RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Journal Name

RSCPublishing

ARTICLE

Site activation effects promoted by intramolecular Hydrogen Bond interactions in S_NAr reactions.

Cite this: DOI: 10.1039/xoxxoooooox

Sebastián Gallardo-Fuentes[1*], Ricardo A. Tapia[2], Renato Contreras[1] and Paola R. Campodónico[3*]

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

Nucleophilic aromatic substitution reaction of benzohydrazide derivatives towards 2-chloro-5-nitropyrimidine is used as model system to experimentally and theoretically show that intramolecular hydrogen-bond formation operates as a perturbation that elicit a dual response at the reaction center of the transition state (TS) structure, by enhancing the electrophilicity of the pyrimidine moiety and the nucleophilicity of the nitrogen atom of benzohydrazide fragment. The electronic mechanism can therefore be described as a (non-local) site activation problem.

Introduction

The effect of hydrogen bonding (HB) in nucleophilic aromatic substitution reactions (S_NAr) has been discussed in literature both experimentally and theoretically.[1-6] The origins of the HB effects are proposed to appear when the attacking amine interacts with the *o*-nitro substituent of the aromatic moiety of the substrate. The resulting HB complexes at the transition state (TS) structures of the reaction produce a significant energy barrier lowering when the orientation of the hydrogen atom of the nucleophile lies on the same plane of the oxygen atom of the $-NO_2$ group. This effect, which may be at first glance attributed to a particular arrangement of this system, may be present in other S_NAr processes involving reagents that not necessarily bear the $-NO_2$ functionality in their structures.

In this work we provide further experimental and theoretical evidences that point out towards the importance of site activation effects promoted by intramolecular HB effects that may be present in substrates that bear a heteroatom on the aromatic ring instead of a $-NO_2$ group as substituent. The site activation[7-9] mechanism is revealed as a non-local effect involving two regions at the TS associated to the rate determining step, namely a perturbation at the site of HB, and the response at the electrophilic center in the form of electrophilic activation at the substrate and nucleophilic activation at the attacking nucleophile moiety. The model system used is the reaction of 2-chloro-5-nitropyrimidine towards benzohydrazide derivatives. In round words: the effect of the intramolecular HB between the α hydrogen atom of the nucleophile and the nitrogen atom of the pyrimidine moiety, is not only relevant for the stability of the TS structure, but its activating effects at the reaction center are clearly more important.

Results and discussion.

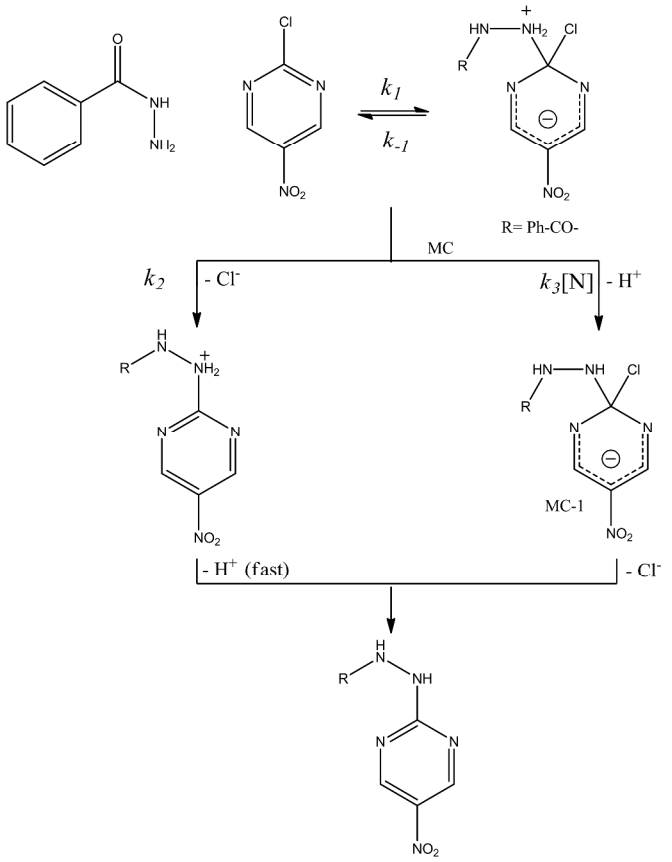
2.1 Kinetic Analysis

Reaction Mechanism: In a typical S_NAr process the first step leads to the formation of a zwitterionic complex named Meisenheimer complex (MC) from which two processes for its decomposition have been postulated:[10, 11] (a) expulsion of the LG followed by fast proton loss to give the reaction product and (b) the base-catalyzed deprotonation of the zwitterionic complex that loss the chlorine atom to give the reaction product as shown Scheme 1.

