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On the Rearrangement in Dioxane/Water of (*Z*)-Arylhydrazones of 5-Amino-3-benzoyl-1,2,4-oxadiazole into (2-Aryl-5-phenyl-2*H*-1,2,3-triazol-4-yl)ureas: Substituent Effects on the Different Reaction Pathways

Francesca D'Anna,[†] Vincenzo Frenna,[†] Gabriella Macaluso,[†] Salvatore Marullo,[†] Stefano Morganti,[‡] Vitalba Pace,[†] Domenico Spinelli,*[,‡] Raffaella Spisani,[‡] and Cinzia Tavani[§]

Dipartimento di Chimica Organica "E. Paternò", Università di Palermo, Viale delle Scienze, Parco d'Orleans 2, 90128 Palermo, Italy, Dipartimento di Chimica Organica "A. Mangini", Università di Bologna, Via San Giacomo 11, 40126 Bologna, Italy, and Dipartimento di Chimica e Chimica Industriale, Università di Genova, Via Dodecaneso 31, 16146 Genova, Italy

domenico.spinelli@unibo.it

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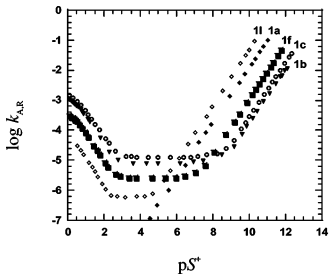

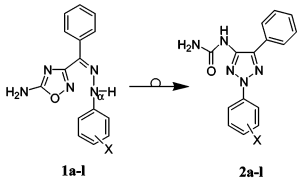

We have recently evidenced an interesting differential behavior in the reactivity in dioxane/water between the (*Z*)-2,4-dinitrophenylhydrazone (**1a**) and the (*Z*)-phenylhydrazone (**1b**) of 5-amino-3-benzoyl-1,2,4-oxadiazole. The former rearranges into the relevant triazole **2a** only at pS^+ > 4.5 while undergoing hydrolysis at high proton concentration (pS^+ < 3.5); on the contrary, the latter rearranges into **2b** in the whole pS^+ range examined ($0.1 \leq pS^+ \leq 14.9$). Thus, for a deeper understanding of these differences we have now collected kinetic data on the rearrangement in dioxane/water of a series of 3- or 4-substituted (*Z*)-phenylhydrazones (**1c**−**l**) of 5-amino-3-benzoyl-1,2,4-oxadiazole in a wide range of proton concentrations (pS^+ 0.1−12.3) with the aim of gaining information about the effect of the substituent on the course of the reaction. All of the (*Z*)-arylhydrazones studied rearrange via three different reaction routes (specific-acid-catalyzed, uncatalyzed, and general-base-catalyzed), and the relevant results have been examined by means of free energy relationships.

Introduction

Ring-to-ring interconversions continue to attract the attention of organic chemists because of their utility in the synthesis of heterocyclic compounds,[1] to be used as such (in medicinal[2] and in veterinary chemistry[3] as well as in material science[4]) or as synthones[5] of several functional groups.

In the framework of our studies on the applications[1c,d,j,6] and on the mechanism[1c,d,7,8] of the azole-to-azole rearrangement, we have investigated some particular cases of the more general "monocyclic rearrangement of heterocycles" (MRH; also called the Boulton−Katritzky reaction, BKR)[1c−g,6b,8] by examining the rearrangement of several *Z*-hydrazones of 5-substituted 3-acyl-1,2,4-oxadiazoles.[1c,d,7,8] Thus, we have recently addressed our attention to the behavior of some (*Z*)-hydrazones of 3-benzoyl-1,2,4-oxadiazole containing an electron-donating amino group at C(5),[8] which was expected to affect the course of the reaction by enforcing the ring protonation at N(4) at high proton concentrations.

Actually, we have focused on the rearrangement of the (*Z*)-2,4-dinitrophenylhydrazone[8a] (**1a**) and the (*Z*)-phenylhydrazone[8b] (**1b**) of 5-amino-3-benzoyl-1,2,4-oxadiazole into the relevant

* To whom correspondence should be addressed. Phone: +39-051-2095689. Fax: +39-051-2095688.
[†] Università di Palermo.
[‡] Università di Bologna.
[§] Università di Genova.

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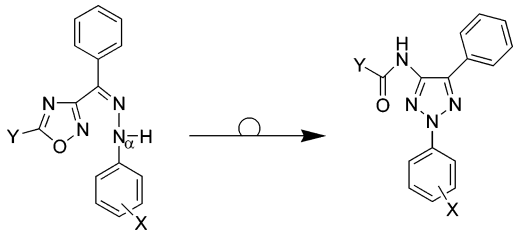
SCHEME 1



1,3a-l **2,4a-l**

1,2: Y = NH_2
3,4: Y= Ph

a: X =2,4-$(NO_2)_2$ **e**: X = 4-Me **i**: X = 4-Br
b: X = H **f**: X = 3-Cl **j**: X = 4-CN
c : X = 4-OMe **g**: X = 4-Cl **k**: X = 3-NO_2
d: X = 3-Me **h**: X = 3-Br **l**: X = 4-NO_2

1,2,3-triazoles (**2a**,**b**) (Scheme 1) in dioxane/water (D/W; 1:1, v:v) in a wide range of proton concentrations (pS^+ 4.5−14.1 and 0.1−14.9, respectively; for further details on pS^+, see the Experimental Section).[7,8]

In the case of **1a**, the wide reactivity range explored (at 293.1 K, $k_{A,R}$, the apparent first-order rate constant for the rearrangement, varies between 10^{-8} s^{-1} and 4 s^{-1};[8a] Figure 1a) as a function of the proton concentration has evidenced a general-base-catalyzed pathway and the occurrence of a fast acidic hydrolysis to 5-amino-3-benzoyl-1,2,4-oxadiazole and 2,4-dinitrophenylhydrazine at high proton concentration (pS^+ < 3.5),[8a,9] strictly recalling the parallel behavior of the *Z*-2,4-dinitrophenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**3a**) (Figure 1a).[7,8a]

In contrast, in the case of **1b** (see Figure 1a) it has been possible to study the rearrangement in a much wider pS^+ range:[8b] this is because at high proton concentration (0.1 <

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(9) Interestingly in a solvent such as anhydrous toluene, where the hydrolysis of the (*Z*)-hydrazones cannot occur, both **1a** and **1b** rearrange via an acid-catalyzed pathway. See: D'Anna, F.; Frenna, V.; Macaluso, G.; Morganti, S.; Nitti, P.; Pace, V.; Spinelli, D.; Spisani, R. *J. Org. Chem.* **2004**, *69*, 8718−8722.

