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The First Kinetic Evidence for Acid Catalysis in a Monocyclic Rearrangement of Heterocycles: Conversion of the *Z*-Phenylhydrazone of 5-Amino-3-benzoyl-1,2,4-oxadiazole into *N*,5-Diphenyl-2*H*-1,2,3-triazol-4-ylurea

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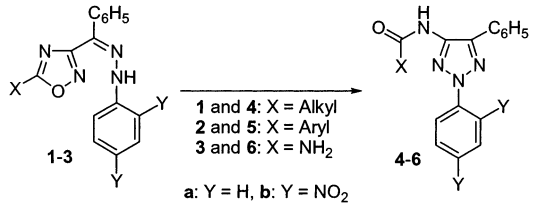
The title reaction has been studied in dioxane/water in a large (0.1−14.9) pS^+ range, evidencing, together with an uncatalyzed process at intermediate (3.5−8.0) pS^+ values, the occurrence of a catalyzed pathway both in the acidic (pS^+ 0.1−3.5) and in the basic region (pS^+ 8.0−14.9): specific-acid catalysis and general-base catalysis, respectively, have been found to take place by means of kinetic investigations at different buffer concentrations. Mechanisms for the three pathways have been advanced on the grounds of structural features. In a comparison with previous data particular attention has been paid to the acid-catalyzed pathway, herein **observed for the first time** in an azole-to-azole interconversion. The mechanistic hypotheses seem well supported by ab initio calculations.

Introduction

In the framework of our interest on ring-to-ring interconversions, we have deeply investigated the azole-to-azole rearrangement, with particular regard to the conversion of *Z*-arylhydrazones of 3-benzoyl-5-X-1,2,4-oxadiazoles **1**−**3** into the relevant triazoles **4**−**6** (Scheme 1).[1]

This reaction represents an interesting example of the "monocyclic rearrangements of heterocycles" (MRHs) recognized by Boulton and Katritzky[2a−c] as a general class of rearrangements (Scheme 2) reportedly occurring[1,2a−c] when D = O. This statement has received strong support from considerations on the aromaticity of five-member heterocycles[3] and on its dependence on the nature of the heteroatom(s).[3−7] The interest of MRHs derives from both their intriguing mechanistic as-

SCHEME 1



SCHEME 2

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(1) (a) Ruccia, M.; Vivona, N.; Spinelli, D. *Adv. Heterocycl. Chem.* **1981**, *29*, 141−169. (b) Vivona, N.; Buscemi, S.; Frenna, V.; Cusmano, G. *Adv. Heterocycl. Chem.* **1993**, *56*, 49−154. (c) Frenna, V.; Vivona, N.; Consiglio, G.; Corrao, A.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1325−1328. (d) Cosimelli, B.; Guernelli, S.; Spinelli, D.; Buscemi, S.; Frenna, V.; Macaluso, G. *J. Org. Chem.* **2001**, *66*, 6124−6129. (e) Guernelli, S.; Laganà, M. F.; Spinelli, D.; Lo Meo, P.; Noto, R.; Riela, S. *J. Org. Chem.* **2002**, *67*, 2948−2953.

(2) (a) Boulton, A. J. *Lectures in Heterocyclic Chemistry*; Hetero-Corporation: Provo, UT, 1973. (b) Boulton, A. J.; Katritzky, A. R.; Majid-Hamid, A. *J. Chem. Soc. C* **1967**, 2005−2007. (c) Katritzky, A. R.; Gordev, M. F. *Heterocycles* **1993**, *35*, 483−518. (d) Van der Plas, H. C. *Ring Transformations of Heterocycles*; Academic Press: London, 1973; Vols. 1 and 2. (e) L'abbé, G. *J. Heterocycl. Chem.* **1984**, *21*, 627−638.

(3) (a) Bird, C. W. *Tetrahedron* **1985**, *41*, 1409−1414. (b) Bird, C. W. *Tetrahedron* **1992**, *48*, 335−340.

(4) Several indexes have been used to evaluate the aromaticity of five- and six-membered heterocycles.[3,5−7] "The relative 'diene character' or 'bond fixation' .... may be considered a measure of their lack of aromaticity."[6] In line with these considerations "a new index of aromatic character has been devised upon a statistical evaluation of the deviation in peripheral bond orders" by Bird.[3a] His results, strengthened by Katritzky et al.[5,7] and by Bean,[6b] indicate the following aromaticity sequence: 2*H*-1,2,3-triazole ≫ 1,2,4-oxadiazole (Bird's I_5 indexes: 88 and 39, respectively). The higher aromaticity of isoxazole (I_5 = 47) with respect to 1,2,4-oxadiazole is in turn confirmed (also compare data in ref 13).

(5) A recent comprehensive paper of Katritzky et al. (Katritzky, A. R.; Jug, K.; Oniciu, D. C. *Chem. Rev.* **2001**, *101*, 1421−1449) has revisited quantitative measures of aromaticity, giving further statistical support to Bird's treatment.[3]

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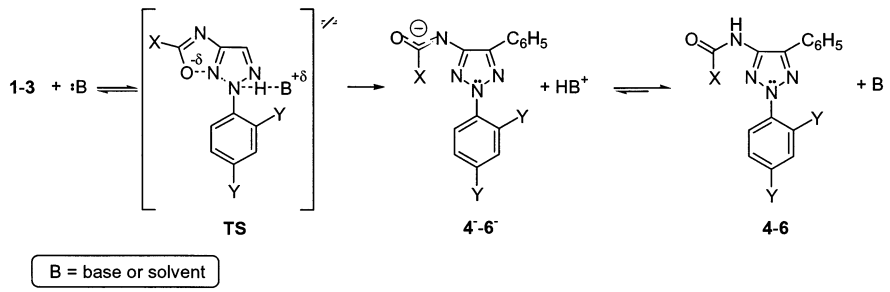
SCHEME 3



pects[1,2,8,9] and their wide synthetic applicability,[1a,b,2,8] also considering, at this regard, that several azoles show interesting pharmacological activity[10] or can be used as masked functionalities.[11]

On the basis of our kinetic studies (thoroughly carried out both in dioxane/water in the presence of buffers and in organic solvents in the presence of several amines), we have pointed out[1] that the MRHs are S_{Ni} processes, whose driving force is strictly linked to the different stability of starting and final compounds. Thus, particular relevance is beared by the aromaticity of starting and final ring, the derivatives of 1,2,4-oxadiazole (Bird's I_5 index 39),[3a,4,12] e.g., being easily rearranged into the more aromatic 2*H*-1,2,3-triazoles (I_5 index 88)].[3a,4,12] The different stability of the two heterocycles is in line with the general observation that "the presence of an oxygen atom has a particular aromaticity-reducing effect".[3a,5,6] Moreover, it must be remarked that "the resonance-stabilization is not confined to rings, and these reactions must derive some of their driving force from the stability of the amide side chain produced. Resonance-stabilization in the side chain is of course one contributory aspect of its leaving group ability",[2a] as we have quantitatively estimated[13] by comparing the reactivity of the *Z*-phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**2a**, X = C_6H_5) and -isoxazole [$(k_{obs})_{\mathbf{2a}}/(k_{obs})_{\mathbf{iso}} \simeq 1000$].