According to Scheme 1, one can suggest that the reaction proceed through two main intermediates (a zwitterionic adduct MC and its deprotonated form MC-1). The pseudo-first-order rate constant (k_{obs}) for the reactions can be expressed as eq 1, in which [N] represents the concentration of nucleophile (benzohydrazide derivatives).

$$k_{obs} = (k_1k_2[N] + k_1k_3[N]^2)/(k_{-1} + k_2 + k_3[N]) \quad (1)$$

The second-order rate constants (k_N) for the reaction between 2-chloro-5-nitropyrimidine and benzohydrazide derivatives in water have been determined from the slope of the linear plots of k_{obs} *vs.* free benzohydrazide concentration. All the plots are linear with intercept at the origin (Figures S1-S5 in ESI). This outcome strongly suggests that step (b) can safely be discarded and that the contribution of the reaction media may be negligible.[11, 12] Thus, the pseudo-first-order rate constant (k_{obs}) can be expressed as eq 2, where the second-order rate constants (k_N) is determined from the slope of the linear plots.



Scheme 1: Possible reaction mechanism for the reaction between benzohydrazide derivatives and 2-chloro-5-nitropyrimidine

$$k_{obs} = k_N[N], \text{ where } k_N = k_1k_2/(k_{-1} + k_2) \quad (2)$$

Table 1 summarizes the second order rate constants and the pKa values[13] used to derive the Brønsted plot from which the reaction mechanism is deduced. According to the β value 0.52 a stepwise mechanism may be proposed, where the nucleophilic attack is rate determining. Brønsted-type plot for k_N values exhibit good linear correlations and pKa are statistically corrected by using p (numbers of protons which can be deprotonated from the conjugate acid of the amine) and q (numbers of nucleophilic sites of the amine).[14] This material is given as ESI.

Table 1 Second order rate values (k_N) for the reactions of the benzohydrazide derivatives with 2-chloro-5-nitropyrimidine in water, at 25.0 ºC, ionic strength 0.2 M (KCl).

Benzohydrazide derivatives	pK_a	$k_N/(s^{-1}\ M^{-1})$
4-methoxybenzohydrazide	3.46	0.127
4-methylbenzohydrazide	3.30	0.115
benzohydrazide	3.00	0.069
4-chlorobenzohydrazide	2.80	0.054
4-(trifluoromethyl)benzohydrazide	2.70	0.056

Evidences for intramolecular HB: We further performed the kinetic analysis of the reaction of 1-chloro-2,4-dinitrobenzene towards 4-methoxybenzohydrazide under the same experimental conditions, in order to compare the role of the intramolecular HB. No significant amount of products was detected after five hours. This result indicates that even though there may be an stabilizing HB effect promoted by HB between the -NO_2 group of 1-chloro-2,4-dinitrobenzene and the alpha hydrogen atom of the nucleophile, the electrophilic center is not sufficiently activated at the TS stage of the reaction, as illustrated in Figure 1. This effect will be further discussed using theoretical arguments below.

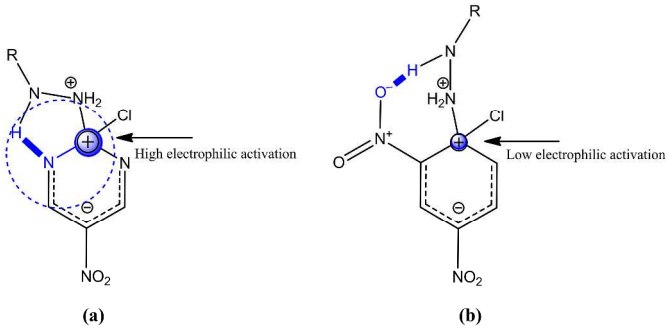


Figure 1. Possible hydrogen bond interactions at the TS structure.