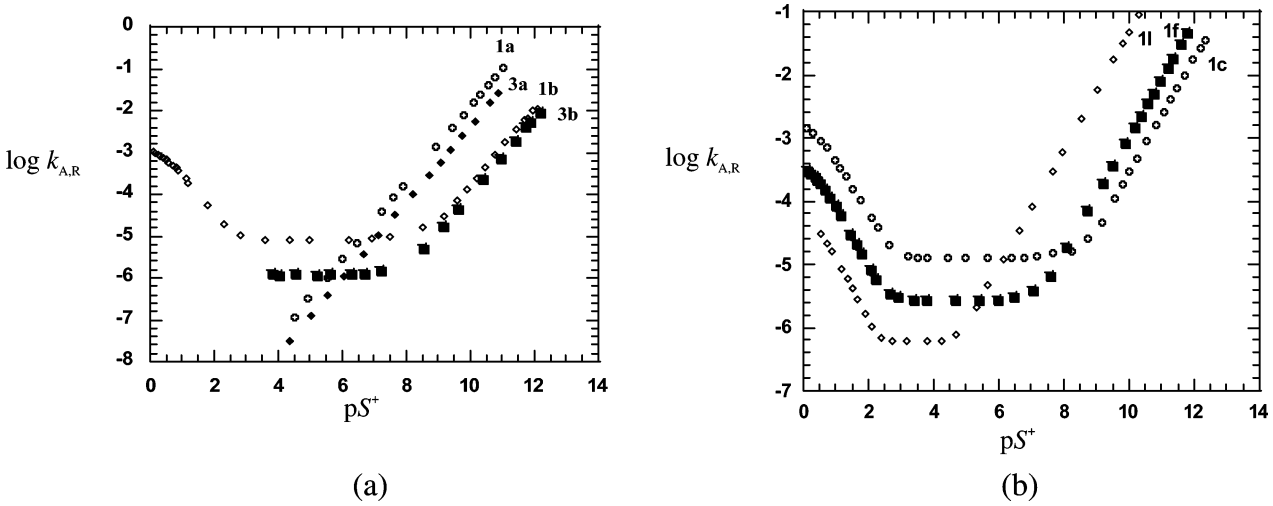

FIGURE 1. (a) Plot of log $k_{A,R}$ at 313.1 K for the rearrangement of **1a** and **1b** into the relevant triazoles **2a** and **2b** in D/W versus pS^+. Data concerning the rearrangement of **3a** and **3b** are reported for comparison. (b) Plot of log $k_{A,R}$ at 313.1 K for the rearrangement of **1c**, **1f**, and **1l** into the relevant triazoles **2c**, **2f**, and **2l** in D/W versus pS^+.

pS^+ < ca. 3.0) the fast specific-acid-catalyzed pathway prevents any hydrolysis from being observed. As foreseeable, **3b** failed to give any acid-catalyzed rearrangement.

At higher pS^+ values both **1b** and **3b** displayed the usual uncatalyzed (pS^+ ca. 3.0−8.5)[7,8b,10] and general-base-catalyzed pathways (pS^+ ca. 8.5−14.9).[7,8b]

The differential behavior of **1a** and **1b** fulfilled our expectations for a significant role of the amino group at C(5), clearly indicating, at the same time, that the competition between rearrangement and hydrolysis is substituent-dependent.[8]

Herein we report some kinetic results on the rearrangement of a wide range of (*Z*)-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole (**1c**−**l**: X = 4-MeO, 3-Me, 4-Me, 3-Cl, 4-Cl, 3-Br, 4-Br, 4-CN, 3-NO_2, 4-NO_2) into the relevant triazoles (**2c**−**l**). The following aims will be pursued: (a) starting from the above-mentioned different behavior of **1a** and **1b**, the effect of the aryl substituent on the different possible reaction pathways will be evaluated and the kinetic data for each pathway will be treated according to suitable free-energy relationships (FER), and (b) the reactivity of **1b**−**l** will be compared to that of the (*Z*)-arylhydrazones (**3b**−**l**) of 3-benzoyl-5-phenyl-1,2,4-oxadiazole in the uncatalyzed[7b] as well as in the base-catalyzed[7e] region to gain information on how the variation in the structure of the 1,2,4-oxadiazole moiety affects the substituent effect.

Results and Discussion

Rearrangement of 1c−l in D/W (1:1, v/v). Qualitative Features. The $k_{A,R}$ values for the rearrangement of **1c**−**l** into the relevant (2-aryl-5-phenyl-2*H*-1,2,3-triazol-4-yl)ureas (**2c**−**l**) have been measured in the range 283−333 K in D/W (1:1, v:v) in a wide interval of pS^+ values (complete kinetic data and thermodynamic parameters are reported in Tables 3−12 of the Supporting Information). Rate constants at 313.1 K have been recalculated from activation parameters ($k_{A,R}$ values and thermodynamic data at pS^+ 1.00, 3.80, and 11.50 are collected in Table 1), and the log $k_{A,R}$ versus pS^+ plots for some representative derivatives (**1c**, **1f**, **1l**) are reported in Figure 1b.

An examination of Figure 1b evidences the occurrence of each of the three possible reaction pathways. In particular, in the right side of the figure the reactivity increases linearly with the base concentration, while in the left side the curves tend to limiting values. These facts forecast the occurrence of general-base- and of specific-acid-catalysis,[11] respectively, at high and low pS^+ values. At the same time, an uncatalyzed pathway occurs at intermediate pS^+ values.[10]

Anyway, the dependence of the reactivity on the proton concentration varies appreciably with the substituent, giving rise to some crossover of the log $k_{A,R}$ versus pS^+ plots as the nature of the substituent makes each pathway effectively contribute to the rearrangement in different pS^+ ranges.

Quantitative Features: Structure−Reactivity Treatment of Kinetic Data. Quantitative structure−reactivity treatments have been carried out following the criteria already used in the study of the (*Z*)-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole **3b**−**l**.[7b,e]

The (General) Base-Catalyzed Pathway. All of the (*Z*)-arylhydrazones **1c**−**l** rearrange at high pS^+ values showing a pS^+-dependent reactivity, i.e., following a base-catalyzed pathway. The log $k_{A,R}$ versus pS^+ plots display quasiunitary slopes[11a] in a wide pS^+ range (average value: +0.915 ± 0.009; data in Table 1): similar slopes (average value: +0.921 ± 0.009) have been calculated[7e] for the (*Z*)-hydrazones **3b**−**l** (data in Table 1).