The nitrogen-onto-nitrogen nucleophilic attack and the oxygen−nitrogen bond rupture represent (Scheme 3) an intramolecular concerted process, whose intermolecular counterpart is not known.[8b,c] In dioxane/water the process is usually characterized by the presence of two different reaction pathways: a base-catalyzed one,[1] occurring at higher pS^+ values,[14] and an uncatalyzed,[1] pS^+-independent one, showing up at lower pS^+ values. In some instances (e.g., when one or more nitrogroups are present in the arylhydrazono moiety), the second pathway could not be evidenced (see below).[1d]

While many facets of MRHs have been deeply investigated by us[1,13,16] (such as in particular the nature of the nucleophilic side chain[16] and of the starting aromatic ring[13]), an interesting aspect that has never been investigated is the incidental occurrence of acid catalysis. As

(6) (a) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon: Oxford, 2000; pp 101−102. (b) Bean, P. G. *J. Org. Chem.* **1998**, *63*, 2497−2506. (c) Andrianov, V. G.; Shikken, M. A.; Eremeev, A. V. *Khim. Geterotsikl. Soedin* **1989**, 508−511 (English Trans., pp 423−425).

(7) Katritzky, A. R.; Barczynsky, P.; Musumarra, G.; Pisano, D.; Szafran, M. *J. Am. Chem. Soc.* **1989**, *111*, 7−15.

(8) (a) Korbonits, D.; Kanzel-Szvoboda, I.; Horváth, K. *J. Chem. Soc., Perkin Trans. 1* **1982**, 759−766. (b) Horváth, K.; Korbonits, D.; Náray-Szabó, G.; Simon, K. *THEOCHEM* **1986**, *136*, 215−227. (c) Korbonits, D.; Bakó, E. M.; Horváth, K. *J. Chem. Res., Synop.* **1979**, 64−65; *J. Chem. Res., Miniprint* 801−875.

(9) Semiempirical and ab initio calculations for both monocyclic and bicyclic rearrangements of heterocycles have been reported. For the first reaction the fully degenerate rearrangement of the anion of 3-acetylamino-5-methyl-1,2,4-oxadiazole has been deeply examined [for example, see: La Manna, G.; Buscemi, S.; Frenna, V.; Vivona, N.; Spinelli, D. *Heterocycles* **1991**, *32*, 1547−1557. La Manna, G.; Buscemi, S.; Vivona, N. *THEOCHEM* **1998**, *452*, 67−74. Andrianov, V. G.; Makushenkov, S. V.; Eremeev, A. V. *Mendeleev Commun.* **1992**, 129−130], for the second one several cases have been investigated (for example, see: Eckert, F.; Rauhut, G. *J. Am. Chem. Soc.* **1998**, *120*, 13478−13484. Rauhut, G.; Eckert, F. *Science Progress* **1999**, *82*, 209−231. Rauhut, G. *J. Org. Chem.* **2001**, *66*, 5444−5448 and references therein).

(10) The development of the biological importance of 1,2,4-oxadiazoles originated from the idea that this ring represents a hydrolysis-resistant bioisoster of an ester or (in its imidic form) of an amide functionality. Thus, 1,2,4-oxadiazoles have been suggested as antitussive agents (Palazzo, G.; Corsi, G. *Arzneim.-Forsch.* **1962**, *12*, 545−546. De Gregorio, M. *Panminerva Med.* **1962**, *4*, 90−93. Harsànyi, K.; Kiss, P.; Korbonits, D.; Malyàta, I. R. *Arzneim.-Forsch.* **1966**, *16*, 615−617), as coronary vasodilators (Sterne, J.; Hirsch, C. *Therapie* **1965**, *20*, 89−94, 95−100), as local anaesthetics (Eloy, F.; Lenaers, R. *Bull. Chim. Therap.* **1966**, *12*, 347−350), as antitussive, antispasmodic, antiinflammatory, and/or analgesic agents (Palazzo, G.; Tavella, M.; Strani, G.; Silvestrini, B. *J. Med. Pharm. Chem.* **1961**, *4*, 351−367), as muscarinic agonist (Freedman, S. B.; Harley, E. A.; Marswood, R. S.; Patel, S. *Eur. J. Pharmacol.* **1990**, *187*, 193−199. Showell, G. A.; Gibbons, T. L.; Kneen, C. O.; MacLeod, A. M.; Merchant, K.; Saunders, J.; Freedman, S. B.; Patel, S.; Baker, R. *J. Med. Chem.* **1991**, *34*, 1086−1094) and antagonist agents (Saunders, J.; Cassidy, M.; Freedman, S. B.; Harley, E. A.; Iversen, L. L.; Kneen, C.; MacLeod, A. M.; Merchant, K. J.; Snow, R. J.; Baker, R. *J. Med. Chem.* **1990**, *33*, 1128−1138), as depressants of CNS (Cavalleri, B.; Volpe, G.; Rosselli Del Turco, B.; Diena, A. *Il Farmaco Ed. Sci.* **1976**, *66*, 393−402), as agents for the treatment of diabetes-associated disorders (Mylari, B. L.; Beyer, T. A.; Scott, P. J.; Aldinger, C. E.; Dee, M. F.; Siegel, T. W.; Zembrowski, W. J. *J. Med. Chem.* **1992**, *35*, 457−465), etc. The discovery (Takemoto, T.; Takagi, N.; Nakaiima, T.; Koike, K. *Yakugata Zhassi* **1975**, *95*, 176−179) of the neuroexcitatory activity of L-quisqualic acid (a naturally occurring 1,2,4-oxadiazole derivative) has also increased the interest in the study of saturated 1,2,4-oxadiazoles.

(11) On the use of heterocycles as masked functionalities, see: (a) Dondoni, A.; Marino, P. *J. Org. Chem.* **1991**, *56*, 5294−5301. (b) Dondoni, A. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Verlag Helvetica Chimica Acta: Basel, Switzerland, 1992; pp 377−437. (c) Dondoni, A.; Marra, A. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; M. Dekker: New York, 1997; Chapter 9, pp 173−205. (d) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585−4595.

(12) In a second time, Bird[3b] proposed the unified aromaticity indices (I_A): the new values for 1,2,4-oxadiazole, isoxazole, and 2*H*-1,2,3-triazole were 48, 52 and 109, respectively.

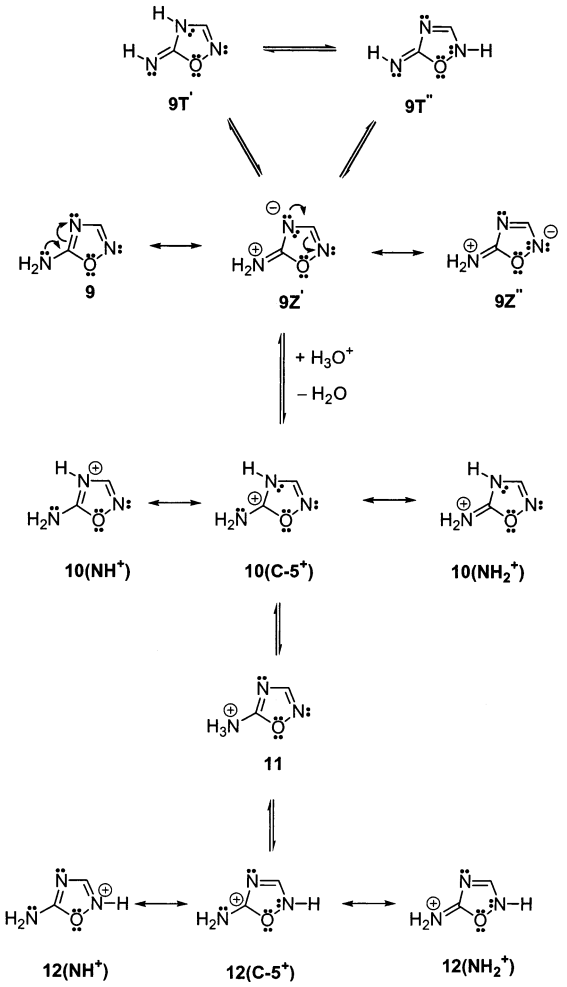
(13) Frenna, V.; Vivona, N.; Macaluso, G.; Spinelli, D.; Consiglio, G. *J. Chem. Soc., Perkin Trans. 2* **1987**, 537−540.