2.2 Theoretical Study

Local and global reactivity analysis: In order to quantitatively evaluate the electrophilic character of pyrimidine and 2,4-dinitrobenzene moiety, the global and local electrophilicity indexes were evaluated. Moreover, the local nucleophilicty index has been calculated in order to evaluate the regional nucleophilicity at the nucleophilic center in benzohydrazide moiety. The expressions for these reactivity indexes are as follows:[15, 16]

$$\omega^+_{(k)} = \omega^+ f_k^+ \ ; \omega^+ = \frac{\mu^2}{2\eta} \quad (2a)$$

and

$$\omega^-_{(k)} = \omega^- f_k^- \ ; \ \omega^- = -I \cong \epsilon_{HOMO} \ (2b)$$

The global electrophilicity index[17] is expressed in terms of the electronic chemical potential (μ, the negative of electronegativity) and the chemical hardness (η) which may be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO.[18] The global nucleophilicity may readily be obtained as the negative of the vertical ionization potential.[16] The regional quantities are projected onto atoms or groups by using the appropriate electrophilic and nucleophilic Fukui functions using a method described elsewhere.[19, 20]

The results show that in the ground-state, benzohydrazide derivatives display a poor nucleophilic character at the reaction

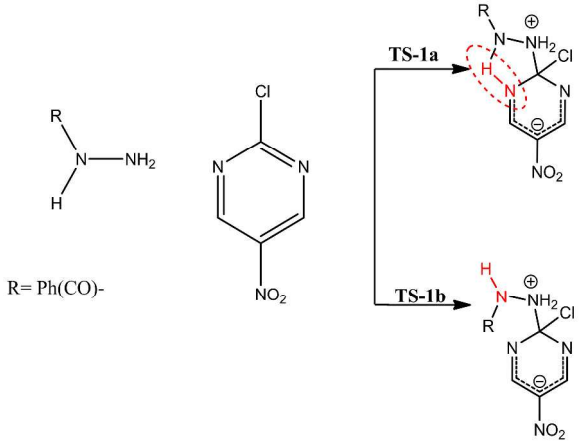
center ($\omega_N^- = 0.04$e.V). Furthermore, the electrophilicity in both aromatic rings display similar values ($\omega_{Pyr}^+ = 1.20$e.V; $\omega_{2,4DNB}^+ = 1.25$ e.V). These results highlight the key role of specific interaction at the TS stage that provides a key piece of information to explain the kinetics of this reaction.

Potential energy surface (PES) analysis: In order to further understand the effects of the intramolecular HB on the reaction mechanism, a full exploration of the PES was performed at the M05-2X/6-31G(d,p) level of theory.[21, 22] The first task is to obtain the reaction profile in the reference gas phase, to introduce explicit solvation effects afterwards. Gas phase calculations provide an energy profile consistent with a stepwise route, but with the detachment of the nucleofuge as the rate determining step (see Table 2). In order to obtain reliable stationary points in solution, we relied on continuum dielectric models that could help stabilizing these ionic structures. A PCM[23] correction was added to the reference gas phase calculation, and the results shown in Table 2 were obtained. Note that the relative energy profile with PCM corrections is now consistent with the recorded kinetic data.

Table 2: Relative energies (kcal/mol) for the stationary points of the reactions between 2-chloro-5-nitropyrimidine and benzohydrazide at M05-2X/6-31G(d,p) level of theory.

Structures	$\Delta E^{\neq}(gas)$	$\Delta E^{\neq}(water)$
Reactants	0.0	0.0
TS-1	18.0	14.9
MC	12.0	6.9
TS-LG	21.1	10.2
Products	-11.5	-13.5

In order to understand the effect of intramolecular HB in the rate determining TS1 structure, two transition states were explored, according to Scheme 2:



Scheme 2: Possible transition state structures for the reaction between benzohydrazide and 2-chloro-5-nitropyrimidine.

The differences in activation energy obtained for both of the possible reactions paths highlights the key role of the intramolecular HB. The TS structure in the mode **TS-1b** in Scheme 2 that does not involve intramolecular HB is 5.2 kcal/mol higher in energy.

We further explored the PES in search of TS structures for the reaction of benzohydrazide and 2,4-dinitro-chlorobenzene (**TS-2** in Figure 2). Note that, at the TS, the α-hydrogen of benzohydrazide establishes a HB interaction with -NO_2 group of 2,4-dinitro-chlorobenzene. However, the activation energy is 10.4 kcal/mol greater than that corresponding to the reaction between benzohydrazide and 2-cloro-5-nitropyrimidine; a result in line with the recorded kinetic data. This result suggests that the electronic activating effect promoted by HB effects at the reaction center becomes more important than energy stabilization of the TS structure.