In some representative cases (**1c**, **1f**, and **1l**), the rearrangement has been studied at various buffer concentrations in the range 283−323 K (kinetic data recalculated at 298 K from thermodynamic parameters are reported in Tables 13−15 in the

(10) The occurrence of an uncatalyzed pathway in the rearrangement of (*Z*)-arylhydrazones of 3-benzoyl-1,2,4-oxadiazole has been always observed in the absence of strong electron-withdrawing groups (such as, for example, two nitro groups in conjugated positions) in the arylhydrazono moiety.[1c,d,7]

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TABLE 1. Kinetic and Thermodynamic[a] Data for the Rearrangement of 1b−l into 2b−l at Various pS^+ and at 313.1 K in D/W (1:1, v/v)

substrate	$k_{A,R}$ (s^{-1}) at pS^+ 11.50[b] ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$)	slopes[c,d] (base-catalyzed range)	$k_{A,R}$ (s^{-1}) at pS^+ 3.80[b] ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$)	$k_{A,R}$ (s^{-1}) at pS^+ 1.00[b] ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$)	slopes[c] (acid-catalyzed range)	k_H (L mol^{-1} s^{-1}) ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$)	K (L mol^{-1}) ($\Delta H°$, $\Delta S°$)
1b[e]	3.68×10^{-3} (88, −12)	0.891 (0.905)	7.94×10^{-6} (95, −38)	2.86×10^{-4} (85, −40)	−0.900	1.58×10^{-3} (85, −27)	1.23 (10, 32)
1c	3.95×10^{-3} (86, −17)	0.910 (0.923)	1.24×10^{-5} (97, −28)	4.22×10^{-4} (85, −38)	−0.820	2.13×10^{-3} (77, −51)	1.40 (1, 6)
1d	6.41×10^{-3} (85, −17)	0.912 (0.916)	9.18×10^{-6} (97, −31)	3.16×10^{-4} (84, −46)	−0.869	1.77×10^{-3} (79, −46)	1.23 (8, 27)
1e	4.67×10^{-3} (88, −7)	0.920 (0.925)	1.19×10^{-5} (100, −22)	3.71×10^{-4} (87, −35)	−0.831	1.88×10^{-3} (78, −47)	1.34 (0, 2)
1f	2.69×10^{-2} (87, −12)	0.913 (0.919)	2.71×10^{-6} (99, −35)	7.83×10^{-4} (81, −64)	−0.931	5.33×10^{-4} (79, −54)	0.976 (2, 6)
1g	1.61×10^{-2} (90, +7)	0.916 (0.906)	3.99×10^{-6} (99, −31)	1.19×10^{-4} (85, −50)	−0.911	7.26×10^{-4} (81, −49)	1.08 (4, 13)
1h	3.12×10^{-2} (87, +5)	0.923 (0.924)	2.64×10^{-6} (100, −33)	7.46×10^{-5} (83, −54)	−0.939	4.95×10^{-4} (77, −63)	0.983 (7, 22)
1i	2.00×10^{-2} (84, −10)	0.902 (0.905)	3.44×10^{-6} (99, −36)	1.05×10^{-4} (83, −54)	−0.927	6.52×10^{-4} (84, −40)	1.06 (0, 0)
1j	3.21×10^{-1} (87, +24)	0.930 (0.942)	9.50×10^{-7} (99, −45)	2.22×10^{-5} (83, −70)	−0.968	1.55×10^{-4} (82, −57)	0.880 (1, 2)
1k	1.58×10^{-1} (86, +13)	0.921 (0.926)	9.95×10^{-7} (99, −46)	2.43×10^{-5} (84, −67)	−0.966	1.80×10^{-4} (77, −74)	0.868 (8, 24)
1l	1.19 (83, +21)	0.932 (0.935)	6.10×10^{-7} (99, −49)	1.24×10^{-5} (82, −78)	−0.970		

[a] $\Delta H^{\ddagger}$: kJ mol^{-1}, the maximum error is 3 kJ mol^{-1}; $\Delta S^{\ddagger}$: J K^{-1} mol^{-1}, the maximum error is 8 J K^{-1} mol^{-1}. [b] Values calculated from activation parameters. The experimental first-order rate constants were measured in the range 283−333 K and were reproducible within ±3% (see Tables 3−12 in the Supporting Information). [c] Uncertainty ±0.5%. [d] The slopes for the rearrangements of **3b−l** into **4b−l** under comparable experimental conditions are reported in parentheses. [e] Data from ref 8b.

TABLE 2. Multiple Linear Regression Analysis[a] of Kinetic Data According to Eq 1 at 298.1 K

compd	10^5 k_u (s^{-1})	$k_{OH} \pm s_{OH}$ (L mol^{-1} s^{-1})	$k_B \pm s_B$ (L mol^{-1} s^{-1})	$k_A \pm s_A$ (L mol^{-1} s^{-1})	$k_{A,B} \pm s_{A,B}$ (L^2 mol^{-2} s^{-1})	$k_{B,OH} \pm s_{B,OH}$ (L^2 mol^{-2} s^{-1})	R
1c	0.9 ± 0.7	10.4 ± 0.0	0.034 ± 0.001				0.9999
	1 ± 1	10.4 ± 0.0	0.034 ± 0.001	0.00 ± 0.00			0.9999
	1 ± 1	10.2 ± 0.5	0.034 ± 0.001			16 ± 37	0.9999
	0.9 ± 0.7	10.4 ± 0.1	0.036 ± 0.003		−0.05 ± 0.07		0.9999
1f	−0.37 ± 0.76	39.6 ± 0.2	0.153 ± 0.001				0.9999
	0.41 ± 1.39	39.5 ± 0.2	0.153 ± 0.002	0.00 ± 0.00			0.9999
	1.33 ± 0.69	38.5 ± 0.3	0.148 ± 0.002			147 ± 98	0.9999
	−0.17 ± 0.66	38.9 ± 0.3	0.163 ± 0.003		−0.29 ± 0.09		0.9999
1l	5 ± 5	1694 ± 30	7.94 ± 0.08				1.000
	22 ± 9	1638 ± 35	8.1 ± 0.1	−620 ± 265			1.000
	9 ± 6	1658 ± 48	7.8 ± 0.1			(6 ± 7) × 10^5	1.000
	5 ± 5	1700 ± 91	7.9 ± 0.7		0.7 ± 11		1.000

[a] s_{OH}, s_B, s_{kA}, $s_{A,B}$, and $s_{B,OH}$, standard deviations of k_{OH}, k_B, k_A, $k_{A,B}$, and $k_{B,OH}$, respectively. R, multiple correlation coefficient. The number of points is 28 for **1c**, 31 for **1f**, and 19 for **1l**, respectively (see Tables 13−15 in the Supporting Information).

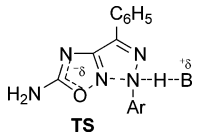
Supporting Information) in order to determine the very nature (specific or general) of the base catalysis.[11]

As the $\log(k_{A,R})_{\mathbf{1c-l}}$ versus pS^+ plots do not show any curvature also at high base concentration, the fitting of experimental data to the most general equation for catalyzed reactions (eq 1, data in Table 2) enlightens the significant catalytic contribution of hydroxide ion (k_{OH}) and of the basic component (borate anion) of the buffer (k_B). No contribution by the bimolecular pathway involving the acidic components of the buffer or by termolecular pathways has been evidenced.