(14) An operational p*H* scale, pS^+,[15a] was established in aqueous dioxane by employing the pK_a values of acids determined by interpolation from the data reported by Harned and Owen.[15b] 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.

(15) (a) Bates, R. G. In *Solute−Solvent Interactions*; Coetze, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; p 46. (b) Harned, H. S.; Owen, B. B. *The Physical Chemistry of Electrolytic Solution*, 3rd ed.; ACS Monograph No. 137; Reinhold: New York, 1970; pp 716, 755.

(16) (a) Frenna, V.; Spinelli, D.; Consiglio, G. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1289−1295. (b) Frenna, V.; Vivona, N.; Consiglio, G.; Spinelli, D.; Mezzina, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1339−1343.

SCHEME 4



a matter of fact the protonation (or the interaction with a Lewis acid) in the A=B portion of the starting heteroring of Scheme 2 would create conditions suitable for the occurrence of acid catalysis.

Interesting substrates for this purpose would be the derivatives of 5-amino-1,2,4-oxadiazole **9**. As a matter of fact the 5-amino group should play two different roles: (i) in the neutral form it could conjugate with both N(4) and N(2) of the 1,2,4-oxadiazole ring affecting both its aromaticity and structure (perhaps increasing the leaving group ability of the ring oxygen and thus favoring the ring-to-ring interconversion); (ii) in the acidic range it could provide conjugative assistance to protonation of the substrate [presumably occurring at N(4), see below] creating conditions favorable to acid catalysis.

Results and Discussion

Preliminary Theoretical Study. A preliminary theoretical investigation[17] of the protonation of **9** (see Scheme 4) has been carried out at the density functional theory (DFT) level. In Scheme 4, the zwitterionic canonical structures **9Z′**−**9Z″** and the neutral tautomers **9T′**−**9T″** are also reported. For sake of comparison, the unsubstituted 1,2,4-oxadiazole (**13**) has also been investigated. The most relevant geometrical parameters (bond lengths) and the Mulliken atomic charges are collected in Table 1;[18] for clarity sake, the O(1)−N(2) bond lengths and the

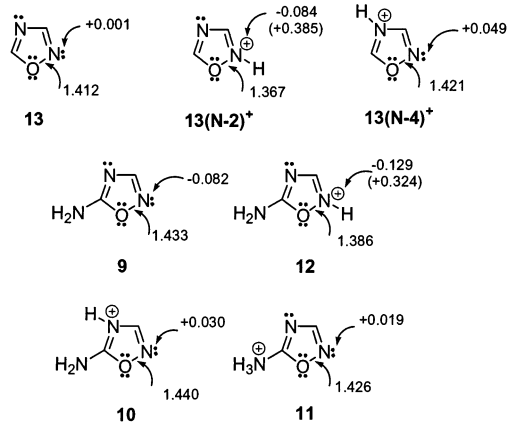


FIGURE 1. Lengths (Å) of the O(1)−N(2) bonds and atomic charges on N(2) (in parentheses: group charges) for **9**−**13**.

atomic and group charges on N(2) are evidenced in Figure 1. The results obtained for 1,2,4-oxadiazole are in quite good agreement with the experimental values available in the literature.[6a] It is worth pointing out that our data significantly differ from those[6b] obtained at the Hartree−Fock level with the 6-31G* basis, indicating that a correlated approach is required to obtain a reliable description of these systems. Moreover, our results concerning the site of protonation in 1,2,4-oxadiazole well match calculated proton affinities.[6c]

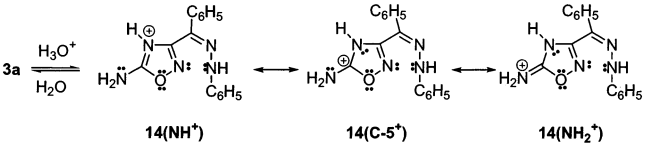
Inspection of Figure 1 and Table 1[18] enlightens the following interesting points: (a) on going from **13** to **9** [as well as from **13(N-2)**$^+$ and **13(N-4)**$^+$ to **12** and **10**, respectively], a sizable elongation of the O(1)−N(2) bond is observed ($\Delta\lambda$ ca. 0.02 Å). Thus, the presence of an amino group at C(5) causes a "significant weakening" of the bond to be broken in the rearrangement; (b) in agreement with previous results,[6c] the protonation of both **13** and **9** seems to occur preferably at N(4): **13(N-4)**$^+$ is more stable than **13(N-2)**$^+$ (ΔE 19.3 kJ mol^{-1}), and **10** is more stable than **12** and **11** (ΔE 8.4 and 109.7 kJ mol^{-1}, respectively). This finding agrees with the prediction based on the comparison of the various resonance structures and on the behavior of other aminoazoles.[19,20] It is worth pointing out that, on going from **9** to **10**, some elongation and consequent weakening of the O(1)−N(2) bond occurs, thus favoring the S_{Ni} process; on the contrary, protonation at the amino group and at N(2) determines a small and large shortening (and hence

(17) (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision *A*.6, Gaussian, Inc.: Pittsburgh, PA, 1998. (b) Godbout, N.; Salahub, D. R.; Andzelm, J.; Wimmer, E. *Can. J. Chem.* **1992**, *70*, 560−571. *UniChem DGauss*, version 2.3.1, **1994**, Cray Research, Inc.

(18) Tables 1−4 and 6 are given in the Supporting Information.

(19) (a) Katritzky, A. R.; Lagowski, J. M. *The Principles of Heterocyclic Chemistry*; Methuen and Co.: London, 1967; p 157. (b) Reference 6a, pp 375−379 and 450. (c) Forlani, L. In *Targets in Heterocyclic Systems, Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Italian Chemical Society: Rome, 1997; pp 76−81.

SCHEME 5



strengthening) of the O(1)−N(2) bond, respectively; (c) on going from 1,2,4-oxadiazole (**13**) to 5-amino-1,2,4-oxadiazole (**9**) an increase of electron density on N(2) has been found. This makes less likely the nitrogen-onto-nitrogen nucleophilic attack, which represents the first stage of the ring-to-ring interconversion. Protonation of the amino nitrogen or of N(4) causes a decrease of electron density on the N(2) atom, restoring conditions favorable to the S_{Ni} process.