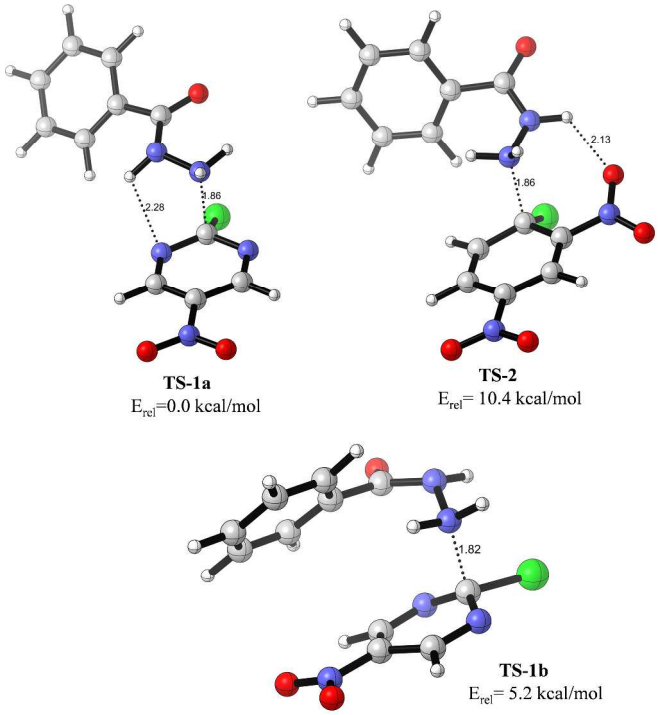


Figure 2: Transition state structures and relative energies calculated at the M05-2X/6-31G(d,p) level of theory. Distances are in Å.

Electrophilic activation at the TS structures brought about by HB interaction: In order to understand the activating effects of HB and the nature of the specific interactions at the TS structures we further analyzed the intramolecular HB effect, within the framework of the NBO[24] procedure. The NBO second-order perturbation energies of interaction are calculated as:

$$E^{(2)} = \Delta E_{ij} = q_i \frac{F_{ij}^2}{\varepsilon_i - \varepsilon_j} \qquad (1)$$

where q_i is the *ith* donor orbital occupancy, ε_i and ε_j are diagonal elements (orbital energies) and F_{ij} are the off diagonal elements

of the Fock matrix, respectively. ΔE_{ij} measures the strength of the donor-acceptor interaction between orbitals φ_j and φ_i. This analysis has been suggested to be well suited for examining HB interactions in S_NAr reactions.[6] The NBO analysis for **TS-1a** in Scheme 2 reveals a weak HB interaction between α-hydrogen of benzohydrazide and nitrogen atom of pyrimidine moiety with a second-order perturbation energy of 5.3 kcal/mol ($n_N \rightarrow \sigma^*_{N-H}$). Similar results were obtained for **TS-2** in Figure 2: the $n_O \rightarrow \sigma^*_{N-H}$ interaction is only 0.8 kcal/mol lowest than that established in **TS-1a**.

On the other hand, in order to evaluate activating effects promoted by HB at the reaction center, local electrophilicity were evaluated at the ipso carbon of pyrimidine moiety at the TS stage. The results show that the pyrimidine moiety is more electrophilic in **TS-1a** than in **TS-1b**. On the other hand, nucleophilic activation at the nitrogen atom of benzohydrazide moiety of **TS-1a** is approximately twice larger than in **TS-2**. These results are summarized in Table 2.

Table 3: Global and local contributions to the nucleophilic and electrophilic activation in the transition state stage. All values are in e.V. Values in parentheses are referred to ipso carbon atom.

Structure	ω^+	ω^-	site *(k)*	ω_k^-	ω_k^+
Benzohydrazide	0.40	-9.23	N_1	0.04	0.00
Pyrimidine	1.20	-11.34	C_1(ipso)	-1.32	0.23
DNCB	1.25	-10.83	C_1(ipso)	-1.21	0.26
TS-1a	0.64	-9.35	N_1	-1.06	0.02
			Pyrimidine moiety	-0.44	0.53 (0.08)
TS-1b	0.63	-9.33	N_1	-1.01	0.02
			Pyrimidine moiety	-0.45	0.51 (0.07)
TS-2	0.73	-8.78	N_1	-0.68	0.00
			Ring	-6.15	0.39 (0.02)

These results show that the preference for establishing an intramolecular HB between benzohydrazides derivatives and 2-chloro-5-nitropyrimidine at the TS stage of the reaction results in a simultaneous nucleophilic activation of benzohydrazide and an electrophilic activation of the pyrimidine moieties, respectively. This result also confirms the hypothesis previously advanced on the basis of the comparison with the reaction of 1-chloro-2,4-dinitrobenzene towards 4-methoxybenzohydrazide under the same experimental conditions. The lower energy of **TS-1a** relative to **TS-2** appears as the response to the ability of the benzohidrazide derivatives to withdraw a fraction of electron density from the electrophilic site by intramolecular HB to the nitrogen of pyrimidine.

