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On the use of multi-parameter free energy relationships: the rearrangement 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

Francesca D'Anna [a], Vincenzo Frenna [a], Camilla Zaira Lanza [b], Gabriella Macaluso [a], Salvatore Marullo [a], Domenico Spinelli [b,*], Raffaella Spisani [c], Giovanni Petrillo [d]

[a] *Dipartimento di Chimica Organica 'E. Paternò', Viale delle Scienze-Parco d'Orleans II, 90128 Palermo, Italy*
[b] *Dipartimento di Chimica 'G. Ciamician', University of Bologna, Via Selmi 2, 40126 Bologna, Italy*
[c] *Dipartimento di Chimica Organica 'A. Mangini', Via San Giacomo 11, 40126 Bologna, Italy*
[d] *Dipartimento di Chimica e Chimica Industriale, via Dodecaneso 31, 16146 Genova, Italy*

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ABSTRACT

By using a multi-parameter approach (a combination of Hammett/Ingold-Yukawa-Tsuno/Fujita-Nishioka free energy relationships) the mononuclear rearrangements of heterocycles (MRH) rates for five new *ortho*-substituted and ten new di-, tri-, or tetra-substituted (*Z*)-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole into the relevant (2-aryl-5-phenyl-2*H*-1,2,3-triazol-4-yl)ureas (in dioxane/water and in a large range of pS^+ values) have been related to the electronic and proximity effects exerted by the present substituents, also considering previous results on some mono *meta*- and *para*-substituted (*Z*)-arylhydrazones. In every case, excellent correlation coefficients have been calculated (r^2 or $R^2 \geq 0.996$). Once more the study of MRH has furnished an interesting panel of different reactivity (three pathways of reaction have been evidenced: general-base-catalyzed, uncatalyzed, and specific-acid-catalyzed) and this has been useful in enlightening how polysubstitution can differently affect the MRH rates. Moreover 2,6-disubstitution on the (*Z*)-arylhydrazono moiety causes a significant increase of the reactivity in all of the three studied pathways. All of the collected data appear useful for understanding structure-reactivity/activity relationships in polysubstituted compounds.

1. Introduction

The study of free energy relationships (FERs) has represented in the past, and still represents, one of the milestones in the chemistry research area. This kind of study introduced by Burkhardt[1] and Hammett[2] in the early part of the twentieth century has been frequently used to investigate reaction mechanisms, allowing the rationalization of the outcome of many classical organic reactions.[3] However, on the years, they have had significant influence on very different fields of chemistry, as testified by the large number of papers published on this subject.[4]

Thus, recently FERs have been used to explain the solvent effect on the formation of π-stacks of functional dyes in solution[5] and have proven to be valuable tools for the estimation of binding constants of complexes of Hamilton-receptor-connected merocyanine chromophores.[6] In the materials chemistry area, FER allowed to correlate the structure of some thiosemicarbazone derivatives with their ability to inhibit the corrosion processes of metallic glasses.[7]

Moreover, the basic role that FERs can play in medicinal chemistry is well known:[8] they have a predictive role in quantitative structure/activity relationship (QSAR) studies allowing an appropriate substituent choice to achieve the right balance between a drug's electronic, steric and lipophilic effects, able to enhance their activity.

On the years, some of us have been involved in the use of FERs to get information in different fields of organic chemistry (from reactions mechanisms[9] to spectrometric properties,[10] and so on).[11] Particular attention has been devoted to the study of the mononuclear rearrangement of heterocycles (MRH, as named by Boulton and Katritzky),[12] a reaction that plays a central role in the large field of ring-to-ring interconversion.[13] In this research line, we have *inter alia* measured the rearrangement rates[14] of several substituted (*Z*)-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1a**–**38a**; see Scheme 1) into the relevant 2-aryl-4-benzoylamino-5-phenyl-1,2,3-triazole (**1b**–**38b**) in dioxane/water (D/W; 1:1; v:v) in a wide range of pS^+ (an operational scale of proton concentration in D/W).

* Corresponding author. E-mail address: domenico.spinelli@unibo.it (D. Spinelli).

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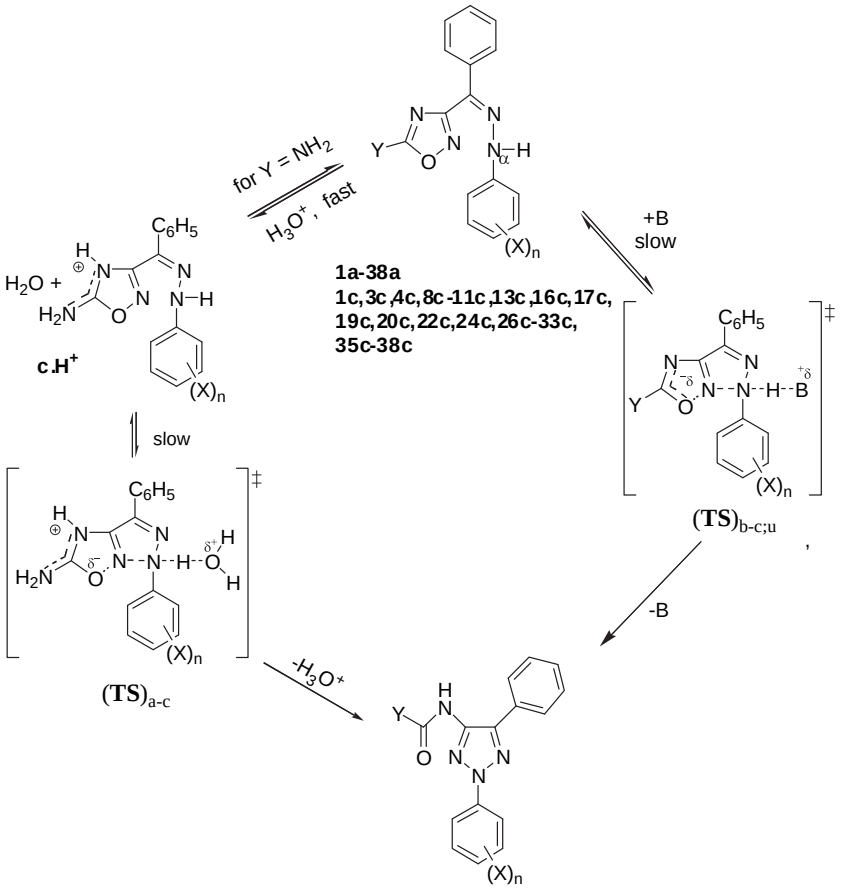