Selection of the Most Suitable Candidates for the Occurrence of Acid Catalysis in the MRH Process. The considerations above induced us recently to address attention to the rearrangement of the *Z*-2,4-dinitrophenylhydrazone of 5-amino-3-benzoyl-1,2,4-oxadiazole (**3b**) into the relevant triazole (**6b**).[1d] Unluckily, though, because of the low rate of the rearrangement of **3b** at large proton concentrations, i.e., in the pS^+ range where substrate protonation could be significant (and thus suitable for the appearance of acid catalysis), the only reaction observed was its acidic hydrolysis to give 2,4-dinitrophenylhydrazine and 5-amino-3-benzoyl-1,2,4-oxadiazole.[1d,21]

Considering that at low pS^+ values the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**2a**, X = C_6H_5)[1c,22] rearranges faster [e.g., $(k_{A,R})_{\mathbf{2a}}/(k_{A,R})_{\mathbf{2b}} = 61$ at 293.15 K and at pS^+ 4.5] than the *Z*-2,4-dinitrophenylhydrazone (**2b**, X = C_6H_5),[1d] we have now addressed our attention to the rearrangement of the *Z*-phenylhydrazone of 5-amino-3-benzoyl-1,2,4-oxadiazole (**3a**) into the relevant triazole (**6a**). The higher nucleophilic character of the *Z*-phenylhydrazono moiety with respect to the 2,4-dinitro derivative at low pS^+ values should hopefully offer the opportunity of reaching proton concentrations where a significant protonation at N(4) of **3a**[23] would generate a cation [the resonance hybrid **14** (Scheme 5)] provided with a "particularly effective" leaving group (see the following text), thus causing the appearance of acid catalysis.

Synthesis of the *Z*-Phenylhydrazone of 5-Amino-3-benzoyl-1,2,4-oxadiazole (3a). Attempts to prepare the title compound from 5-amino-3-benzoyl-1,2,4-oxadiazole[24] and phenylhydrazine following the standard procedure successfully applied to the synthesis of the *Z*-arylhydrazones of several 3-benzoyl-5-X-1,2,4-oxadiazoles[1,22,25,26] (X = H, alkyl, or aryl) led to the isolation of triazole **6a** together with the *E*-isomer of the expected hydrazone. Thus, the presence of small quantities of acids (HCl or CH_3COOH) presumably causes a fast rearrangement of any formed *Z*-phenylhydrazone **3a** into the relevant triazole: an outcome representing a first confirmation of the correctness of our hypothesis on the possible occurrence of acid catalysis in the rearrangement of **3a**.

As a matter of fact, by carrying out the reaction in ethanol at room temperature with a phenylhydrazine excess, we obtained after 24 h a reaction mixture that by flash chromatography on neutral allumina allowed the separation of some **3a** from both its *E*-isomer and the relevant triazole (**6a**). The isolated **3a** easily rearranged in ethanol in the presence of acids or bases, as well as in DMSO, in agreement with the general behavior observed for MRH processes[1,8a,27] or by heating above its melting point.[1,2]

Kinetic Study of the Rearrangement of the *Z*-Phenylhydrazone of 5-Amino-3-benzoyl-1,2,4-oxadiazole (3a) into *N*,5-Diphenyl-2-*H*-1,2,3-triazol-4-ylurea (6a). The apparent first-order rate constants $[(k_{A,R})_{\mathbf{3a}}]$ for the rearrangement of **3a** into **6a** in 1:1 (v/v) dioxane/water in the presence of buffers in the 0.1−14.9 pS^+ range have been measured at different temperatures. The only reaction observed was the expected rearrangement: even at the lowest pS^+ values no competitive acidic hydrolysis of **3a** to 5-amino-3-benzoyl-1,2,4-oxadiazole and phenylhydrazine was observed.

In Table 2[18] are collected the kinetic data at 293.15 K (calculated from the reported activation parameters[28] or directly measured, for the fastest reactions): a logarithmic plot versus pS^+ is reported in Figure 2, where, for comparison sake, data relevant to the rearrangement of **3b** and **2a** (X = C_6H_5) at the same temperature are also reported.

From Figure 2, a number of interesting conclusions can be drawn:

(i) The reactivity of **3a** as well as that of all the previously studied compounds is strongly affected by the proton concentration.[1]

(ii) In the case of **3a**, two catalyzed regions [one in the acidic interval (e.g., in the pS^+ range 0.89−2.30: *s* −0.90 ± 0.01, *r* 0.9996, *n* 8), the other in the basic one (e.g., in the pS^+ range 9.88−14.90: *s* 0.95 ± 0.00, *r* 0.9998, *n* 25)][29] together with an intermediate uncatalyzed (or solvent-catalyzed) region have been observed.

(iii) In the acidic region a rearrangement occurs only in the case of **3a**, while **2a** (X = C_6H_5)[22] and **3b**[1d] are hydrolyzed.

(20) (a) It seems also relevant to recall that in a STO-3G study of proton affinities,[20b] protonation of 3-amino-1,2,5-oxadiazole was found to occur at N(2) rather than at the exocyclic nitrogen, the amino derivative being more basic than the parent 1,2,5-oxadiazole (ΔPA ca. 91 kJ mol^{-1}). (b) Andrianov, V. G.; Shikken, M. A.; Eremeev, A. V. *Khim. Geterotsikl. Soedin.* **1989**, 1261−1264 (English Trans., pp 1056−1059).

(21) Arylhydrazones are usually hydrolyzed in acidic conditions. At low pS^+ this reaction effectively competes with the rearrangement, overwhelming it as we have observed in the cases of the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole[22] and of the *Z*-2,4-dinitrophenylhydrazone of 5-amino-3-benzoyl-1,2,4-oxadiazole.[1d]

(22) Spinelli, D.; Corrao, A.; Frenna, V.; Vivona, N.; Ruccia, M.; Cusmano, G. *J. Heterocycl. Chem.* **1976**, *13*, 357−360.

(23) On the basis of the ab initio results reported above in the text we can confidently neglect protonation at N(2) and at the exocyclic nitrogen (**12**-like and **11**-like structures, respectively).

(24) Cavalleri, B.; Bellani, P.; Lancini, G. *J. Heterocycl. Chem.* **1973**, *10*, 357−362.

(25) Frenna, V.; Vivona, N.; Consiglio, G.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 541−545.

(26) Spinelli, D.; Frenna, V.; Corrao, A.; Vivona, N. *J. Chem. Soc., Perkin Trans. 2* **1978**, 19−22.

(27) Frenna, V.; Vivona, N.; Consiglio, G.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1199−1202.

(28) In the base- and in the acid-catalyzed regions a discussion on thermodynamic parameters is meaningless, as the rate constants are composite values. Anyway the reactivity variation appears to be more entropy than enthalpy-dependent, as already observed.[22,25]

(29) As pointed out,[30a] in water the slope would be −1 and +1 in the acidic and basic range, respectively. In mixed solvents containing large amount of water the observed slopes are quite near to unity.

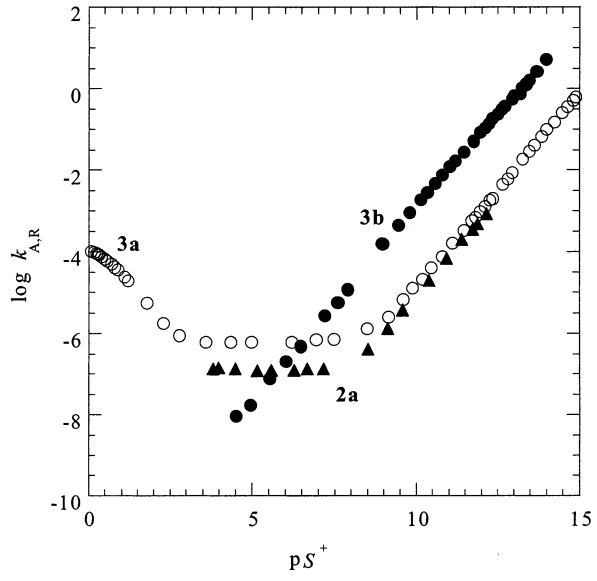


FIGURE 2. Plot of $\log(k_{A,R})_{\mathbf{3a}}$, $\log(k_{A,R})_{\mathbf{3b}}$, and $\log(k_{A,R})_{\mathbf{2a}}$ for the rearrangement of **3a**, **3b**, and **2a** into **6a**, **6b**, and **5a**, respectively, in dioxane/water at 293.15 K versus pS^+.