Finally, we explored the possible rate determining TS for the reaction between benzohydrazide and 2-chloro-5-nitropyrimidine including an explicit water molecule, in order to evaluate competitive HB interaction between water and pyrimidine moiety. Two possible TS structures are possible. The first one involves an intramolecular HB between α-hydrogen of benzohydrazide and pyrimidine moiety (**TS-1wHB** in Figure 3). A second scenario involves intermolecular HB between a hydrogen atom of the water molecule and the nitrogen atom of pyrimidine (**TS-1nHB** in Figure 3).

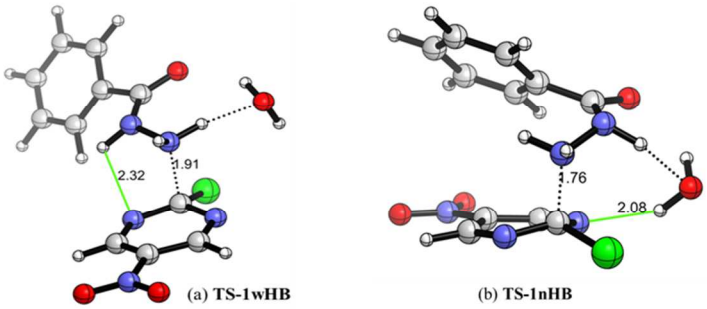


Figure 3. Transition state structures calculated at the M05-2X/6-31G(d,p) level of theory. Distances are in Å. (a) (**TS-1wHB**); (b) (**TS-1nHB**)

The results obtained indicate that, even in water, there is a preference towards the TS structure that involves an intramolecular HB. The transition state **TS-1wHB** with the intramolecular HB between α-hydrogen of the alpha-nucleophile and pyrimidine is 3.0 kcal/mol lower in energy than transition state **TS-1nHB**. The differences in activation energies obtained for both of the possible reactions paths show that the interaction by HB established between nucleophile/pyrimidine outweighs that obtained for water/pyrimidine.

Finally, the electrophilic activation pattern at the TS shows that pyrimidine moiety is more electrophilic in **TS-1wHB** than in **TS-1nHB** (0.49 e.V and 0.16 e.V respectively). In summary, in this study we have demonstrated that the reactivity of some alpha-nucleophiles in S_NAr reactions towards heteroaromatic rings is modulated by intramolecular HB at the TS of the rate determining step. This interaction allows a simultaneous nucleophilic activation of benzohydrazide and an electrophilic activation of the pyrimidine moieties, respectively.

Conclusions

In this work we have illustrated both experimental and theoretically the importance of site activation effects promoted by intramolecular HB effects that may be present in substrates that bear a heteroatom on the aromatic ring instead of a $-NO_2$ group as substituent. The site activation mechanism is revealed as a non-local effect involving two regions at the TS associated to the rate determining step, namely a perturbation at the site of HB, and the response at the electrophilic center in the form of electrophilic

activation at the substrate and nucleophilic activation at the attacking nucleophile moiety.

The theoretical analysis reveals that the TS more energetically favored involve an intramolecular HB. This interaction entails: (i) a favorable donor/acceptor interaction established between the lone pair at the nitrogen atom of pyrimidine moiety and the α-hydrogen of the nucleophile and (ii) electrophilic activation at the ipso-carbon of pyrimidine moiety and nucleophilic activation at the nitrogen atom in the benzohydrazide moiety.

Experimental

Materials.

Substrates and nucleophiles were of the highest quality available as commercial products by Sigma-Aldrich.

Synthesis of 4-methoxy-*N´*-(5-nitropyrimidin-2-yl) benzohydrazide.