1: Ar = 2,3-Me_2
2: Ar = 2,4-Me_2
3: Ar = 2,5-Me_2
4: Ar = 3,4 -Me_2
5: Ar = 2,4-F_2
6: Ar = 2,5-F_2
7: Ar = 3,5-F_2
8: Ar = 2,3-Cl_2
9: Ar = 2,4-Cl_2
10: Ar = 2,5-Cl_2
11: Ar = 2,6-Cl_2
12: Ar = 3,4-Cl_2
13: Ar = 3,5 -Cl_2
14: Ar = 3-Cl-4-F
15: Ar = 2,4-$(NO_2)_2$
16: Ar = 2,4,6-Cl_3
17: Ar = 2,3,5,6-F_4
18: Ar = 2,3,4,5,6-F_5
19: Ar = 4-OMe
20: Ar = 4-Me
21: Ar = 4-Et
22: Ar = 3-Me
23: Ar = 3-Et
24: Ar = H
25: Ar = 4-F
26: Ar = 4-Cl
27: Ar = 4-Br
28: Ar = 3-Cl
29: Ar = 3-Br
30: Ar = 3-NO_2
31: Ar = 4-CN
32: Ar = 4-NO_2
33: Ar = 2-Me
34: Ar = 2-Et
35: Ar = 2-F
36: Ar = 2-Cl
37: Ar = 2-Br
38: Ar = 2-NO_2

Scheme 1. B=Water or dioxane; hydroxide or borate ions. $(\mathbf{TS})_{a-c}$: transition state for the acid-catalysed pathway; $(\mathbf{TS})_{b-c;u}$ transition state for the general-base-catalyzed as well as for the uncatalyzed pathways.

As shown in Scheme 1, besides *m*- and *p*-substituted (*Z*)-phenylhydrazones, also *ortho*- and poly-substituted arylhydrazones have been considered. The interest of polysubstitution in medicinal chemistry has been already evidenced: in a drug skeleton causing overcrowding could strongly influence the general effect of the drug, decreasing or increasing the drug/receptor interactions. In some cases this makes the use of a simple QSAR for the understanding of pharmacological activity quite difficult.[8,15,16]

The above MRH (Scheme 1) usually occurs via two reaction pathways (general-base-catalyzed and uncatalyzed at higher and at lower pS^+ values, respectively): an analysis of kinetic results by means of FER[17a,b] has allowed an S_Ni mechanism to be proposed for the studied reaction: the transition state of which [$(\mathbf{TS})_{b-c;u}$, see Scheme 1], involving 10 electrons for the studied reaction, in a bicyclic and quasi-aromatic structure, is characterized by a concerted 'asynchronous' bond forming (N_α—N_2) and bond breaking (O_1—N_2), as strongly supported by DFT calculations.[18,19]

According with the theory of the variable structure of the TS[22,23] the transition state $(TS)_{b-c,u}$ structure is not only pathway-dependent, but also dependent on the substituent in the arylhydrazonic moiety, and different weights for 'the formation of the new N_α—N_2 bond'/'the rupture of the relevant O—N_2 bond'/'the loosening of the N_α—H bond' have been observed.[17a,b]

Thus, different FERs have been applied depending on the number, position, and nature of the substituents. Indeed, while for *meta*- and *para*-substituted (*Z*)-phenylhydrazones (**19a**—**32a**) simple FERs, such as Hammett (H),[2] Yukawa-Tsuno (YT),[24] and Ingold-Yukawa-Tsuno (IYT)[24,25] equations have been used; in the case of *ortho*-substituted (**33a**—**38a**) and of several polysubstituted (**1a**—**18a**) (*Z*)-arylhydrazones, the use of a multiparametric FER,

such as the Fujita-Nishioka equation (FN, Eq. 1)[26] (able to evaluate also proximity and primary steric effects) has been proven necessary (see later).[14] All of the FER obtained (mono- or multiparametric) showed excellent statistical results (r^2 or $R^2 \geq 0.998$).

$$\log\left[(k_{A,R})_X/(k_{A,R})_H\right] = \rho\sum\sigma_{o,m,p} + \delta E_s + fF_o + i \quad (1)$$

It is noteworthy that the very particular kinetic behavior observed in the instance of 2,6-dihalogeno (*Z*)-phenylhydrazones (**11a**, **16a**–**18a**) has been rationalized on the grounds of a kinetic steric acceleration which also depends on the bulkiness of the halogens.[14]

Recently we have addressed our attention to the research of acidic catalysis in MRH processes: via a well-designed modification of the structure of the 1,2,4-oxadiazole ring (an amino group introduced at C-5 has strongly increased the basic character of N_4)[27] we have obtained (*Z*)-arylhydrazones able to rearrange 'also' via a specific-acid-catalyzed pathway.

Moreover by investigating the MRH of some *meta*- and *para*-substituted (*Z*)-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole (**19c**, **20c**, **22c**, **24c**, **26**–**32c**)[28] we have gained a general FER-picture of *meta*- and *para*-substituents effects in the arylhydrazonic moiety on the different reaction pathways (general-base-catalyzed, uncatalyzed, and specific-acid-catalyzed).

We have been able also to evidence some interesting relationships between the break points (i.e., the pS^+ at which the switch from one mechanism to the other occurs) or the width of the uncatalyzed pathway and the electronic effects of the present substituents.[29]

Starting from the above results we have now synthesized five new *ortho*-substituted (X=2-Me, 2-F, 2-Cl, 2-Br, and 2-NO_2: **33c**, **35c**–**38c**) and ten new polysubstituted (di-, tri-, and four-substituted: X_2=2,3-Me_2, 2,5-Me_2, 3,4-Me_2, 2,3-Cl_2, 2,4-Cl_2, 2,5-Cl_2, 2,6-Cl_2, 3,5-Cl_2; X_3=2,4,6-Cl_3; X_4=2,3,5,6-F_4: **1c**, **3c**, **4c**, **8c**–**11c**, **13c**, **16c**, **17c**) (*Z*)-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole and studied their MRH into the relevant (2-aryl-5-phenyl-2*H*-1,2,3-triazol-4-yl)ureas with the following aims:

(1) to compare the 'classical' electronic effects and the 'proximity polar' and 'primary steric' effects in this series of compounds with those previously observed in the rearrangement of **1a**–**38a**[14]
(2) to gain information on the 'global' effects of *ortho* and multiple substituents on the course of the acid-catalyzed path;
(3) to ascertain if the kinetic steric acceleration observed in 2,6-dihalogeno (*Z*)-phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**11a**, **16a**–**18a**)[14] represents a general behavior in the MRH of (*Z*)-arylhydrazones of 3-benzoyl-1,2,4-oxadiazoles and in that case, looking if it also works in the acid-catalyzed pathway;
(4) to understand how the several electronic and steric effects of the substituents can work in a multi-pathway process and how the general picture obtained could be useful to get information for studies concerning structure/reactivity or/activity relationships. Some considerations on changeover between the different mechanism pathways as a function of substituent shall also be made.

2. Results and discussion

2.1. A general examination of MRH reactivity data

In order to get a quick comparison among data previously obtained[14] and those we are now collecting, we are reporting in Table 1 the most significant results of FER applied to the MRH of (*Z*)-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1a**–**38a**; see Scheme 1) into the relevant 2-aryl-4-benzoylamino-5-phenyl-1,2,3-triazole (**1b**–**38b**).

