1**)–(**3**), at various time intervals, samples were quenched in D, PhH, and AN, respectively, and their UV–VIS spectra recorded. Given the values of the molar absorbance for the three compounds present, we used the absorbances in the range 340–380 nm, as reported in Tables 1–3, to calculate the concentrations of (**1**) and (**2**). In this range, (**3**) did not absorb and its concentration

was calculated by difference. At each wavelength, equation (1)

$$D = \varepsilon_1[(\mathbf{1})]l + \varepsilon_2[(\mathbf{2})]l$$

holds. Therefore, it is possible to calculate the concentrations of (**1**) and (**2**) by measuring the absorbances at two wavelengths. To minimize errors we have calculated the concentrations by a least-squares treatment on eight experimental absorbances.

For (**1i**) we used absorbances in the range 325–400 nm to calculate the concentrations of (**1i**), (**2i**), and (**3i**). In fact, in this range, (**3i**) does absorb and its concentration was calculated by a least-squares treatment on sixteen experimental absorbances.

The concentration so obtained allowed us to calculate the kinetic constants of the (**1a–k**) ⟶ (**2a–k**) isomerizations which we treated as irreversible reactions.

The experimental values obtained for the concentrations of (**1**)–(**3**) agreed well with the values calculated by applying the kinetic treatment relative to consecutive reactions.[16]

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