To a stirred solution of 4-methoxybenzhydrazide (91.4 mg, 0.55 mmol) in THF (15 mL) containing potassium carbonate (76 mg, 0.55 mmol) was added 2-chloro-5-nitropyrimidine (79.8 mg, 0.5 mmol) disolved in THF (5.0 mL). The reaction mixture was stirred for 24 hours at room temperature, filtered and concentratated in vacuo. Purification by flash chromatography (ethyl acetate/hexane 1:2) gave of 4-methoxy-*N*-(5-nitropyrimidin-2-yl)benzohydrazide (97 mg, 67%), mp 252-253 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6) d : 3.87 (s, 3H), 6.96 (d, J = 8.7 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H), 9.10 (s, 1H), 9.12 (s, 1H), 10.4 (s, 1H), 10.5 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) d : 55.4, 114.2 (2C), 124.7, 129.9 (2C), 135.7, 155.6, 155.8, 162.3, 164.6, 165.6; FT-IR (KBr) 3270, 3108, 1626, 1599, 1538, 1434, 1346 cm^{-1}. Anal. Calcd for $C_{12}H_{11}N_5O_4$: C, 49.83; H, 3.83; N, 24.21. Found: C, 49.70; H, 3.68; N, 24.32.

Kinetic Measurement.

The kinetics of the reactions were carried out spectrophotometrically by means of a diode array spectrophotometer in aqueous solution, at 25.0 ± 0.1 °C, ionic strength 0.2 M (KCl), at three different pH values maintained by partial protonation of the amines. The reactions studied under excess of the amine over the substrate were started by injection of a substrate stock solution in acetonitrile (10 µL) into the amine aqueous solution (2.5 mL in the spectrophotometric cell). The initial substrate concentration was about 10^{-4} M. Pseudo-first order rate coefficients (k_{obs}) were found for all reactions; these were determined by means of the spectrophotometer kinetic software for first order reactions at 315 nm corresponding to the N´-(5-nitropyrimidin-2-yl)benzohydrazide derivative as reaction products.

Computational Details.

All of the TS structures were fully optimized at the M05-2x/6-31G(d,p) level of theory. After the optimization procedure, frequency calculations were performed in order to verify the presence of only one anomalous vibration associated to the bond-forming/bond-breaking process. With this information, an IRC calculation was performed to obtain the reaction profile that smoothly connects reactants and the MC intermediate. Finally, the Fukui function analysis was performed on TS structures and reagents using a method described elsewhere.[17,18] All of the calculations were performed using the Gaussian 03[25] suite of programs.

Acknowledgment This work was supported by Project ICM-P10-003-F-CILIS, granted by Fondo de Innovacion para la Competitividad del Ministerio de Economia Fomento y Turismo, Chile; project of Clínica Alemana-Universidad del Desarrollo 23400026 and FONDECYT of Chile, projects 1100492, 1110062. S.G-F thanks Conicyt of Chile for a doctoral fellowship.

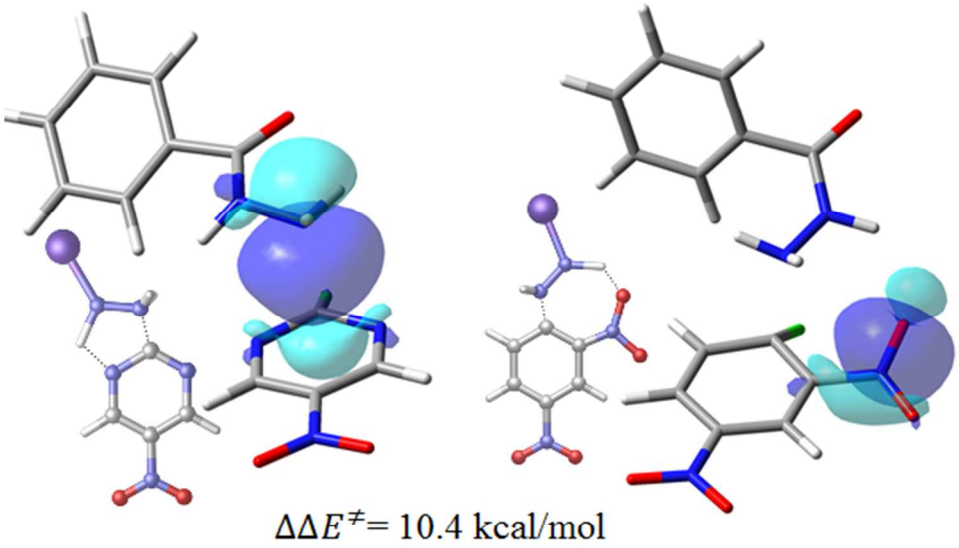
Notes and references

[a] Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile.
[b] Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, Santiago 6094411, Chile.
[c] Centro de Química Médica, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, código postal 771-0162, Santiago, Chile.