Table 1
A summary of the FER application to the rearrangement of (*Z*)-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1a**–**38a**) into the relevant 2-aryl-4-benzoylamino-5-phenyl-1,2,3-triazole (**1b**–**38b**)[a]

Substrate	FER[b]	Pathway	Substituents	ρ or ρ^-	r^+	r^-	ρ^+	f	δ
24a–**32a**	YT *n* 9	Base-catalyzed	Electron-withdrawing	2.22		0.60			
19a–**24a**	YT *n* 6	Base-catalyzed	Electron-donating				−0.33		
19a–**32a**	IYT *n* 14	Uncatalyzed	All the substituents	−1.29	0.11	0.26			
5a–**10a**, **12a**–**15a**, **24a**–**32a**, **35a**–**38a**	IYT/FN *n* 23	Base-catalyzed	Electron-withdrawing	2.30		0.60		0.32	1.50
1a–**4a**, **19a**–**24a**, **33a**–**34a**	YT/FN *n* 12	Base-catalyzed	Electron-donating				−0.33	2.33	0.62
1a–**10a**, **12a**–**14a**, **19a**–**38a**	IYT/FN *n* 33	Uncatalyzed	All the substituents	−1.29	0.11	0.26		−0.92	−0.52

[a] Data from Ref. 14.
[b] YT, IYT, and FN refer to Yukawa-Tsuno, Ingold-Yukawa-Tsuno, and Fujita-Nishioka relationships, respectively.

The course of the MRH of **1c**, **3c**, **4c**, **8c**–**11c**, **13c**, **16c**, **17c**, **19c**, **20c**, **22c**, **24c**, **26c**–**33c**, **35c**–**38c** into the relevant (2-aryl-5-phenyl-2*H*-1,2,3-triazol-4-yl)ureas **1d**, **3d**, **4d**, **8d**–**11d**, **13d**, **16c**, **17d**, **19d**, **20d**, **22d**, **24d**, **26d**–**33d**, **35d**–**38d** has been investigated in the range 283–333 K in D/W over a wide range of pS^+ values (complete kinetic data and thermodynamic parameters are reported in Tables A–Q, while Table R collects a summary of the obtained data. See Supplementary data). The *A*pparent first-order rate constants for the *R*earrangements [$k_{A,R}$; calculated at 313.1 K from activation parameters] and the thermodynamic parameters at pS^+ 1.00, 3.80, and 11.50 have been collected in Table 2 together with the different substituents constants used (σ_{calcd}, see notes of Table 2).

A first examination of the results reported in Table 2 [log $k_{A,R}$ versus pS^+ plots for some representative derivatives (**1c**, **13c**, **24c**, **37c**, and **38c**) are summarized in Figure 1] shows that all of the examined compounds can rearrange via the general-base-catalyzed and the uncatalyzed pathways. Looking at the specific-acid-catalyzed pathway, only **38c** does not rearrange at low pS^+ values.

Once more the log $k_{A,R}$ versus pS^+ plots display quasi-unitary slopes over a wide pS^+ range (see data in Table R of Supplementary data; average values: 0.912±0.004 and −0.930±0.009 in the base- and in the acid-catalyzed ranges, respectively, as expected for this kind of process carried out in water-like solvents), thus replicating the situations observed in the instances of **1a**–**38a** (0.913, in the base-catalyzed range)[14] and of the *meta*- and *para*-substituted (*Z*)-arylhydrazones **19c**, **20c**, **22c**, **24c**, **26c**–**32c** in both base- and acid-catalyzed paths.[28]

Table 2
Kinetic and thermodynamic data[a] and parameters used in FER treatments for the rearrangement of **1c**, **3c**, **4c**, **8c**–**11c**, **16c**, **17c**, **19c**, **20c**, **22c**, **24c**, **26c**–**33c**, **35c**–**38c** into **1d**, **3d**, **4d**, **8d**–**11d**, **16d**, **17d**, **19d**, **20d**, **22d**, **24d**, **26d**–**33d**, **35d**–**38d** at various pS^+ and at 313.1 K in D/W (1:1, v/v)