Study of the Nature of Base and Acid Catalysis in the Rearrangement of 3a. The apparent first-order rate constants for the rearrangement of **3a** in dioxane/water would obey in the most general case eq 1,[30] where k_u represents the rate constant for the uncatalyzed pathway; k_H, k_{OH}, k_A, and k_B represent the second-order rate constants for the pathways catalyzed by proton, hydroxide, every acidic or basic component of the buffer, respectively; and finally, $k_{H,A}$, $k_{H,B}$, etc. refer to all the termolecular pathways involving mixed catalysis by any possible couple of components present in the buffer.

$$(k_{A,R})_{\mathbf{3a}} = k_u + k_H[H_3O^+] + \Sigma k_A[HA] + k_{OH}[OH^-] + \Sigma k_B[B] + \Sigma k_{H,A}[H_3O^+][HA] + \Sigma k_{H,B}[H_3O^+][B] + ... \quad (1)$$

Considering the proton (and then the hydroxide) concentrations at different pS^+ values, eq 1 can be simplified to eqs 2−4 in the pS^+ ranges 0.1−3.5, 3.5−8.0 and 8.0−14.9, respectively.

$$(k_{A,R})_{\mathbf{3a}} = k_u + k_H[H_3O^+] + \Sigma k_A[HA] + \Sigma k_B[B] + \Sigma k_{H,A}[H_3O^+][HA] + \Sigma k_{H,B}[H_3O^+][B] + \Sigma k_{A,B}[HA][B] \quad (2)$$

$$(k_{A,R})_{\mathbf{3a}} = k_u \quad (3)$$

$$(k_{A,R})_{\mathbf{3a}} = k_u + k_{OH}[OH^-] + \Sigma k_B[B] + \Sigma k_A[HA] + \Sigma k_{OH,B}[OH^-][B] + \Sigma k_{OH,A}[OH^-][HA] + \Sigma k_{A,B}[HA][B] \quad (4)$$

By applying eqs 2 and 4, information about the nature of the catalysis can be obtained.

(1) Acid Catalysis. The most interesting aspect of the work herein is represented by the occurrence of acid catalysis, i.e. "by the first kinetic evidence of acid catalysis in a ring-to-ring interconversion". Moreover, an examination of the left side of Figure 2 shows that the reactivity tends to a limiting rate constant. This fact suggests a specific-acid-catalyzed mechanism according to eqs 5 and 6.

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

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

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

$$(k_{A,R})_{\mathbf{3a}} = k_u + Kk_H[H_3O^+]/[1 + K[H_3O^+]] \quad (7)$$

As a matter of fact, the study of the rearrangement at different temperatures in sodium citrate/citric acid and sodium chloride/hydrochloric acid buffers (data in Table 3;[18] see line *a* on the left side of Figure 3, where the relevant data at 298.15 K are reported), at various buffer concentrations in the 1−6 pS^+ range (where the hydroxide concentration can be neglected) indicates that there is no increase of the $(k_{A,R})_{\mathbf{3a}}$ values with increasing buffer concentration at constant pS^+:[31] thus, only the bimolecular reaction pathway with catalysis by the proton is effective and the absence of any significant contribution by other bimolecular or termolecular pathways confirms the occurrence of specific-acid catalysis.[31]

By fitting the data of Table 3[18] to eq 7 (in the pS^+ range 0.1−2.5$_5$; *r* 0.9999, *n* 23) $(1.58 \pm 0.01) \times 10^{-4}$ s^{-1} and (1.23 ± 0.02) l mol^{-1} are calculated for k_H (equation 6, the limiting rate constant for the acid-catalyzed rearrangement of **3a**) and *K* (the equilibrium constant of eq 5), respectively. It must be remarked that the *K* value herein is in line with previsions based on the basicity of aminoazoles of similar structure.[19,20b]

The value calculated for k_u $(0.03 \pm 0.20) \times 10^{-6}$ is clearly not significant, an outcome that can be easily understood considering that it represents the small intercept of the regression analysis for a two-parameter equation and is then affected by a large inherent uncertainty.[32] Thus, the average value (0.60×10^{-6} s^{-1} at 293.15 K), measured in the pS^+ independent region, is certainly more reliable.

(2) Base Catalysis. The results obtained by studying the base catalysis in the rearrangements of the *Z*-phenylhydrazone **2a** (X = C_6H_5)[1c] and of the *Z*-dinitrophenylhydrazone **3b**[1d] suggest the occurrence of a general-base catalysis. As a matter of fact, the study of the rearrangement at 298.15 K in sodium borate−boric acid buffers (data in Table 4;[18] see the lines on the right side

(30) (a) Laidler, K. J. *Chemical Kinetics*; McGraw-Hill: London, 1965; pp 450−463. (b) Hammett, L. P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970; Chapter 10. (c) Laidler, K. J.; Bunting, P. S. *The Chemical Kinetics of Enzyme Action*; Clarendon Press: Oxford, 1973: pp 60−62. (d) Ritchie, C. D. *Physical Organic Chemistry, The Fundamental Concepts*; M. Dekker: New York, 1975, chapter 7. (e) Exner, O. *Correlation Analysis of Chemical Data*; Plenum Press: New York and London, 1988, chapter 7.4. (f) Williams, A. *Concerted Organic and Bio-organic Mechanisms*; CRC Press: Boca Baton, FL, 2000. (g) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*; Kluwer Academic/Plenum Publishers: New York, 2000; Chapter 4.8.

(31) This outcome fits Hammett's criterion[30b] for the identification of the kind of catalysis (specific or general).

(32) The same statistical situation had been observed by studying the base catalysis for the rearrangement of the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole.[1c]