This observation recalls the situation observed in the base-catalyzed rearrangement of **1a**,**b**[8] as well as of all the (*Z*)-arylhydrazones of 3-benzoyl-1,2,4-oxadiazoles so far studied by us[7d,8] and once more confirms the intermediacy of a van't Hoff complex[11] whose formation is always rate-determining (see Chart 1).

$$k_{A,R} = k_u + k_H[H_3O^+] + \Sigma k_A[HA] + k_{OH}[OH^-] + \Sigma k_B[B] + ... \quad (1)$$

CHART 1. Structure of the Transition State (TS) for the MRH of 1b−l into 2b−l[a]



[a] In the general-base-catalyzed pathway, B represents hydroxide or borate ion. In the uncatalyzed pathway (see below), B represents water or dioxane.

The calculated k_{OH} values are much higher than the k_B (B = borate ion) values, as expected on the grounds of the different basic strength of hydroxide and borate ions.[7d,8,11] Anyway, at each buffer concentration the k_B term gives a significant contribution, well fitting the Hammett's criterion for discriminating between specific and general base-catalysis.[11b]

Looking for FER, in the base-catalyzed range (for example at pS^+ 11.50) the occurrence of two separate FER's (versus classical Hammett substituent constants) is clearly defined (see Figure 6 in Supporting Information), with the unsubstituted (*Z*)-

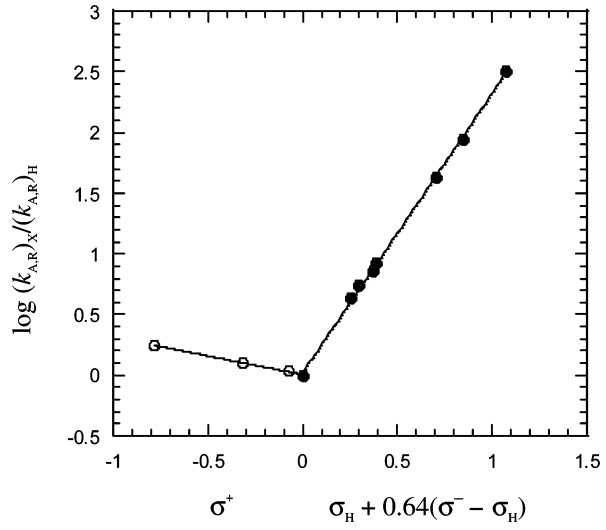


FIGURE 2. Plot of $\log(k_{A,R})_X/(k_{A,R})_H$ at 313.1 K and at pS^+ 11.50 (see eqs 2 and 3) for the rearrangement of **1b**−**l** into the relevant triazoles **2b**−**l** versus σ^+ or ($\sigma_H + r^- \Delta\sigma^-$) (YT plots).

phenylhydrazone (**1b**) showing the lowest reactivity. Such a result strictly recalls that observed for the base-catalyzed rearrangement of **3b**−**l**:[7e] the nonlinear concave-upward Hammett curve indicating a substituent-dependent change of mechanism,[12] due to different timings in the formation of the new N_α−N(2) bond and in the breaking of the N_α−H bond, as already deeply discussed.[7e,j]

However, the two FER's of Figure 6 ($\rho = +2.87 \pm 0.31$ and $\rho = -0.89 \pm 0.15$, $n = 8$ and 4, $r = 0.966$ and 0.973, for electron-withdrawing and -repelling substituents, respectively) show statistical parameters which are not more than satisfactory. For this reason we attempted a multiparameter approach for the treatment of data.

Looking at the behavior of (*Z*)-phenylhydrazones containing electron-withdrawing substituents, we have first considered the 3-substituted derivatives (**1f**, **1h**, and **1k**) together with the unsubstituted one (**1b**), finding an excellent correlation ($\rho_m = 2.30 \pm 0.03$, $n = 4$, $r = 0.9998$, $i = 0.01 \pm 0.01$, CL > 99.9%). The positive deviation of all the 4-substituted Z-phenylhydrazones (**1g**, **1i**, **1j**, and **1l**) indicates the occurrence of a significant through-resonance interaction between the 4-substituent and the reaction center: this can be estimated by using the Yukawa−Tsuno (YT) equation[13] (see Figure 2), which furnishes the excellent correlation of eq 2 at pS^+ 11.50 ($n = 8$; $r = 0.9995$; $i = 0.02 \pm 0.02$; CL > 99.9%).

$$\log(k_{A,R})_X/(k_{A,R})_H = (2.30 \pm 0.03)[\sigma_H + 0.64(\sigma^- - \sigma_H)] \quad (2)$$

As far as the electron-releasing substituted *Z*-arylhydrazones examined (**1b**−**e**) are concerned, because of their limited number and in line with previous results[7e,j] we directly correlated the reactivity data by using the σ^+ values[14] (i.e., assuming $r^+ = 1.0$) obtaining an excellent relationship (eq 3: $n = 4$; $r = 0.9991$; $i = 0.01 \pm 0.00$; CL > 99.9%; Figure 2).

$$\log(k_{A,R})_X/(k_{A,R})_H = (-0.30 \pm 0.01)\sigma^+ \quad (3)$$

The susceptibility constants calculated for electron-withdrawing ($\rho = +2.30$, $r^- = +0.64$) and electron-releasing substituents ($\rho^+ = -0.30$) appear strictly comparable, both in sign and absolute value, to those calculated for the rearrangement of *Z*-arylhydrazones **3**[7e,j] [$\rho = 2.21$ ($r^- = 0.60$) and $\rho^+ = -0.33$] and mirror the same different weight of the general-base-catalyzed breakage of the N_α−H bond and formation of the N_α−N(2) bond as a function of the substituent.[7e,j]

In agreement with the results above, k_{OH} and k_B show a nonlinear, concave-upward trend versus the substituent constant; thus, at 298.1 K, k_{OH} and k_B decrease from 1700 and 8 (L mol^{-1} s^{-1}) for **1l** (X = 4-NO_2) to 39.6 and 0.153 (L mol^{-1} s^{-1}) for **1f** (X = 3-Cl) and to 5.7 and 0.021 (L mol^{-1} s^{-1}) for **1b**[8b] (X = H: lowest reactivity) and then increase to 10.4 and 0.034 (L mol^{-1} s^{-1}) for **1c** (X = 4-OCH_3).

Although the number of k_{OH} and k_B values measured is quite small, two nice FER's have been observed versus the substituent constant at pS^+ 11.50: they can be confidently regarded as significant, because they strictly replicate those obtained by the relevant treatment of $k_{A,R}$ values, as a comparison between Figures 7 (see the Supporting Information) and 2 clearly indicates. Of course, an excellent correlation between k_{OH} and k_B values ($s = 0.94 \pm 0.01$; $n = 5$; $i = 2.36 \pm 0.02$; $r = 0.9996$; CL > 99.9%) has been observed by considering data concerning **1a**,[8a] **1b**,[8b] **1c**, **1f**, and **1l**.