Comp.	Subst.[b] (E_s, F)	$k_{A,R}$ (s^{-1}) at pS^+ 11.50[c] ($\Delta H^{\#}$, $\Delta S^{\#}$)	$(\sigma_{calcd})_{11.50}$[d,e]	$k_{A,R}$ (s^{-1}) at pS^+ 3.80[c] ($\Delta H^{\#}$, $\Delta S^{\#}$)	$(\sigma_{calcd})_{3.80}$[e,f]	$k_{A,R}$ (s^{-1}) at pS^+ 1.00[c]	$(\sigma_{calcd})_{1.00}$[e,g]	k_H ($L\,mol^{-1}\,s^{-1}$) ($\Delta H^{\#}$, $\Delta S^{\#}$)	K ($L\,mol^{-1}$)
1c	2,3-Me_2 (−1.24, −0.04)	6.62×10^{-4} (89.8, −19.4)	−0.379	4.53×10^{-6} (99.9, −29.0)	−0.190	1.59×10^{-4} (82.8, −54.3)	−0.187	7.89×10^{-4} (79.9, −49.8)	1.34
3c	2,5-Me_2 (−1.24, −0.04)	7.24×10^{-4} (88.8, −22.4)	−0.379	4.67×10^{-6} (99.4, −30.3)	−0.190	1.63×10^{-4} (82.7, −55.4)	−0.187	7.97×10^{-4} (79.0, −52.7)	1.37
4c	3,4-Me_2	4.83×10^{-3} (89.7, −3.8)	−0.379	1.40×10^{-5} (99.8, −19.6)	−0.190	5.18×10^{-4} (82.7, −45.6)	−0.187	2.55×10^{-3} (79.1, −42.4)	1.31
8c	2,3-Cl_2 (−0.97, 0.41)	5.70×10^{-3} (86.2, −13.2)	0.626	2.52×10^{-7} (98.7, −55.8)	0.645	6.36×10^{-6} (82.9, −80.2)	0.648	4.66×10^{-5} (85.7, −55.0)	0.90
9c	2,4-Cl_2 (−0.97, 0.41)	3.52×10^{-3} (85.4, −20.5)	0.506	3.17×10^{-7} (97.8, −57.7)	0.544	7.80×10^{-6} (85.0, −72.1)	0.550	5.33×10^{-5} (82.4, −64.2)	0.956
10c	2,5-Cl_2 (−0.97, 0.41)	6.27×10^{-3} (85.5, −15.0)	0.626	2.45×10^{-7} (98.5, −56.4)	0.645	6.14×10^{-6} (83.4, −79.5)	0.648	4.35×10^{-5} (82.5, −65.6)	0.895
11c	2,6-Cl_2 (−1.94, 0.82)	1.48×10^{-2} (83.0, −15.2)	0.506	1.41×10^{-6} (99.3, −42.5)	0.544	4.36×10^{-5} (84.9, −57.2)	0.550	2.89×10^{-4} (79.6, −62.2)	0.984
13c	3,5-Cl_2	0.172 (84.2, +8.4)	0.746	9.31×10^{-7} (97.2, −50.7)	0.746	2.34×10^{-5} (83.2, −68.4)	0.746	1.80×10^{-4} (83.3, −51.2)	0.807
16c	2,4,6-Cl_3 (−1.94, 0.82)	0.0836 (85.3, +5.2)	0.759	7.89×10^{-7} (98.4, −48.1)	0.816	2.19×10^{-5} (84.2, −66.4)	0.825	1.58×10^{-4} (76.0, −75.6)	0.870
17c	2,3,5,6-F_4 (−0.92, 0.86)	3.65 (80.2, +20.4)	0.948	2.22×10^{-6} (98.9, −36.7)	0.986	4.67×10^{-5} (83.2, −62.7)	0.992	3.33×10^{-4} (80.4, −55.3)	0.901
19c[h]	4-OMe	6.41×10^{-3} (85.5, −16.7)	−0.78[i]	1.24×10^{-5} (97.4, −28.0)	−0.158	4.22×10^{-4} (84.9, −37.7)	−0.147	2.13×10^{-3} (77.0, −51.5)	1.40
20c[h]	4-Me	4.67×10^{-3} (88.3, −6.7)	−0.31[i]	1.19×10^{-5} (99.6, −22.2)	−0.121	3.71×10^{-4} (86.6, −34.7)	−0.118	1.88×10^{-3} (78.2, −46.7)	1.34
22c[h]	3-Me	3.95×10^{-3} (85.7, −17.4)	−0.069[j]	9.18×10^{-6} (97.5, −31.0)	−0.069[j]	3.16×10^{-4} (83.7, −45.6)	−0.069[j]	1.77×10^{-3} (79.1, −46.4)	1.23
24c[h]	H	3.68×10^{-3} (88.2, −12.4)	0.000[j]	7.94×10^{-6} (94.8, −37.8)	0.000[j]	2.86×10^{-4} (84.9, −40.2)	0.000[j]	1.58×10^{-3} (85.4, −26.8)	1.23
26c[h]	4-Cl	1.61×10^{-2} (89.5, +6.7)	0.253	3.99×10^{-6} (99.2, −31.4)	0.272	1.19×10^{-4} (84.9, −50.2)	0.275	7.26×10^{-4} (80.8, −48.5)	1.08
27c[h]	4-Br	2.00×10^{-2} (84.1, −10.2)	0.300	3.44×10^{-6} (98.7, −35.6)	0.285	1.05×10^{-4} (83.3, −54.5)	0.287	6.52×10^{-4} (83.7, −39.7)	1.06
28c[h]	3-Cl	2.69×10^{-2} (87.6, −12.1)	0.373[j]	2.71×10^{-6} (99.2, −34.7)	0.373[j]	7.83×10^{-4} (81.2, −63.6)	0.373[j]	5.33×10^{-4} (79.5, −54.0)	0.976
29c[h]	3-Br	3.12×10^{-2} (87.0, +4.6)	0.391[j]	2.64×10^{-6} (100.0, −33.1)	0.391[j]	7.46×10^{-5} (83.3, −60.2)	0.391[j]	4.95×10^{-4} (77.0, −62.8)	0.983
30c[h]	3-NO_2	1.58×10^{-1} (85.9, +13.2)	0.71[j]	9.95×10^{-7} (98.7, −46.0)	0.71[j]	2.43×10^{-5} (83.7, −66.5)	0.71[j]	1.80×10^{-4} (76.7, −73.6)	0.868
31c[h]	4-CN	3.21×10^{-1} (87.2, +24.3)	0.846	9.50×10^{-7} (98.7, −45.2)	0.770	2.22×10^{-5} (82.8, −70.5)	0.784	1.55×10^{-4} (82.0, −57.3)	0.880
32c[h]	4-NO_2	1.19 (83.1, +21.3)	1.07	6.10×10^{-7} (98.7, −49.4)	0.886	1.24×10^{-5} (82.4, −78.3)	0.909	1.78×10^{-4} (77.0, −71.1)	0.414
33c	2-Me (−1.24, −0.04)	6.89×10^{-4} (88.7, −23.4)	−0.31[i]	3.20×10^{-6} (96.7, −41.2)	−0.121	1.07×10^{-4} (82.0, −60.2)	−0.118	5.81×10^{-4} (81.5, −47.2)	1.31
35c	2-F (−0.46, 0.43)	2.33×10^{-3} (89.2, −12.1)	0.137	1.49×10^{-6} (98.7, −41.8)	0.155	4.57×10^{-5} (85.7, −55.2)	0.159	2.82×10^{-4} (82.1, −51.3)	1.15
36c	2-Cl (−0.97, 0.41)	7.80×10^{-4} (89.8, −20.2)	0.253	6.76×10^{-7} (96.5, −55.6)	0.272	1.97×10^{-5} (82.6, −72.1)	0.275	1.18×10^{-4} (82.0, −59.5)	1.08
37c	2-Br (−1.16, 0.44)	4.56×10^{-4} (90.9, −19.4)	0.300	4.30×10^{-7} (99.1, −50.8)	0.285	1.17×10^{-5} (85.8, −65.8)	0.287	7.48×10^{-5} (85.2, −52.4)	1.04
38c	2-NO_2 (−2.52, 0.67)	2.43×10^{-4} (94.1, −15.4)	1.07	1.25×10^{-8} (97.8, −84.5)	0.886				

[a] $\Delta H^{\#}$: kJ mol^{-1}, the maximum error is 2 kJ mol^{-1}; $\Delta S^{\#}$: J K^{-1} mol^{-1}, the maximum error is 5 J K^{-1} mol^{-1}.
[b] E_s and F values from Ref. 26 are reported.
[c] 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 A–Q in the Supplementary data).
[d] $\sigma_{calcd}=\Sigma(\sigma_H+0.64\ \Delta\sigma^-)$.
[e] Calculated sigma values (notes d, f, and g) come from YT or IYT treatment concerning kinetic data for the rearrangement of *meta*- and *para*-substituted (*Z*)-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazoles in D/W at pS^+ 11.50, 3.80, and 1.00, respectively. Values from Ref. 28.
[f] $\sigma_{calcd}=\Sigma(\sigma^n+0.10\ \Delta\sigma_R^+ +0.24\ \Delta\sigma_R^-)$.
[g] $\sigma_{calcd}=\Sigma(\sigma^n+0.08\ \Delta\sigma_R^+ +0.29\ \Delta\sigma_R^-)$.
[h] Values from Ref. 28 and references therein.
[i] Values of σ^+ from Ref. 2d.
[j] σ values defined by Hammett from Ref. 2c.