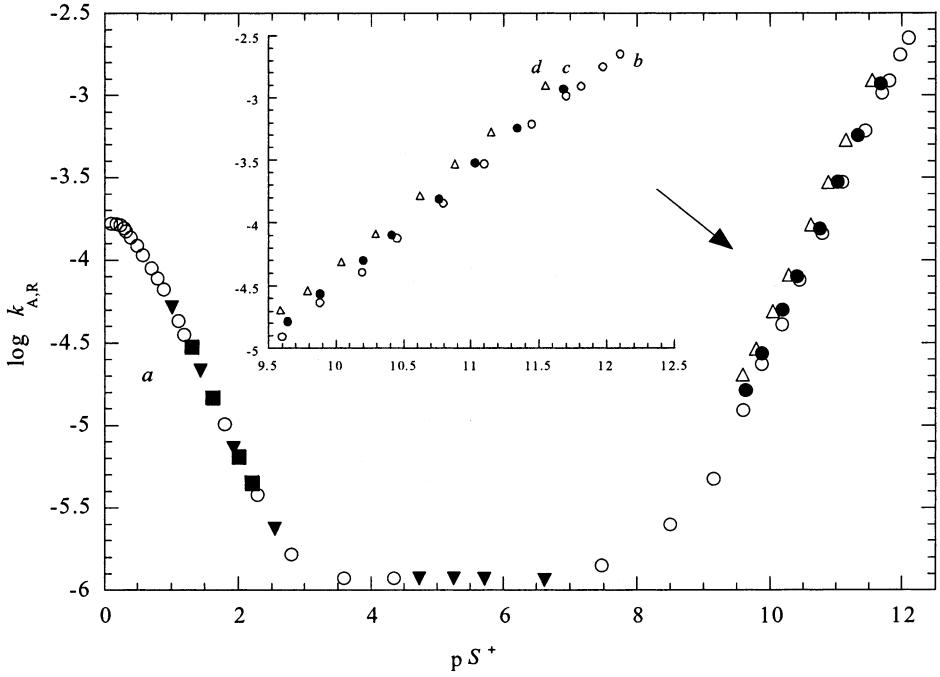


FIGURE 3. Plot of $\log(k_{A,R})_{\mathbf{3a}}$ vs pS^+ for the rearrangement of **3a** into **6a** at 298.15 K in dioxane/water at various buffer concentrations: ○ (NaCl/HCl, sodium citrate/citric acid or sodium borate/boric acid) [buffer] = 0.0125 M; ▼ (sodium citrate/citric acid) and ● (sodium borate/boric acid) [buffer] = 0.0250 M; ■ (sodium citrate/citric acid) and △ (sodium borate/boric acid) [buffer] = 0.0500 M. An enlargement of the pS^+ scale (9.5−12.5) is shown.

TABLE 5. Multiple Linear Regression Analysis of Kinetic Data According to eq 4 at 298.15 K

$10^5 k_u$ (s^{-1})	$k_{OH} \pm s_{k_{OH}}$ (1 mol^{-1} s^{-1})	$k_B \pm s_{k_B}$ (1 mol^{-1} s^{-1})	$k_A \pm s_{k_A}$ (1 mol^{-1} s^{-1})	$k_{A,B} \pm s_{k_{A,B}}$ (1^2 mol^{-2} s^{-1})	$k_{B,OH} \pm s_{k_{B,OH}}$ (1^2 mol^{-2} s^{-1})	R
−1.0 ± 0.8	5.67 ± 0.07	0.021 ± 0.001	0	0	0	0.999
0.3 ± 0.8	5.1 ± 0.2	0.018 ± 0.001	0	0	63 ± 19	0.999
−0.8 ± 0.5	5.37 ± 0.7	0.03 ± 0.002	0	−0.31 ± 0.06	0	0.999

[a] $s_{k_{OH}}$, s_{k_B}, s_{k_A}, $s_{k_{A,B}}$, and $s_{k_{B,OH}}$, standard deviation 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 throughout.

of Figure 3), at various buffer concentrations in the 9.2−12.1 pS^+ range indicates an increase of the $(k_{A,R})_{\mathbf{3a}}$ with increasing buffer concentration at constant pS^+.[31] The experimental rate constants at 298.15 K well fit eq 4, indicating significant values (see Table 5[18]) only for the bimolecular reaction pathways with catalysis by hydroxide ion (k_{OH} 5.67 ± 0.07 l mol^{-1} s^{-1}) and by the basic component of the buffer (borate ion, k_B 0.021 ± 0.001 l mol^{-1} s^{-1}), excluding any significant contribution by other bimolecular or termolecular pathways, thus recalling previously observed behaviors[1c,d] and confirming the occurrence of a simple general-base catalysis.

Also in this case, the k_u value is affected by a large inherent uncertainty and is therefore devoid of any physical meaning [(−1.0 ± 0.8) × 10^{-5} s^{-1}].

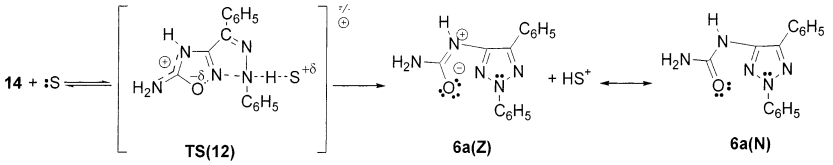
Reactivity Comparison between the *Z*-Arylhydrazones 3a, 2a (X = C_6H_5) and 3b. A comparison with our previous data[1c,d] can now be drawn, remembering that in this rearrangement (an S_{Ni} process, hence an S_N2-like reaction) the reactivity depends on such factors as (a) the nucleophilicity of the attacking center (the −NH− group of the phenylhydrazono moiety); (b) the electrophilicity of the attacked center [N(2) of the 1,2,4-oxadiazole ring]; and (c) the leaving group ability [the nucleofugacity of O(1) of the 1,2,4-oxadiazole ring]. Together with the different stability of the starting and the final compounds (see above), these factors determine both the thermodynamic and the kinetic aspects of the process.

Comparison between 2a and 3a. In these two substrates, the nucleophilic center (that is the −NH− group of the phenylhydrazono moiety) is the same, while the ring to be cleaved contains two different substituents at C(5): a phenyl and an amino group, respectively [which by chance have similar inductive substituent constants: $(\sigma_I)_{C6H5}$ 0.12, $(\sigma_I)_{NH2}$ 0.17].[33] As expected on the basis of the similar apparent first-order rate constants [at 298.15 K, $(k_{A,R})_{\mathbf{3a}}/(k_{A,R})_{\mathbf{2a}}$ 4.5 and 1.6 in the base-catalyzed and in the uncatalyzed ranges have been calculated] and thermodynamic parameters observed, likewise similar contributions of the base(hydroxide and borate)-catalyzed pathways have been determined [at 298.15 K: $(k_{OH})_{\mathbf{3a}}/(k_{OH})_{\mathbf{2a}}$ and $(k_B)_{\mathbf{3a}}/(k_B)_{\mathbf{2a}}$ 1.5 and 2.1]. The comparison between $(k_u)_{\mathbf{3a}}$ and $(k_u)_{\mathbf{2a}}$ indicates in turn a similar contribution for the uncatalyzed pathway [at 293.15 and 298.15: $(k_u)_{\mathbf{3a}}/(k_u)_{\mathbf{2a}}$ 4.5 and 4.1].

The observed higher reactivity of **3a** with respect to **2a**[1c,22] in both the uncatalyzed and the base-catalyzed region derives from a balance between factors that differently affect the catalyzed and uncatalyzed pathways as a function of the position of the transition state along

(33) Data from ref 30e, p 143.

SCHEME 6



the relevant reaction coordinates: (1) the "diaryloid effect",[22,34] a stabilizing effect observed when an aromatic ring (herein, the 5-phenyl substituent in **2a**) is linked to the starting heterocycle, which lowers the reactivity of **2a**; (2) the "specific" effect of the 5-amino substituent which causes two opposite effects, weakening the O(1)−N(2) bond (thus favoring the S_{Ni} process), but increasing the charge density on N(2) (thus reducing its electrophilicity and disfavoring the S_{Ni} process).

Comparison between 3a and 3b.[1d] In these two substrates, the starting ring is the same while the nucleophilic centers (that is the −NH− group of the phenylhydrazono and of the 2,4-dinitrophenylhydrazono moieties) are predicted to have, by themselves, very different nucleophilicities (which do affect the uncatalyzed pathway) as well as very different acidities (which do affect the base-catalyzed pathways). Thus, in the base-catalyzed region the *Z*-2,4-dinitrophenylhydrazone **3b** rearranges[1d] faster than the *Z*-phenylhydrazone **3a** [e.g., $(k_{A,R})_{\mathbf{3b}}/(k_{A,R})_{\mathbf{3a}}$ 82 at pS^+ 10.79]; in contrast, due to a crossing at pS^+ ca. 6.4, **3a** becomes more reactive at lower pS^+ values [e.g., $(k_{A,R})_{\mathbf{3b}}/(k_{A,R})_{\mathbf{3a}}$ ca. 1.5×10^{-2} at pS^+ 4.52]. As a consequence, in the case of **3a** we have pointed out a significant contribution of the uncatalyzed reaction pathway, while in the case of **3b** from the application of eq 4 we have collected[1d] only doubtful hints for the occurrence of an uncatalyzed pathway.