In both the base- and the acid-catalyzed (see after) region a discussion on the absolute values of thermodynamic parameters calculated from the apparent first-order rate constants is meaningless, considering that such rate constants are composite values.[7]

Anyway, some comments are possible: as a matter of fact, the reactivity variations observed with either the substituent or the pS^+ value are essentially entropy-dependent. Thus, one can observe (see Table 1) that at pS^+ 11.50 the activation enthalpies (average value: $\Delta H^\ddagger$ 86.5 ± 1.5 kJ mol^{-1}) are not significantly affected by the variation of the substituent while the activation entropies range from −20 to +19 J K^{-1} mol^{-1}. Likewise, in the case, e.g., of **1c**, we observed that the activation enthalpy remains practically unchanged with the pS^+ (data in Table 3 in Supporting Information; for example, in the pS^+ range 9.1_5−12.3, average value: $\Delta H^\ddagger$ 85.7 ± 1.0 kJ mol^{-1}, see above) while the activation entropy changes from −51 to −5 J K^{-1} mol^{-1}. An analogous trend for the activation parameters has been evidenced (data in Tables 4−12 in the Supporting Information) in the rearrangement of all the other (*Z*)-arylhydrazones (**1d**−**l**) examined.

The Uncatalyzed Pathway. An analysis of the rearrangement rate at pS^+ 3.80 (as well as in the entire uncatalyzed range) shows that the reactivity is only moderately affected by the nature of the substituent. Moreover, in line with the mechanism proposed (see Chart 1),[7b] the introduction of an electron-repelling or -withdrawing substituent causes an increase or a decrease in the reactivity, reflecting the increase or the decrease of the nucleophilicity of N_α and then of its ability to attack N(2).

The simple Hammett treatment to the kinetic data furnishes interesting results: a negative susceptibility constant ($\rho = -1.26 \pm 0.05$) with good statistical results ($n = 11$, $r = 0.993$, $i = -0.04 \pm 0.02$, CL > 99.9%) has been calculated, but some

(12) (a) Schreck, O. *J. Chem. Educ.* **1971**, *48*, 103−107. (b) See ref 11e, Chapter 2.5. (c) See ref 11h, Chapters 3 and 7.

(13) Tsuno, Y.; Ibata, T.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 960−965. Yukawa, Y.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 965−971. Yukawa, Y.; Tsuno, Y.; Sawada, M. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2274−2286. Yukawa, Y.; Tsuno, Y.; Sawada, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1198−1205.

(14) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979−4987.

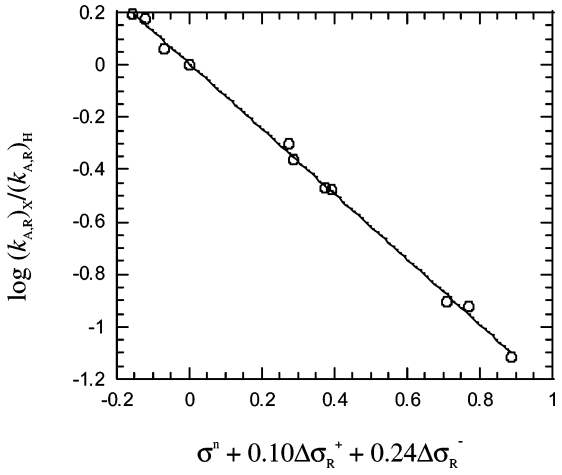


FIGURE 3. Plot of $\log(k_{A,R})_X/(k_{A,R})_H$ at 313.1 K and at pS^+ 3.80 (see eq 4) for the rearrangement of **1b**−**l** into the relevant triazoles **2b**−**l** versus ($\sigma^n + r^+\Delta\sigma^+ + r^-\Delta\sigma^-$) ("overall" IYT plot).

random and unexpected (e.g., **1k**, $\sigma_{m-NO2} + 0.71$, is more reactive than the **1j**, $\sigma_{p-CN} + 0.66$) dispersion of experimental points with respect to the calculated FER can be evidenced (Figure 8 in the Supporting Information). For this reason, we have performed a multiparameter treatment of data by means of an approach of the Ingold−Yukawa−Tsuno (IYT) type.[13,15]

Thus, we have observed that the reactivity of all of the 3-substituted (*Z*)-phenylhydrazones, together with the unsubstituted one (**1b**, **d**, **f**, **h**, and **k**), falls on a straight line with excellent statistical results ($\rho_m = -1.24 \pm 0.02$, $n = 5$, $r = 0.9995$, $i = -0.01 \pm 0.01$, CL > 99.9%). On the other hand, all of the 4-substituted (*Z*)-phenylhydrazones disclose a reactivity lower than that expected on the basis of their σ_p values (see Figure 9 in the Supporting Information). Considering the S_{Ni} nature of the reaction studied (Chart 1), the effect of the para-electron-withdrawing substituents is in line with the occurrence of through-resonance.[16] In contrast, only in a limited number of instances a similar behavior has been observed with electron-repelling substituents.[17]

We have then applied the IYT approach following Wepster's suggestion,[18] obtaining a correlation with excellent statistical parameters (eq 4: $n = 11$, $R = 0.999$, $i = 0.01 \pm 0.01$, CL > 99.9%; Figure 3) characterized by small positive through-resonance contributions[18b] from both electron-repelling and -withdrawing substituents.

$$\log(k_{A,R})_X/(k_{A,R})_H = (-1.24 \pm 0.02)[\sigma^n + (0.10 \pm 0.04)\,\Delta\sigma_{R^+} + (0.24 \pm 0.09)\,\Delta\sigma_R\text{-}] \quad (4)$$

The relatively low susceptibility constant (unexpected if considering the polar nature of the transition state[1c,d,7,19] and the proximity of the substituent to the reaction center[20]) well agrees with the hypothesis, already formulated,[7b] that, in the absence of an effective catalysis, two "opposite" effects of a substituent would be enforced to show up. For example, an electron-donating group would increase the nucleophilicity of N_α [thus favoring the formation of the new N_α−N(2) bond], but at the same time it would disfavor the breaking of the N_α−H bond by the solvent, which acts as a feeble base.[7b] On the contrary, an electron-withdrawing substituent would favor the N_α−H breaking (making the hydrogen more acidic), but would disfavor the N_α−N(2) bond formation.[7b] The balancing between the two counteracting effects thus generates both a low susceptibility constant and similarly low through-resonance contributions, in line with results obtained on the rearrangement of the (*Z*)-phenylhydrazones **3** ($\rho = -1.31$, $r^+ = 0.10$, $r^- = 0.25$).[7b]

In the instance of the uncatalyzed pathway, variations of thermodynamic parameters are significant and their discussion is definitely appropriate. Interestingly, the reactivity variations as a function of the substituent are again essentially entropy-dependent. As a matter of fact, at pS^+ 3.80 the activation enthalpy remains practically unaffected by the substituent (data in Table 1; average value: $\Delta H^{\ddagger} = 98.5 \pm 1.1$ kJ mol^{-1}) while the activation entropy varies from −49 to −22 J K^{-1} mol^{-1}. As expected, for all the cases examined both enthalpy and entropy of activation are not significantly affected by pS^+ (for example, in the pS^+ range 3.5−6.4; Tables 3−12): in the instance of **1c**, the average values are $\Delta H^{\ddagger} = 97.2 \pm 0.8$ kJ mol^{-1} and $\Delta S^{\ddagger} = -28.5 \pm 2.5$ J K mol^{-1} (Table 3).