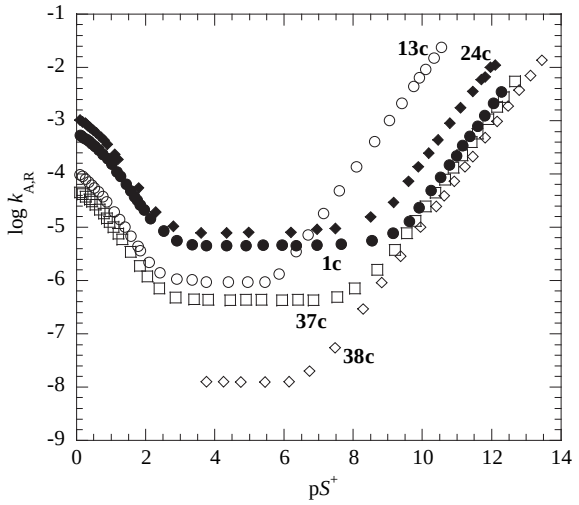

Figure 1. Plot of log $k_{A,R}$ at 313.1 K for the rearrangement of **1c**, **13c**, **24c**, **37c**, and **38c** into the relevant triazoles **1d**, **13d**, **24d**, **37c**, and **38d** in D/W versus pS$^+$.

2.2. 'Classical' electronic, 'proximity polar', and 'primary steric' effects in MRH of (*Z*)-arylhydrazones of series c: a comparison with the reactivity of the relevant (*Z*)-arylhydrazones of series a

(*Z*)-Arylhydrazones of series **a** (at C-5 a phenyl group is present) can rearrange via the general-base-catalyzed and the uncatalyzed pathways,[14,17] while those of series **c** (at C-5 an amino group is present) can rearrange also via the pS$^+$-dependent specific-acid-catalyzed pathway.[27,28]

Thus the comparison between the effect of substituents in the MRH of (*Z*)-arylhydrazones of series **a** and **c** can be carried out for the first two pathways. To get initial information, we plotted the log $k_{A,R}$ (the logarithms of the rearrangement rate constants for the MRH) of compounds of series **c** versus those of the relevant ones of series **a** for both general-base-catalyzed and uncatalyzed paths (Fig. 2).

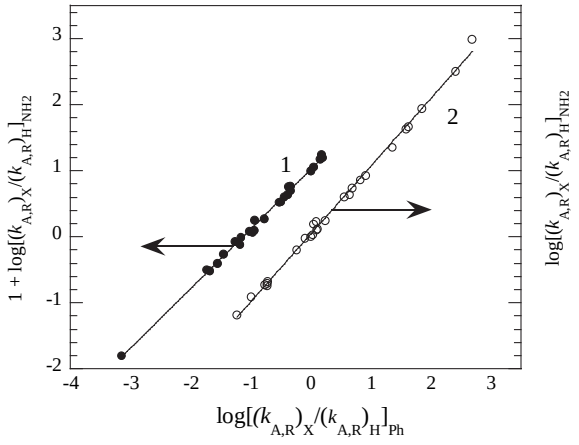

Figure 2. Cross-correlations of $\log[(k_{A,R})_X/(k_{A,R})_H]_{NH_2}$ at pS$^+$ 11.50 (○) [*s* 1.03±0.01; *i* 0.04±0.01; *n* 26; *r* 0.998] or $\{1+\log[(k_{A,R})_X/(k_{A,R})_H]_{NH_2}\}$at pS$^+$ 3.80 (●) [*s* 0.903±0.012; *i* 1.02±0.01; *n* 25; *r* 0.998] concerning **1c**, **3c**, **4c**, **8c**–**11c**, **13c**, **16c**, **17c**, **19c**, **20c**, **22c**, **24c**, **26c**–**33c**, **35c**–**38c** versus the relevant $\log[(k_{A,R})_X/(k_{A,R})_H]_{Ph}$ for **1a**, **3a**, **4a**, **8a**–**11a**, **13a**, **16a**, **17a**, **19a**, **20a**, **22a**, **24a**, **26a**–**33a**, **35a**–**38a** at 313.1 K.

Looking at Figure 2 the following comments appear evident at a first sight:

(1) in both cases excellent relationships have been observed ($r \geq 0.998$), interestingly also including the 2,6-dihalogeno (*Z*)-arylhydrazones (**11c**, **16c**, and **17c**) in the correlation: thus, the acceleration from the 'primary steric' effects observed in the MRH of 2,6-dihalogeno (*Z*)-phenylhydrazones of series **a**[14] does work also in those of series **c**, giving a general significance to this effect. This observation induced us to exclude these three substrates in all of the following FERs. As a matter of fact we calculated (see Figs. A, B, and C of Supplementary data) that they are much more reactive than foreseen (by factors of 103, 153, and 53 in the base-catalyzed path, 27, 33, and 59 in the uncatalyzed path, and 23, 25, and 33 in the acid-catalyzed path, respectively).

Moreover the nice linear relationship clearly indicates that similar 'classical' electronic, 'proximity polar', and 'primary steric' effects are operating in the two series of compounds (**a** and **c**) in both pathways and this induces us to use the previous substituent constants (σ_m, σ_p, σ_n, σ^+, σ^-, as well as the relevant r^+ and r^- parameters, E_s, and F_o) in all of the following FERs. Of course, the additivity rule of the substituents' effects has also been applied (for details see Supplementary data);

(2) the calculated slopes are quite near to unity (see Fig. 2), even if some difference between the two reaction pathways seems to occur: in fact, in the uncatalyzed path the slope calculated (*s* 0.903±0.012) appears to be lower then unity, out of the statistical error (this agrees with the observation[30] that for similar reactions the relationship higher reactivity=lower selectivity does work. See after at point 3) while in the base-catalyzed path, the slope calculated appears to be unitary in the range of the statistical uncertainty (*s* 1.03±0.01); the calculated values of intercepts are only a little different from zero;

(3) looking at the differences in reactivity between (*Z*)-arylhydrazones of series **a** and **c** we have observed that (*Z*)-arylhydrazones of series **c** are on average more reactive than those of series **a**.[14,31] Thus, in the presence of the same substituents the reactivity ratios $[(k_{A,R})_c/(k_{A,R})_a]$ in the base-catalyzed can range between 1.4 (for **1c**) and 3.0 (for **17c**) (1.7 represents the average value) and in the uncatalyzed pathways between 6.4 (for **24c**) and 14.3 (for **38c**), with 8.3 as the average value. This observation can be responsible for the unexpected result that the (*Z*)-arylhydrazone **17c** also rearranges via the uncatalyzed pathway while in contrast **17a** is not able to do it;

(4) this difference in the reactivity between the two series of (*Z*)-arylhydrazones appears of some interest: it can be related to the different effects of 5-amino (series **c**) and 5-phenyl (series **a**) groups. In turn they could 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 stability of both starting and final products.