General Comments on the Nature of the Catalytic Pathways. Why is there an occurrence of specific-acid catalysis and, in contrast, of general-base catalysis in the rearrangement of **3a**?

As pointed out by several authors,[30,31] the occurrence of specific or general catalysis is in agreement with the formation of an Arrhenius or of a Van't Hoff complex, respectively. It means that in the first case an acid−base equilibrium really exists, and the reaction occurs through the fast formation of an intermediate that slowly rearranges. In the second case the initial acid−base equilibrium is strongly shifted toward the starting reagents and the rearrangement occurs in a single step assisted by the catalyst, where old and new bonds are broken and formed, respectively.

In the specific-acid-catalyzed range (pS^+ 0.1−3.5), the data are well in agreement with a preequilibrium protonation at N(4) of the 1,2,4-oxadiazole ring, leading to an intermediate (**14**) which undergoes a concerted S_N2-like reaction thanks to the presence of a "particularly effective" leaving group. The favorable effect played by the formation of the Arrhenius complex **14** and, thus, the meaning attached to the expression "particularly effective" are better understood when considering the rearrangement pathways of compounds **1**−**3** in the base-catalyzed and in the uncatalyzed regions (see Scheme 3). Under such conditions, the leaving group is a resonance-stabilized anion, with the negative charge delocalized on the oxygen as well as on the nitrogen atoms [O(1) and N(4) of the starting 1,2,4-oxadiazole ring, respectively]. For the rearrangement of **3a** in the acid-catalyzed range, we can observe that the leaving group, by way of **protonation at N(4)**, is now a "neutral" leaving group [again resonance-stabilized: **6a**(**Z**) ↔ **6a**(**N**), Scheme 6], i.e. the conjugated acid of the $\mathbf{6}^-$ anion (see Scheme 3): it must be, therefore, a much better (a "particularly effective") leaving group.

Another important factor strongly affects the course of the rearrangement in the acid-catalyzed range. In a S_N2-like process the reactivity depends on the electrophilic character of the reaction center: now it is easily foreseeable that the protonation of the starting substrate shall affect the electronic density on N(2) (the reaction center) largely increasing its electrophilic character. Ab initio calculations (see Table 1[18] and Figure 1) have demonstrated that the charges located on O(1) and N(2) change on going from **9** to **10**, thus suggesting that the formation of the intermediate **14** strongly favors the nucleophilic attack at N(2) and increases the leaving group ability of O(1).[35]

The data in the uncatalyzed and in the general base-catalyzed regions (pS^+ 3.5−14.9) agree with a different course of the reaction, that is the formation of a transition state (a Van't Hoff complex) where all bond-breaking and -forming processes occur concertedly as foreseen for a solvent- or base-assisted S_N2-like reaction (see Scheme 3), the energy necessary for bond cleavage being supplied by the simultaneous formation of the new bonds. In this pathway, the very low acidic character of the proton of the phenylhydrazono moiety makes meaningless its base-assisted preliminary detachment.

In the whole pS^+ range studied, the higher thermodynamic stability of the final product with respect to the substrate plays an important role.[1−9,12,13] Ab initio calculations have largely confirmed the previsions we have recently made considering the different stability of starting (1,2,4-oxadiazole) and final (2*H*-1,2,3-triazole) ring[1d] and the additional influence of the resonance stabilization of the side-chain in the final product:[2a,13] as a matter of fact a ΔE of 125.6 kJ mol^{-1} between **3a** and **6a** has been calculated.

Conclusion

The kinetic study of the rearrangement of the *Z*-phenylhydrazone of 5-amino-3-benzoyl-1,2,4-oxadiazole

(34) Vivona, N.; Cusmano, G.; Ruccia, M.; Spinelli, D. *J. Heterocycl. Chem.* **1975**, *12*, 985−988.

(35) A comparison between the reactivity of **3a** in the acid-catalyzed and in the uncatalyzed regions appears very interesting. As a matter of fact the apparent kinetic constants at 293.15 K increase from 6.0×10^{-7} s^{-1} (in the 3.6−6.2 pS^+ range) to 1.0×10^{-4} s^{-1} (at pS^+ 0.1). The nucleofugacity increase of O(1) and the higher electrophilicity of N(2), both determined by the protonation of the substrate, cause a large increase in the reactivity (rate ratio 1.67×10^2).

3a in a large (0.1−14.9) pS^+ range in dioxane/water has evidenced a complex, pS^+-dependent, reactivity pattern: the occurrence of three different regions of reactivity makes such a rearrangement an interesting example of the most general and complete case of proton-concentration-dependent catalysis. Specific-acid catalysis and general-base catalysis have been ascertained in the 0.1−3.5 and 8.0−14.9 pS^+ regions, respectively, while an uncatalyzed pathway predominates in the intermediate (3.5−8.0) pS^+ region. In the latter region, the reaction only advantages from solvent assistance: both dioxane and water, because of their significant donicity and permittivity,[36] are able to do it. As a matter of fact we have observed that the k_u values of **2a** (X = C_6H_5) and of **3a** shift to zero[27,37] in solvents (such as benzene or toluene) with unfavorable characteristics:[36] therefore no spontaneous reaction occurs, as indicated also by the fact that, in the solid state, both **2a** and **3a** are stable for long time.

The reasons for the dependence of the reaction course on pS^+ have been deeply discussed[1] and both the starting points and the conclusions have received solid support from ab initio calculations.

The occurrence of both acid- and base-catalysis (herein besides an uncatalyzed pathway) in the reactions of simple organic systems is not a common pattern: it requires particular structural constraints (presence of basic and acidic centers, appropriate alignments between the interacting functional groups, and so on). Conversely, it can easily happen in complex systems, such as enzymes, where the contemporary presence of many active catalytic sites (acidic as well as basic) favors this opportunity causing large rate enhancements.[30,38]

Interestingly, in this study we have found the first kinetic evidence of acid-catalysis in a mononuclear heterocyclic rearrangement.

Actually, some experimental evidence in favor of acid catalysis has been already reported and/or proposed for ring-opening reactions: e.g., Crow and Gosney[39] pointed out that the nucleophilic attack of cyanide ion on 3-hydroxyisothiazole, at p*H* lower than 3.50, occurs via a fast attack by cyanide onto the conjugate acid of the substrate; moreover Tsolomitis and Sandris,[40] in an attempt to prepare ketone derivatives (such as oximes or arylhydrazones) of 2-substituted-5-aryl-3(2*H*)-isothiazolones, evidenced the formation of some unexpected 1,2,5-oxathiazoles and 1,2,3-thiadiazoles with excellent yields (>90%) in the presence of acids assuming that the reaction occurs through an intramolecular nucleophilic attack onto the sulfur atom (that is a S_{Ni} reaction) once more again with cleavage of the S−N bond on the conjugate acids of the starting isothiazolones.