The (Specific) Acid-Catalyzed Pathway. At pS^+ < 2.3 all of the (*Z*)-arylhydrazones studied show the occurrence of an acid-catalyzed pathway, while at extreme proton concentrations the reactivity tends to a limiting value, suggesting the formation of an Arrhenius complex, as in the case of **1b**.[8b] For this reason, we have studied, in the case of **1c**, the rearrangement in the 1.0_5−6.1 pS^+ range at different buffer concentrations (Table 16 and Figure 10 in the Supporting Information) at various temperatures (303−323 K), observing no increase of $k_{A,R}$ with increasing buffer concentration at constant pS^+. As only the bimolecular proton-catalyzed pathway is effective, the occurrence of a specific-acid catalysis according to eqs 5 and 6 is confirmed.

$$S + H_3O^+ \overset{K}{\rightleftharpoons} SH^+ + H_2O \quad (5)$$

$$SH^+ \xrightarrow{k_H} \text{products} \quad (6)$$

When applying the steady-state approximation to the SH^+ intermediate, eq 7 can be obtained.

(15) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca, 1969; pp 1217−1218.

(16) (a) Arcoria, A.; Fisichella, S.; Scarlata, G.; Sciotto, D. *J. Org. Chem.* **1973**, *38*, 32−36. (b) Ryan, J. J.; Humffray, R. A. *J. Chem. Soc. B* **1967**, 1300−1305. (c) Chapman, N. B.; Chandhury, D. K.; Shorter, J. *J. Chem. Soc.* **1962**, 1957−1986.

(17) Spinelli, D.; Consiglio, G.; Noto, R.; Frenna, V. *J. Org. Chem.* **1976**, *41*, 968−971.

(18) (a) Wepster, B. M. *J. Am. Chem. Soc.* **1973**, *95*, 102−104. Hoefnagel, A. J.; Monshouwer, J. C.; Snorn, E. C. G.; Wepster, B. M. *J. Am. Chem. Soc.* **1973**, *95*, 5350−5356. Hoefnagel, A. J.; Wepster, B. M. *J. Am. Chem. Soc.* **1973**, *95*, 5357−5366. (b) Concerning the meaning, the value, and the use of $\Delta\sigma_{R^+}$ and $\Delta\sigma_{R^-}$ see as primary references the papers cited in refs 13−15 and 18a and as examples of applications also papers cited in refs 7b, 16, and 17.

(19) Bottoni, A.; Frenna, V.; Lanza, C. Z.; Macaluso, G.; Spinelli, D. *J. Phys. Chem. A* **2004**, *108*, 1731−1740.

(20) A comparison with the susceptibility constant calculated for the protonation of some substituted phenylhydrazines in water (ρ −1.21) [see, Stroh, H.-H.; Westpal, G. *Chem. Ber.* **1963**, *96*, 184−187; Fischer, A.; Happer, D. A. R.; Vaughan, J. *J. Chem. Soc.* **1964**, 4060−4063], which concerns the β-nitrogen atom, could induce to expect a higher ρ value for the rearrangement herein, as it concerns the α-nitrogen atom instead. Usually, a shift along the chain of one atom causes a variation of the ρ value, at least, by a factor 2.[21a] Considering also the difference in the solvent,[21] a ρ value significantly higher than −2 would be envisaged.

$$k_{A,R} = k_u + Kk_H[H_3O^+]/(1 + K[H_3O^+]) \quad (7)$$

By means of eq 7, from the experimental $k_{A,R}$ (Tables 3−12) we calculated a series of K and k_H values. In agreement with an Arrhenius complex formation, such values (data in Table 1; see also Chart 2) indicate in every case the occurrence of a true and fast acid−base equilibrium (eq 5; the K values at 313.1 K range between 0.87 and 1.4 L mol^{-1}) followed by a slow rearrangement of the intermediate (eq 6; the k_H values at 313.1 K range between 1.55×10^{-4} and 21.3×10^{-4} L mol^{-1} s^{-1}).

In agreement with an acid-catalyzed pathway in the 0.8−2.3 pS^+ range, quasiunitary slopes[11a] for the $\log(k_{A,R})_{\mathbf{1c-l}}$ versus pS^+ plots have been calculated (data in Table 1; average value: -0.912 ± 0.042). This result parallels those obtained for both **1b**−**l** and **3b**−**l** in the base-catalyzed region (see above and data in Table 1) matching the expectations for near-unity slopes in a mixed solvent containing large amounts of water.[11a]

Because of the composite nature of $k_{A,R}$ (eq 7), any consideration of the substituent effect on the global rearrangement rate should be preceded by an examination of the effect on the single component steps (viz. k_H and K) of the acid-catalyzed pathway.

The foreseeable effect of substituents in the arylhydrazono moiety on k_H values should be strictly comparable and of the same sign (negative susceptibility constant) of that observed in the uncatalyzed range (compare the structures of the involved TSs in Charts 1 and 2). Moreover, electron-donating and -withdrawing substituents in the arylhydrazono moiety should increase and decrease, respectively, the basicity of N(4) of the 1,2,4-oxadiazole ring (again determining a negative susceptibility constant).

The expected effect on K[22,23] would be quite low because the substituent is far from the basic N(4) atom of the 1,2,4-oxadiazole ring and would be confidently quantifiable by means of the classical Hammett constants because of the absence of through-conjugation. Of course, the substituent effect on $k_{A,R}$ would be the largest one, being the sum of the two previous effects, which operate in the same direction.