Interestingly, the differences of reactivity observed between compounds of series **a** and **c** can be rationalized, probably considering the terms b and c as the most important: in both pathways the process overall is a S_Ni reaction, but the weaker the nucleophile, the more the leaving group ability becomes important [in MRH the nucleophile (the >NH of the arylhydrazono moiety) is very weak]. Accordingly, an examination of the thermodynamic parameters concerning the rearrangement in the uncatalyzed pathway (for which the reactivity differences are higher and the discussion of thermodynamic parameters is 'correct'),[14,28] shows that the higher reactivity of (*Z*)-arylhydrazones of series **c** with respect to those of series **a** is essentially entropy-dependent (see after data under Section 2.3.2 and in Ref. 14).

2.3. On the MRH of (*Z*)-arylhydrazones of series c in the base-catalyzed, in the uncatalyzed, and in the acid-catalyzed pathways

2.3.1. FERs in the general-base-catalyzed pathway. At high pS$^+$ values all of the examined (*Z*)-arylhydrazones rearrange via this path

showing the pS^+-dependent reactivity typical of a general-base-catalyzed pathway (no limiting reactivity was observed and moreover kinetic tests with different buffers[17c,27] indicate the occurrence of a buffer-dependent reactivity).[15,32] An attempt to apply the FER has again evidenced the presence of two separate relationships (by using the Yukawa-Tsuno approach): the former for electron-withdrawing and the latter for electron-donating substituents.

Looking at all of the (*Z*)-arylhydrazones containing electron-withdrawing substituents (**8c**–**10c**, **13c**, **24c**, **26c**–**32c**, **35c**–**38c**) and by using the calculation procedures previously followed[14] (see details in Supplementary data, complete computational results for all of the three examined pathways are collected in Tables S, T, and U) we obtained the results reported in line 1 of Table 3, showing an excellent correlation coefficient for the YT/FN (Yukawa-Tsuno/Fujita-Nishioka) equation (R^2>0.998).

Table 3
FER application to the rearrangement of (*Z*)-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole (**1c**, **3c**, **4c**, **8c**–**10c**, **13c**, **19c**, **20c**, **22c**, **24c**, **26c**–**33c**, **35c**–**38c**) into the relevant (2-aryl-5-phenyl-2*H*-1,2,3-triazol-4-yl)ureas (**1d**, **3d**, **4d**, **8d**–**10d**, **13d**, **19d**, **20d**, **22d**, **24d**, **26d**–**33d**, **35d**–**38d**)

Substrate	FER[a]	Pathway	Substituents	ρ or ρ^-	r^+	r^-	ρ^+	f	δ
8c–**10c**, **13c**, **24c**, **26c**–**32c**, **35c**–**38c**	YT-FN *n* 16	Base-catalyzed ($k_{A,R}$)	Electron-withdrawing	2.30		0.64		0.67	1.61
1c, **3c**, **4c**, **19c**, **20c**, **22c**, **24c**, **33c**	YT-FN *n* 8	Base-catalyzed ($k_{A,R}$)	Electron-donating				−0.30		0.68
1c, **3c**, **4c**, **8c**–**10c**, **13c**, **19c**, **20c**, **22c**, **24c**, **26c**–**33c**, **35c**–**38c**	IYT/FN *n* 23	Uncatalyzed ($k_{A,R}$)	All the substituent	−1.25	0.10	0.24		−0.79	0.45
1c, **3c**, **4c**, **8c**–**10c**, **13c**, **19c**, **20c**, **22c**, **24c**, **26c**–**33c**, **35c**–**37c**	IYT/FN *n* 22	Acid-catalyzed (k_H)	All the substituents	−1.23	0.08	0.29		−0.79	0.44
1c, **3c**, **4c**, **8c**–**10c**, **13c**, **19c**, **20c**, **22c**, **24c**, **26c**–**33c**, **35c**–**37c**	H *n* 22	Acid-catalyzed (K)	All the substituents	−0.218					
1c, **3c**, **4c**, **8c**–**10c**, **13c**, **19c**, **20c**, **22c**, **24c**, **26c**–**33c**, **35c**–**37c**	IYT/FN *n* 22	Acid-catalyzed ($k_{A,R}$)	All the substituents	−1.42	0.08	0.29		−0.83	0.43

[a] H, YT, IYT, and FN refer to Hammett, Yukawa-Tsuno, Ingold-Yukawa-Tsuno, and Fujita-Nishioka relationships, respectively.

Looking at the values of the various contributing susceptibility constants one can observe that the low (on this point see some our previous comments)[17a] calculated ρ value (−1.25±0.02) is strictly comparable to those previously obtained for both the relevant (*Z*)-arylhydrazones of series **a** (−1.29±0.02)[14] and the *meta*- and *para*-substituted (*Z*)-arylhydrazones of series **c** (−1.24±0.02).[29]

After we looked at (*Z*)-arylhydrazones containing electron-donating substituents (**1c**, **3c**, **4c**, **19c**, **20c**, **22c**, **24c**, **33c**). Considering some our previous results[14,17,28] and because of their limited number and nature (in the instance of disubstituted (*Z*)-arylhydrazones only methyl substituents are present) we directly correlated reactivity data by using σ^+ values and by neglecting the proximity polar effect (its susceptibility constant was calculated near to zero) and obtained the results reported in line 2 of Table 3 again with an excellent correlation coefficient (R^2>0.999).

Overall, the results with (*Z*)-arylhydrazones containing electron-withdrawing as well as electron-donating substituents compare well with the previous ones collected with *meta*- and *para*-substituted (*Z*)-arylhydrazones of series **c**[28] and with the relevant mono- and poly-substituted (*Z*)-arylhydrazones of series **a**,[14] considering both resonance contributions (ρ, r^+, r^-) and proximity effects (δ and f): compare results in Tables 1 and 3.

Because of their composite nature (the base-catalysis is general, therefore depending on the concentration of all of the bases present)[14,28] a discussion on thermodynamic parameters is not strictly correct. Anyway we have observed that the reactivity variations are essentially entropy-dependent, the enthalpy values staying practically unchanged. For example looking at the MRH at pS^+ 11.50 (see data in Table 2) we can observe that the average value of their activation enthalpies is 87.6±1.5 kJ mol^{-1} and in contrast the activation entropies range from −23.4 to +24.3 J K^{-1}, as a function of the present substituent, thus determining the reactivity fluctuations.

Moreover looking at the reactivity of a single (*Z*)-arylhydrazone in the base-catalyzed pathway as a function of the pS^+ we have observed that the activation enthalpies at different pS^+ values again stay practically unchanged and in contrast the activation entropies change significantly. E.g., for **10c** in the pS^+ interval 9.40–12.60 (see data in Table F of SD) the average value of activation enthalpy is 86.2±1.0 kJ mol^{-1} and in contrast the activation entropies range from −45.1 to +5.9 J K^{-1} mol^{-1}, respectively.