In the two examples above, though, a nucleophilic attack on a sulfur atom with cleavage of a S−N bond occurs: a situation which is quite different from the classical azole-to-azole rearrangements, where the nucleophile attacks a nitrogen atom with cleavage of a N−O bond (see Scheme 2).[2a−c]

Looking at the literature, one can perhaps recognize a situation similar to that herein, at least regarding the occurrence of acid-catalysis, in an interesting paper by Ronsisvalle, Guerrera, and Siracusa.[41] They synthesized the oximes of some 3-phenacyl-1,2,4-oxadiazoles, but their "attempts to obtain phenacyl derivatives, failed. 1,2,4-Oxadiazoles underwent ready rearrangement to isoxazoles by refluxing in ethanol containing small amounts of concentrated hydrochloric acid." The AA explained the course of the reaction suggesting the formation of open-chain species as intermediates. In a recent review, some of us[1b] proposed that the reaction could involve the hydrolysis of the oximes into the relevant 3-phenacyl-1,2,4-oxadiazoles "which in turn would undergo an acid-induced rearrangement into the 3-acylaminoisoxazoles via the enolic side-chain reacting on the protonated oxadiazole". Therefore this paper could perhaps offer the first "qualitative indication" for an acid catalysis in a ring-to-ring interconversion, although the relatively small acid concentration used and the low basic character of 1,2,4-oxadiazole derivatives would rather induce us to exclude the protonation of 1,2,4-oxadiazole in favor of a "direct" 1,2,4-oxadiazole → isoxazole rearrangement of the enol (whose formation is possibly acid-catalyzed).

Now, by means of an exhaustive kinetic study, we offer the first "quantitative proof" of the occurrence of acid catalysis in a MRH (a Boulton−Katritzky reaction)[2a−c] concerning an azole-to-azole rearrangement, clearly recognizing the structural conditions that make this kind of catalysis possible.

After all, we are confident that the present results will disclose new and, in some way, unexpected routes to the azole-to-azole interconversions, making "possible" reactions otherwise "impossible".

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded in the Fourier transform mode at 21.0 ± 0.5 °C in DMSO-d_6. Chemical shifts (δ) are in ppm from tetramethylsilane; coupling constants are in Hz. Mass spectra were recorded at chemical ionization (CI).

(*Z*)-(5-Amino-1,2,4-oxadiazol-3-yl)(phenyl)methanone *N*-Phenylhydrazone (3a). A solution of phenylhydrazine (1.3 g, 12 mmol) in absolute ethanol (4 mL) was added dropwise under stirring to a solution of 5-amino-3-benzoyl-1,2,4-oxadiazole (0.76 g, 4 mmol) in the same solvent (80 mL). After standing for 24 h at room temperature in the dark, the orange solution was evaporated. The crude material (three spots by TLC) was flash chromatographed (alumina, ethyl acetate/petroleum ether 40−60 °C = 1:2, v/v) obtaining, in order of elution, the following pure compounds. ***Z*-3a**. R_f = 0.64, 0.37 g, 11%. Mp: 163 °C. NMR δ_H: 11.02 (s, exch, 1H); 8.25 (s, exch, 2H); 7.76 (pd, 2H); 7.74−7.24 (m, 7H); 6.90 (pt, 1H). MS *m*/*z*: 279 (M^+, 1); 262 (100); 236 (11); 91 (87); 77 (46); 64 (21); 51 (30). UV−vis spectrum: in dioxane/water 1:1 (v/v) λ_{max} 357 nm, log ϵ_{max} 4.26. Anal. Calcd for $C_{15}H_{13}N_5O$: C, 64.5; H, 4.7; N, 25.1. Found: C, 64.7; H, 4.6; N, 25.2. ***E*-3a**. R_f = 0.24, 0.13 g, 12%. NMR δ_H: 9.50 (s, exch, 1H); 7.82 (s, exch, 2H); 7.56−7.48 (m, 3H); 7.40−7.38 (m, 2H); 7.27−7.18 (m, 4H); 6.82 (pt, 1H). Anal. Calcd for $C_{15}H_{13}N_5O$: C, 64.5; H, 4.7; N, 25.1.

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(37) Spinelli, D.; Frenna, V. et al. Unpublished results.
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(39) Crow, W. D.; Gosney, I. *Aust. J. Chem.* **1967**, *20*, 2729−2736.
(40) Tsolomitis, A.; Sandris, C. *J. Heterocycl. Chem.* **1984**, *21*, 1679−1683.
(41) Ronsisvalle, G.; Guerrera, F.; Siracusa, M. A. *Tetrahedron* **1981**, *37*, 1415−1420.

Found: C, 64.8; H, 4.8; N, 25.3. Finally, we recovered a product identified as the *N*,5-diphenyl-2*H*-1,2,3-triazol-4-ylurea **6a** (R_f = 0.04, 0.10 g, 9%, mp 185 °C, see below).

***N*,5-Diphenyl-2*H*-1,2,3-triazol-4-ylurea (6a).** A suspension of ***Z*-3a** (0.28 g, 1 mmol) in 5% NaOH (30 mL) was kept, under stirring, at room temperature for 24 h. Then the yellowish precipitate was collected by filtration to give a compound identical (mixed mp, ^{1}H and ^{13}C NMR spectra) with the material reported above and identified as **6a** (0.22 g, 79%, mp 185 °C). NMR δ_H: 8.47 (s, exch, 1H); 8.00 (pd, 2H); 7.87 (pd, 2H); 7.61−7.39 (m, 6H); 6.18 (s, exch, 2H); δ_C 156.22; 142.41; 142.01; 138.94; 129.54; 129.40; 128.51; 128.49; 127.33; 126.54; 117.79. MS *m*/*z* 279 (M^+, 55); 262 ($M^+ - 17$, 45); 236 (99); 131 (12); 104 (13); 91 (100); 77 (45); 64 (18); 51 (18). HRMS: 279.11299, $C_{15}H_{13}N_5O$ requires 279.10933. UV−vis spectrum: in dioxane/water 1:1 (v:v) λ_{max} 296 nm, log ϵ_{max} 4.32.

Computational Details. All the DFT computations reported here have been performed with the Gaussian 98[17] series of programs using the nonlocal hybrid Becke's three-parameter exchange functional denoted as B3LYP.[17] The various molecular structures have been fully optimized with the gradient method available in Gaussian 98 using the DZVP basis set,[17b] which is a local spin density (LSD)-optimized basis set of double-ζ quality in the valence shell plus polarization functions. In all cases, a computation of the harmonic vibrational frequencies has been carried out to verify that the optimized structures are minima of the potential surface.

Further computational details including Cartesian coordinates and computed total energies of optimized structures are reported in Table 6 in the Supporting Information.

pS^+ Scale Definition and Kinetic Measurements. Water and dioxane were purified according to literature methods.[42] Details on the pS^+ scale have already been reported.[14,22] The kinetics were followed spectrophotometrically as previously described[22] by measuring the disappearance of **3a** at 362 nm (where the observed optical-density differences between starting and final products is largest) by using a UV−vis spectrophotometer (pS^+ 0.1−12.1) or a Varian Cary 1E equipped with the rapid kinetic accessory SFA-11 (pS^+ 12.2_5−14.9). The rate constants are accurate within ± 3%. Apparent first-order kinetic constants [$(k_{A,R})_{\mathbf{3a}}$], directly measured or calculated at 293.15 K, are reported in Table 2. The concentrations used were about 7.5×10^{-5} M.

The values of $(k_{A,R})_{\mathbf{3a}}$ for general-base catalysis determination have been calculated at 298.15 K from thermodynamic parameters in the pS^+ range 9.2−12.1 (Table 3) and managed as previously described.[1c]

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Supporting Information Available: Complete kinetic data and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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