In the computation of the substituent effects on k_H we have been limited by the impossibility to calculate the k_H value for the (*Z*)-4-nitrophenylhydrazone **1l**,[22] that is the substrate showing the largest through-resonance effect within the range of electron-withdrawing substituents. The use of the classical Hammett constants gives only a good relationship ($\rho = -1.21 \pm 0.08$, $n = 10$, $r = 0.984$, $i = 0.09 \pm 0.03$, CL > 99.9%), while by considering only the 3-substituted phenylhydrazones together with the unsubstituted one (**1b**, **d**, **f**, **h**, and **k**), an excellent FER could be observed ($\rho_m = -1.28 \pm 0.04$, $n = 5$, $r = 0.999$, $i = -0.01 \pm 0.01_5$, CL > 99.9%). The cross-correlation of the k_H at pS^+ 1.00 versus the $k_{A,R}$ at pS^+ 3.80 furnished statistical results (eq 8; Figure 11 in the Supporting Information) which are much better than those calculated versus the Hammett constants, confirming the expected tight resemblance of the substituent effects in the two cases.

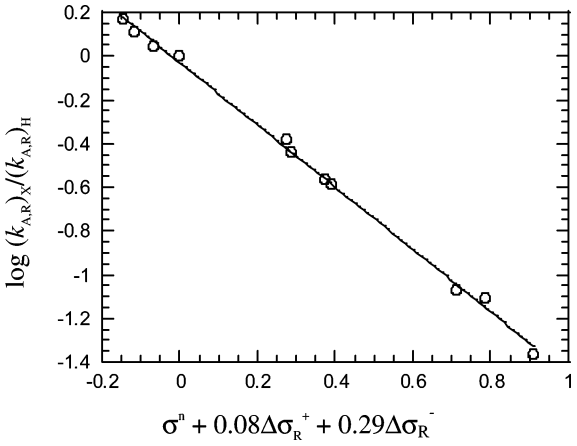
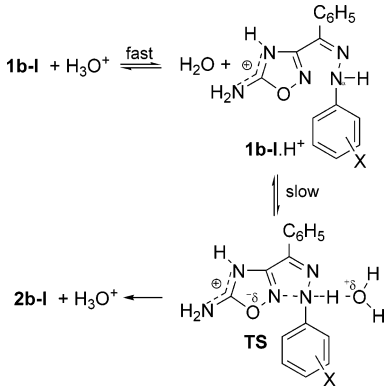


FIGURE 4. Plot of $\log(k_{A,R})_X/(k_{A,R})_H$ at 313.1 K and at pS^+ 1.00 (see eq 10) for the rearrangement of **1b**−**l** into the relevant triazoles **2b**−**l** versus ($\sigma^n + r^+\Delta\sigma^+ + r^-\Delta\sigma^-$) ("overall" IYT plot).

CHART 2



$$s = 1.00 \pm 0.03 \; (n = 10, r = 0.997, i = 0.04 \pm 0.01, \text{CL} > 99.9\%) \quad (8)$$

As far as the substituent effects on K are concerned, the classical Hammett treatment gave excellent results (eq 9: $n = 10$, $r = 0.995$, $i = 0.01 \pm 0.00$, CL > 99.9%, Figure 12 in the Supporting Information), confirming the above expectations of a low susceptibility constant.

$$\log K_X/K_H = (-0.22 \pm 0.01)\sigma_H \quad (9)$$

As concerns the composite substituent effect on $k_{A,R}$, we observed only a good FER with classical Hammett constants ($\rho = -1.45 \pm 0.07$, $i = -0.09 \pm 0.03$, $n = 11$, $r = 0.988$, CL > 99.9%; Figure 13 in the Supporting Information), an excellent correlation for 3-substituted (*Z*)-phenylhydrazones ($\rho_m = -1.45 \pm 0.04$, $i = -0.03 \pm 0.02$, $n = 5$, $r = 0.999$, CL > 99.9%), and finally an excellent application of the IYT equation (eq 10: $n = 11$, $r = 0.999$, $i = 0.03 \pm 0.01$, CL > 99.9%, see Figure 4), once more enlightening (cf. the results for the uncatalyzed pathway) only a modest contribution of through-resonance[18b] from electron-donating substituents.

$$\log(k_{A,R})_X/(k_{A,R})_H = (-1.43 \pm 0.02)[\sigma^n + (0.08 \pm 0.03)\Delta\sigma_{R^+} + (0.29 \pm 0.10)\Delta\sigma_{R^-}] \quad (10)$$

(21) (a) Hine, J. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1962; Chapters 4−5. (b) Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley-Interscience: New York, 1975.

(22) Because of some observed kinetic complications in the case of **1l** the acid-catalyzed pathway has been studied until pS^+ 0.58, that is at a pS^+ at which a linear trend is still operating. For this reason, it has not been possible to calculate the relevant k_H and K values by applying eq 7.

(23) In the following discussion, take into account that these two constants (K and k_H) are not directly measured, but they have been calculated by using eq 7 and, therefore, must be considered secondary computed results; for this reason they are affected by a larger uncertainty of direct data, for example such as $k_{A,R}$.

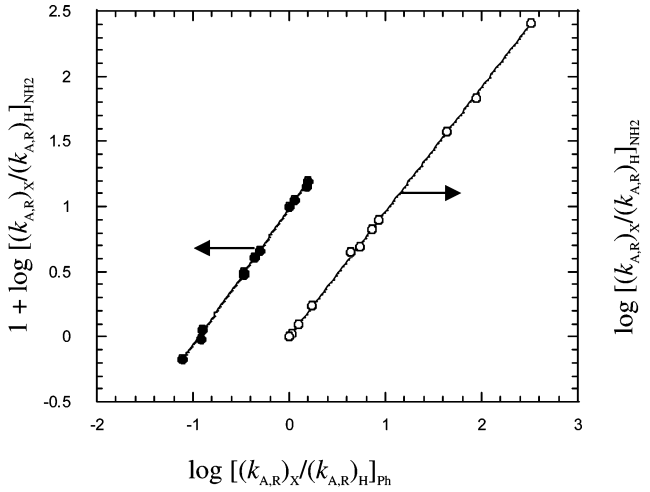


FIGURE 5. Cross-correlations of $\log[(k_{A,R})_X/(k_{A,R})_H]_{NH2}$ at pS^+ 11.50 (○) or $\{1 + \log [(k_{A,R})_X/(k_{A,R})_H]_{NH2}\}$ at pS^+ 3.80 (●) (**1a**−**l**) versus the relevant $\log[(k_{AR})_X/(k_{AR})_H]_{Ph}$ (**3a**−**l**) at 313.1 K.

The excellent cross-correlation between $k_{A,R}$ at pS^+ 1.00 and at pS^+ 3.80 ($s = 1.16 \pm 0.02$, $n = 11$, $r = 0.999$, $i = -0.04 \pm 0.01$, CL > 99.9%, Figure 14 in Supporting Information) definitely confirms the comparability of the substituent effect in the uncatalyzed and in the acid-catalyzed regions. The slope of the cross-correlation, sizeably higher than unity, well reflects the fact that in the acid-catalyzed pathway the substituent-dependent reactivity is the sum of the effects on K and k_H (eqs 5−9).