2.3.2. FERs in the uncatalyzed pathway. All of the examined (*Z*)-arylhydrazones rearrange via an uncatalyzed path. Starting from the results of the IYT relationship applied to *meta*- and *para*-substituted (*Z*)-arylhydrazones (**19c**, **20c**, **22c**, **24c**, and **26**–**32c**)[28] we have enlarged the FN treatment to all of the examined *ortho*- and poly-substituted (*Z*)-arylhydrazones (**1c**, **3c**, **4c**, **8c**–**10c**, **13c**, **33c**, **35c**–**38c**), obtaining an excellent correlation (see line 3 of Table 3, R^2>0.998).

In the uncatalyzed pathway the values of thermodynamic parameters can be appropriately discussed, as rate constants are not composite values. Once more the $k_{A,R}$ values variations are essentially entropy-dependent. E.g., at pS^+ 3.80 the activation enthalpy is practically substituent-independent (ΔH^+ 98.4±1.0 kJ mol^{-1}) and in contrast the activation entropy (ΔS^+) varies from −84.5 to −19.6 J K mol^{-1}. Of course for all of the studied (*Z*)-arylhydrazones in the pS^+ range of the uncatalyzed pathway the values of enthalpy and entropy activation stay practically unchanged: for example in the instance of **13c** in the pS^+ interval 2.90–5.45 (see Table H of Supplementary data) its average values are in the field of 97.5±1.0 kJ mol^{-1} and of −49.1 ± 1.0 J K mol^{-1}, respectively.

2.3.3. FERs in the specific-acid-catalyzed pathway. At low pS^+ values (2.4–2.7) all of the examined (*Z*)-arylhydrazones, except **38c**, rearrange via a specific-acid-catalyzed pathway.[27,28] As a matter of fact, looking at data reported in Figure 1 and in Table 2 one can observe that after an increase of the reactivity with the increase of proton concentration at the lowest pS^+ values, the reactivity tends to a limiting value: moreover kinetic tests with different buffers indicate the occurrence of a buffer-independent reactivity[27,28] (suggesting an Arrhenius complex formation,[15,32] see Scheme 1), thus replicating the situation previously evidenced in some *meta*- and *para*-substituted (*Z*)-arylhydrazones (**19c**, **20c**, **22c**, **24c**, **26c**–**32c**).[28]

The application of steady state treatment to this pathway of the MRH gives Eq. 2

$$\log k_{A,R} = k_u + Kk_H[H_3O^+]/(1+K[H_3O^+]) \quad (2)$$

From the experimental $k_{A,R}$ values (Tables A–Q) the relevant K and k_H values could be calculated.[33] The obtained values are well in line with an Arrhenius complex formation: in fact at 313.1 K the K values range between 0.4 and 1.4 L mol^{-1} and the k_H ones between 0.47×10^{-4} and 25.5×10^{-4} L mol^{-1} s^{-1}. Therefore we have a true acid-base equilibrium followed by a slow rearrangement of the protonated (*Z*)-arylhydrazones according with the occurrence of a specific-acid-catalysis (see Scheme 1).

The three series of calculated values ($k_{A,R}$, K, and k_H) can be related to the substituent effects, electronic as well as steric. We shall firstly examine the effects on the constants concerning the two simple component steps (k_H and K) and then on the composite one ($k_{A,R}$).

Again by enlarging the treatment from *meta* and *para* to all of the examined *ortho*- and poly-substituted (*Z*)-arylhydrazones showing the specific-acid-catalyzed pathway (**1c**, **3c**, **4c**, **8c**–**10c**, **13c**, **33c**, and **35c**–**37c**), that is, applying a IYT/FN treatment, an excellent correlation can be obtained for k_H values (see line 4 of Table 3, $R^2>0.997$).

Moreover a logarithmic plot of k_H versus $k_{A,R}$ at pS^+ 3.80 and at 313.1 K gave an excellent cross-correlation (Eq. 3; $R^2>0.996$) with a unitary slope showing that in the two cases similar electronic and steric effects are operating.

$$\log (k_H)_X/(k_H)_H = (0.999 \pm 0.013)\log\left[(k_{A,R})_X/(k_{A,R})_H\right]_{3.80} + i$$
$$i - 0.04 \pm 0.01; n\ 24; R\ 0.998; \mathrm{CL} > 99.9\% \quad (3)$$

Considering the substituent effects on K an excellent correlation versus Hammett constants (see line 5 of Table 3; $R^2>0.990$) has been evidenced.

Finally in the instance of the apparent rate constants for the acid-catalyzed path at pS^+ 1.00 the data treatment enlarged to all of the *ortho*- and poly-substituted (*Z*)-arylhydrazones gives an excellent relationship (see line 6 of Table 3; $R^2>0.996$).

The results of the above correlations allow some interesting considerations. The susceptibility constant concerning the relationship involving k_H (line 4 of Table 3) is strictly comparable to that calculated for the uncatalyzed path at pS^+ 3.80 (line 3 of Table 3) as indicated by Eq. 3 clearly showing that the same kind of substituent effects are operating.

Concerning the K values (measuring the degree of protonation at N_4 determined by the conjugative effect of the amino group at C_5), they give an excellent simple Hammett FER with a low and negative susceptibility constant. This agrees with: (a) the absence of through-conjugation, (b) the large distance between the substituents and the site of protonation, and (c) the electronic effects of the substituents able to increase and decrease, respectively, the basicity of N_4.

As concerns the FERs for $k_{A,R}$ values at pS^+ 1.00 the obtained results (see line 6 of Table 3) parallel those discussed for the k_H values. The only further comment that can be attached regards the higher susceptibility constant calculated for the electronic effects (ρ −1.42±0.02), which appears in line with the composite nature of the involved $k_{A,R}$ values at pS^+ 1.00 [see Scheme 1 and Eq. 2: from which: $\rho_{kA,R}=\rho_{kH}+\rho_K$, in fact $-1.42\cong-1.23+(-0.22)$; see a discussion on this point in Ref. 28].

The variations of thermodynamic parameters can be appropriately discussed in the instance of k_H. Once more, the activation enthalpies are practically substituent-independent ($\Delta H^{\#}$ 80.8±3.0 kJ mol^{-1}) and in contrast the activation entropies ($\Delta S^{\#}$) vary from −75.6 to −26.8 J K mol^{-1}. In the instance of K the substituent-dependent variations of K are very low and the thermodynamic data are affected by a large uncertainty (for this reason their values are not reported in Table 2), so that a discussion on thermodynamic parameters is not allowed.

Vice-versa the $k_{A,R}$ values are composite values (see Eq. 2): they are essentially entropy-dependent. Again at pS^+ 1.00 the activation enthalpy is practically substituent-independent ($\Delta H^{\#}$ 83.7±1.0 kJ mol^{-1}) and in contrast the activation entropy ($\Delta S^{\#}$) ranges from −34.7 to −80.2 J K mol^{-1}.