Electronic Supplementary Information (ESI) available: Kinetic data (Tables S1−S5); plots of k_{obs} versus [N] for all the reactions (Figures S1−S5); Bronsted type-plot; ^{1}H and ^{13}C NMR spectra for 4-methoxy-N´-(5-nitropyrimidin-2-yl) benzohydrazide as reaction product. Cartesian coordinates, energies, and the number of imaginary frequencies (NIMAG) of all the stationary points considered in this study (Tables S16−S26). See DOI: 10.1039/b000000x/

1. J. F. Bunnett and R. J. Morath, *J. Am. Chem. Soc.*, 1955, **77**, 5051-5055.
2. R. R. Bishop, E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.*, 1952, 437-446.
3. C. Arnone, G. Consiglio, V. Frenna and D. Spinelli, *J. Org. Chem.*, 1997, **62**, 3093-3097.
4. M. D. Wendt and A. R. Kunzer, *Tetrahedron Lett.*, 2010, **51**, 641-644.
5. N. Chéron, L. El Kaïm, L. Grimaud and P. Fleurat-Lessard, *Chem. Eur. J*, 2011, **17**, 14929-14934.
6. R. Ormazabal-Toledo, R. Contreras, R. A. Tapia and P. R. Campodonico, *Org. Biomol. Chem.*, 2013, **11**, 2302-2309.
7. R. Contreras, J. Andrés, P. Pérez, A. Aizman and O. Tapia, *Theor Chem Account*, 1998, **99**, 183-191.
8. A. Aizman, R. Contreras, M. Galván, A. Cedillo, J. C. Santos and E. Chamorro, *J. Phys. Chem. A*, 2002, **106**, 7844-7849.
9. J. Padmanabhan, R. Parthasarathi, V. Subramanian and P. K. Chattaraj, *J. Mol. Struct. THEOCHEM*, 2007, **804**, 17-20.
10. O. Banjoko and I. A. Babatunde, *Tetrahedron*, 2004, **60**, 4645-4654.

11. I.-H. Um, S.-W. Min and J. M. Dust, *J. Org. Chem.*, 2007, **72**, 8797-8803.
12. M. Gazitua, R. A. Tapia, R. Contreras and P. R. Campodonico, *New J. Chem.*, 2014.
13. P. R. Campodónico, M. E. Aliaga, J. G. Santos, E. A. Castro and R. Contreras, *Chem. Phys. Lett.*, 2010, **488**, 86-89.
14. R. Bell, *The Proton in Chemistry; Methuen: London*, 1959, 159.
15. L. R. Domingo, M. J. Aurell, P. Pérez and R. Contreras, *J. Phys. Chem. A*, 2002, **106**, 6871-6875.
16. R. Contreras, J. Andres, V. S. Safont, P. Campodonico and J. G. Santos, *J. Phys. Chem. A*, 2003, **107**, 5588-5593.
17. R. G. Parr, L. v. Szentpály and S. Liu, *J. Am. Chem. Soc.*, 1999, **121**, 1922-1924.
18. R. G. Parr and W. Yang, *Density-Functional Theory of Atoms and Molecules*, Oxford University Press, USA, 1989.
19. P. Fuentealba, P. Pérez and R. Contreras, *J. Chem. Phys.*, 2000, **113**, 2544-2551.
20. R. R. Contreras, P. Fuentealba, M. Galván and P. Pérez, *Chem. Phys. Lett.*, 1999, **304**, 405-413.
21. Y. Zhao and D. G. Truhlar, *Acc. Chem. Res.*, 2008, **41**, 157-167.
22. E. G. Hohenstein, S. T. Chill and C. D. Sherrill, *J. Chem. Theory Comput.*, 2008, **4**, 1996-2000.
23. S. Miertus, E. Scrocco and J. Tomasi, *Chem. Phys.*, 1981, **55**, 117-129.
24. A. E. Reed, L. A. Curtiss and F. Weinhold, *Chem. Rev.*, 1988, **88**, 899-926.
25. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, A. Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople., *Gaussian 03, Rev. E.01, 2004.*



1587x992mm (96 x 96 DPI)