With regard to the thermodynamic parameters, we can only consider the substituent-dependent variations on $k_{A,R}$ and k_H, the variations on K being meaningless (random because too small). Also, in these cases, the substituent-dependent variations are entropy-dependent (data in Table 1; $\Delta S^{\ddagger}$ values range from −78 to −35 and from −74 to −27 J K mol^{-1}, respectively), while the activation enthalpies are essentially constant (data in Table 1; average values: $\Delta H^{\ddagger} = 83.8 \pm 1.3$ and 79.9 ± 2.5 kJ mol^{-1}, respectively).

A Comparison between the Reactivity of the (*Z*)-Arylhydrazones 1b−l and 3b−l. To compare the substituent effect on the rearrangement rates in the two series **1b**−**l** and **3b**−**l**, we attempted cross-correlations between data concerning the base-catalyzed[7e] and the uncatalyzed[7b] pathways.

As pointed out above, the substituent effects on the rearrangement of the (*Z*)-phenylhydrazones **1** and **3** are very similar to each other; accordingly, reactivity plots (Figure 5) give in both regions (for example at pS^+ 11.50 and 3.80) excellent cross-correlations ($n = 11$, $r > 0.9995$, CL > 99.9%) with quasiunitary slopes ($s = 1.05 \pm 0.01$ and 0.952 ± 0.010; $i = 0.00 \pm 0.01$ and 0.01 ± 0.01, respectively).

The relationships observed well agree with the S_{Ni} nature of the rearrangement studied for which structural modifications at C(5) (to which an amino and a phenyl group are linked in **1** and **3**, respectively) substantially affect (a) the electrophilic character of N(2), (b) the leaving group ability of the N(4)−C(5)−O(1) system, and (c) the thermodynamic stability of both starting and final products.

These factors seem able to influence only moderately the absolute reactivity (compounds **1** are on the average more reactive than **3** by a factor ca. 2 and 6 in the base-catalyzed and in the uncatalyzed range, respectively).

Conclusion

The results of the kinetic study of the rearrangement of a series of *Z*-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole (**1b**−**l**) into the relevant (2-aryl-5-phenyl-2*H*-1,2,3-triazol-4-yl)ureas (**2b**−**l**) has allowed us to draw the following considerations:

(1) All of the (*Z*)-arylhydrazones examined rearrange via three different reaction routes, namely a specific-acid-catalyzed, an uncatalyzed and a general-base-catalyzed one. Only in the instance of **1l** (aryl = 4-nitrophenyl) did we observe some competing hydrolysis at high proton concentration.[22]

(2) Different FER's have been found to apply for the various pathways, with different contributions of normal and through-resonance electronic effects: (a) In the base-catalyzed region two YT FERs (showing positive and negative susceptibility constants with electron-withdrawing and -donating substituents, respectively: eqs 2 and 3 and Figure 2) are clearly defined with a nonlinear concave-upward Hammett curvature (the unsubstituted *Z*-phenylhydrazone **1b** showing the lowest reactivity). This fact points out a changeover of the mechanism which recalls the situation observed in the rearrangement of the *Z*-arylhydrazones 5-phenyl substituted **3b**−**l**.[7e] Kinetic data for the rearrangement of **1b**−**l** and **3b**−**l** give excellent cross-correlations, the 5-amino derivatives **1** being slightly more reactive (by a factor ca. 2). (b) In the uncatalyzed region a unique IYT FER (eq 4 and Figure 3; with a modest negative susceptibility constant) has been observed with scarce through-resonance contributions.[18b] Also in this case, kinetic data for the rearrangement of **1b**−**l** and **3b**−**l** give excellent cross-correlations, the first compounds being again more reactive (by a factor ca. 6). (c) In the acid-catalyzed region, $k_{A,R}$, k_H, and K values for the rearrangement have been calculated. The k_H and K values gave a good and an excellent FER versus Hammett substituent constants, respectively. Moreover the $k_{A,R}$ values furnished an excellent IYT relationship (eq 10 and Figure 4) once more with a modest through-resonance contribution. Mechanistic comments have been attached to the calculated susceptibility constants.

(3) Interestingly, in all three regions, the reactivity variations are largely entropy-dependent, the enthalpies remaining practically unchanged.

Experimental Section

Chemistry. ^{1}H and ^{13}C NMR spectra were recorded in the Fourier transform mode at 21 ± 0.5 °C in $CDCl_3$ or in DMSO-d_6 solutions. Chemical shifts (δ) are in parts per million (ppm) from TMS, and coupling constants are in Hz. HRMS and ESI-MS of all the synthesized compounds were recorded reporting isotopes ^{35}Cl and ^{79}Br. Melting points are uncorrected; yields, mps and crystallization solvents concerning (*Z*)-**1c**−**l**, (*E*)-**1c**−**l** and **2c**−**l** are collected in Table 17 together with HRMS. The ^{13}C NMR spectra of (*Z*)-**1c**−**l** were not recorded because of their fast rearrangement.

Silica and alumina neutral gel plates (F_{254}), silica gel 60 (230−400 mesh), and standardized alumina neutral 90 (63−200 mesh) were used for analytical TLC and for column chromatography, respectively.

p*S*$^+$ Scale Definition and Kinetic Measurements. Water and dioxane were purified according to literature methods.[24] Details on the pS^+ scale have already been reported.[7a,25] The kinetics were carried out in D/W (1:1, v/v) and followed as previously described[7a] by measuring the disappearance of **1c**−**l** [using a UV−vis spec-

(24) Weissberger, A. *Technique of Organic Chemistry*, 2nd ed.; Interscience: New York, 1963; Vol. 7.

trophotometer at the wavelength reported in footnote (a) of Tables 3−12 (Supporting Information), where the concentrations used are also indicated]. The rate constants are accurate within ±3%. Apparent first-order kinetic constants [$(k_{A,R})_1$], directly measured or calculated at 313.1 K, are reported in Tables 3−12. The buffer concentration used was 0.0125 M.

The values of ($k_{A,R}$) for general-base and specific-acid catalysis determination have been calculated from thermodynamic parameters in a pS^+ range depending on the nature of the present substituent (Tables 13−16 in Supporting Information) and managed as previously described in detail.[7d,8b]

(25) An operational pH scale, pS^+ (see Bates, R. G. In *Solute−Solvent Interactions*; Coetze, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; p 46), was established in aqueous dioxane by employing the pK_a values of acids determined by interpolation from the data reported by H. S. Harned and B. B. Owen (*The Physical Chemistry of Electrolytic Solution*, 3rd ed.; ACS Monograph No. 137; Reinhold: New York, 1970; pp 716, 755). For dioxane−water (1:1, v/v) the meter reading after calibration against buffers was not significantly different from pS^+, requiring a correction of only +0.16.

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Supporting Information Available: FER plot concerning kinetic and thermodynamic data, apparent kinetic constants, and compound characterization for all new compounds (mp, IR, ^{1}H, ^{13}C, ESI-MS, MS, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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