2.4. The effects of substituents on the break-points and on the widths of the uncatalyzed pathway

Results collected in Figure 1 provide evidence that the switch from one mechanism to the other (named 'break-point') is substituent-dependent, in turn rendering also the width of the uncatalyzed pathway substituent-dependent.[28,29] We shall call $(pS^+)_1$ and $(pS^+)_2$, respectively, the pS^+ values at which the changes from base-catalyzed to uncatalyzed and then from uncatalyzed to acid-catalyzed pathways occur. They represent the pS^+-values at which the substrate shows the same reactivity in the two adjacent paths. Table V (see Supplementary data) collects $(pS^+)_1$ and $(pS^+)_2$ values as well as the width values indicated as ΔpS^+ [i.e., $\Delta pS^+=(pS^+)_1-(pS^+)_2$].

We already carried out a deep discussion on these points in the instance of *meta*- and *para*-substituted (*Z*)-arylhydrazones,[29] for this here we will give only some short comments.

$(pS^+)_1$ values ranges between 4.7_5 and 9.1 showing a strong dependence on the substituent: the lowest values (4.7_5 and 4.8) concern (*Z*)-arylhydrazones containing electron-withdrawing substituents (**32c**: X=4-NO_2; **17c**: X=2,3,5,6-F_4), and in contrast the highest values (8.8 and 9.1) concern (*Z*)-arylhydrazones containing electron-donating substituents (**19c**: X=4-OMe; **3c**: X=2,5-Me_2; **1c**: X=2,3-Me_2).

This behavior is well in line with the fact that electron-withdrawing and -donating substituents in the (*Z*)-arylhydrazones decrease and increase the nucleophilicity of N_α, affecting the uncatalyzed pathway, which in turn starts at lower or at higher pS^+ values.

A comparison between the $(pS^+)_1$ values concerning the rearrangement of the (*Z*)-arylhydrazones of series **a** and **c** shows that their values are strictly correlated. Therefore a plot of $[(pS^+)_1]_\mathbf{c}$ versus $[(pS^+)_1]_\mathbf{a}$ gives an excellent (*r* 0.997) linear plot with a unitary slope (*s* 1.01±0.02; *i* 0.65±0.11; *n* 25; see Fig. D in Supplementary data). A short comment on the intercept value: the effectively high value clearly indicates that the shift from the base-catalyzed to the uncatalyzed pathway occurs in the instance of (*Z*)-arylhydrazones of series **c** at higher pS^+ values than for those of series **a** (i.e.,, it is favored in series **c**). This appears well in line with the higher reactivity of compounds **c**, probably linked to their higher ability to undergo the S_Ni process (see above under Section 2.2).

$(pS^+)_2$ values range between 2.35 and 2.82 showing a very small dependence on the effect of the present substituent: the lowest values (2.35–2.44) concern (*Z*)-arylhydrazones with electron-withdrawing substituents (**32c**: X=4-NO_2; **31c**: X=4-CN; **17c**: X=2,3,5,6-F_4; and **30c**: X=3-NO_2, respectively), and in contrast the highest values (2.70–2.82) concern (*Z*)-arylhydrazones unsubstituted or containing electron-donating substituents (**3c**: X=2,5-Me_2; **24c**: X=H; **22c**: X=3-Me; **21c**: X=4-Me; **19c**: X=4-OMe). The above considerations are valid also in this instance.

Accordingly with previous analyses the smallest and largest ΔpS^+ values have been calculated for (*Z*)-arylhydrazones containing electron-withdrawing substituents (**32c**: X=4-NO_2; **17c**: X=2,3,5,6-F_4), or electron-donating substituents (**19c**: X=4-OMe; **3c**: X=2,5-Me_2; **1c**: X=2,3-Me_2), respectively.[29]

3. Conclusions

The whole of the obtained results allow the following final considerations.

The kinetic study in D/W of the MRH of the 26 considered (*Z*)-arylhydrazones (**1c**, **3c**, **4c**, **8c**–**11c**, **13c**, **16c**, **17c**, **19c**, **20c**, **22c**, **24c**, **26c**–**33c**, **35c**–**38c**) into the relevant triazoles across a large range of temperatures and of pS^+ has furnished the instruments for a wide application of the extended Fujita-Nishioka equation together with

different FER of Hammett, YT, and IYT types. This has allowed a further comparison of electronic and proximity effects in the instance of *ortho*-, *meta*-, and *para*-substituted and of polysubstituted (*Z*)-arylhydrazones of series **c** in the different reaction pathways. Interestingly enough, these new collected data, strictly comparable to those previously collected in the instance of (*Z*)-arylhydrazones of series **a**,[14] well confirm the general applicability of a multi-parameter approach combining H/IYT/FN FERs. We are confident that, collecting new data, a better and better knowledge of factors affecting FER will help not only the understanding of the structure/reactivity relationships but also of the structure/activity ones, allowing applications in different fields of chemistry (material, medicinal, and so on).

Comparing susceptibility constants collected in Table 3 some interesting comments can be carried on:

(a) in the instance of the general-base-catalyzed path, a positive and high ρ^- value has been observed for (*Z*)-arylhydrazones containing electron-withdrawing substituents (line 1 of Table 3) according with a large effect of the substituents able to increase the acidity of the N_α–*H* and in turn to make the general-base-catalysis more efficient; in contrast a negative and low ρ^+ value for (*Z*)-arylhydrazones containing electron-donating substituents (line 2 of Table 3) has been calculated;

(b) in all of the other instances negative and quite low ($-1.2 \div -1.4$; lines 3, 4 and 6 of Table 3) or very low (-0.218; line 5 of Table 3) susceptibility constants have been calculated and discussed as a function of the possible substituent effects in the involved mechanism;

(c) concerning the FN treatment, in the base-catalyzed path a positive medium proximity polar effect and a large primary steric effect (line 1 of Table 3: f=0.67, and δ=1.61) have been observed; in contrast, in the uncatalyzed and acid-catalyzed paths (lines 3, 4, and 6 of Table 3) similar values of the susceptibility constants for the proximity polar effects (negative, f=−0.79, −0.79, and −0.83) and for the primary steric effect (low and positive: δ=0.45, 0.44, and 0.43) have been calculated;

(d) the kinetic acceleration observed in the rearrangement of 2,6-disubstituted (*Z*)-arylhydrazones is present in all of the three pathways, thus it appears to be a general event in MRH processes of (*Z*)-arylhydrazones in line with its interpretation;[14]

(e) both break-points [$(pS^+)_1$ and $(pS^+)_2$] and widths of the uncatalyzed path appear substituent-dependent. Interestingly enough the $(pS^+)_1$ values now determined for the (*Z*)-arylhydrazones of series **c** correlate well with the values measured for the relevant compounds of series **a**. These shifts of reaction mechanism caused by small proton concentration changes could help to enlighten the behavior of some enzymes whose activity can be affected by small proton concentration changes (e.g., disease-dependent).[34]

4. Experimental

Chemistry; syntheses, purification, and characterization of compounds; pS^+ and kinetic measurements; and calculation methods are collected in Supplementary data.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2020.05.025.

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