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ORIGINAL ARTICLE

Assessing the nucleophilic character of 2-amino-4-arylthiazoles through coupling with 4,6-dinitrobenzofuroxan: Experimental and theoretical approaches based on structure-reactivity relationships

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Substituent effect;
Structure-reactivity correlation;
Global electrophilicity/nucleophilicity reactivity indexes;
DFT study

Abstract A kinetic study of the reactions of potentially bioactive 2-amino-4-arylthiazoles with highly reactive 4,6-dinitrobenzofuroxan (DNBF) is reported herein in acetonitrile solution. The complexation reaction was followed by recording the UV–vis spectra with time at λ_{max} = 482 nm. Electronic effects of substituents influencing the rate of reaction have been studied using structure-reactivity relationships. It is shown that the Hammett plot relative to the reaction of DNBF with 2-amino-4-(4-chlorophenyl)thiazole exhibit positive deviation from the log k_1 versus σ correlation, while it showed excellent linear correlation in terms of Yukawa–Tsuno equation. It has be noticed that the nonlinear Hammett plot observed for 2-amino-4-(4-chlorophenyl) thiazole is not attributed to a change in rate-determining step but is due to nature of electronic effect of substituent caused by the resonance of stabilization of substrates. The second-order rate constant (k_1) relating to the bond C–C and C-N forming step of the complexation processes of DNBF with 4-substituted-aminothiazoles and 2-amino-5-methyl-4-phenylthiazole, respectively, is fit into the linear relationship log $k = s_N (N + E)$, thereby permitting the assessment of the nucleophilicity parameter (N)

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of the 2-amino-4-arylthiazoles of the range ($4.90 < N < 6.85$). 2-amino-4-arylthiazoles is subsequently ranked by positioning its reactivity on the general nucleophilicity scale developed recently by Mayr and coworkers (2003) leading an interesting and a direct comparison over a large domain of π-, σ -, and n-nucleophiles. The global electrophilicity/nucleophilicity reactivity indexes of the 2-amino-4-arylthiazoles have been investigated by means of a density functional theory (DFT) method. .

1. Introduction

Compounds that containing sulfur-atoms in their structure are extremely significant in living organisms especially heterocyclic compounds [1]. Scaffolds that have a heterocyclic ring such as thiazole moiety finds several implementations in most common fields, as for instance, liquid crystal materials [3], photonucleases [4], polymers [2], fluorescent compounds [5], antioxidant agents [8] and insecticidal materials [6,7]. Also, thiazole ring is incorporated in natural products, it is a substantial pillar of a large number of biologically active marine compounds that play a very important role in drug discovery. In addition, some aminothiazoles have been proven to be useful antibiotics [9], antitumors, HIV infections [10] and treatment of hyper tension [11].

In the last decades nitrobenzofuroxans, a class of electron-deficient heteroaromatics, has received a great deal of attention, as extremely strong neutral electrophile that display high susceptibility towards substitution or covalent nucleophilic addition processes [12–21]. These heteroaromatics exemplified by 4,6-dinitrobenzofuroxan (DNBF), are capable reacting readily with weak nucleophiles even under smooth conditions [22–26]. More revealing evidence of 4,6-dinitrobenzofuroxan reactivity is in terms of its propensity to undergo facile carbon–carbon couplings with wide variety of molecules such as, π -excessive heterocycles (indoles, pyrroles, etc) or benzenoid aromatics e.g. alkoxybenzenes, polyhydroxybenzenes and anilines, etc.. to afford σ -adducts, which exhibit high thermodynamic stability [27–30]. From biological and medicinal point of view, great attention has been devoted to 4,6-dinitrobenzofuroxan scaffold due to its ability to liberate nitric oxide molecules (NO) under physiological conditions [31,32]. It has to be noticed that, despite that unsubstituted benzofuroxan possesses a biological activity, but this activity remains moderate. Thus, it has been shown that the modification of the nature and the position of the substituent of the aromatic ring of the benzofuroxan moiety allows to a convenient design of new targets compounds leading to suitable biological properties [33]. Indeed, the integrated set of a benzofuroxanyl moieties with other classical drug fragments in a single compound have recently received great interest from researcher and developers in the medicinal chemistry field [34,35]. Taking into consideration the above described beneficial effects of benzofuroxans and thiazoles both exhibiting a wide spectrum of biological activities, we realized that it would be of interest to study the reactivity relative to the formation of new structural hybrids containing both benzofuroxanyl and thiazole fragments.

In continuation to our research work devoted to development and calibration reactivity of new structural hybrids containing benzofuroxanyl moiety [36,37], we herein report a kinetic study of 2-amino-4-arylthiazoles derivatives with 4,6-dinitrobenzofuroxan. A successful calibration of the nucleophilicity of 2-amino-4-arylthiazoles were performed within the N scale developed by Mayr et al. This finding is capable of assessing coupling reactions which can be envisioned with this type of 2-aminothiazole derivatives. Moreover, we report a theoretical inquiry of nucleophilic character through global electrophilicity/nucleophilicity reactivity indices involving the frontier molecular orbitals HOMO and LUMO approach.

2. Experimental

2.1. Materials

4,6-Dinitrobenzofuroxan **1** was prepared according to the procedure by Drost [38] with mp 172 °C. 2-Amino-4-(4-aminophenyl)thiazole **2a**, 4-(4-methylphenyl)-2-thiazolamine **2c**, 2-Amino-4-phenylthiazole **2d** 2-Amino-4-(4-chlorophenyl) thiazole **2f** and 2-amino-5-methyl-4-phenyl thiazole **2g** were commercially available products which were purified as appropriate. 2-Amino-4-(4-methoxyphenyl)thiazole **2b** and 2-Amin o-4-(4-fluorophenyl)thiazole **2e** were prepared according to the procedure by Hari Babu et al. [39] (see Supplementary Information). Acetonitrile was distilled over P_2O_5 and stored under nitrogen.

2.2. Electronic absorption spectra and kinetics measurements

The electronic absorption spectra and kinetic determinations were recorded with a conventional UV–Vis spectrophotometer (Shimadzu model 1800 PC), whose temperature of cell compartments were preserved around 20 ± 0.1 °C. All kinetic-runs were performed no less than three times under conditions of pseudo-first-order with the 4,6-dinitrobenzofuroxan **1** concentration of ~ 3×10^{-5} mol dm^{-3} and a concentration of 2-amino-4-(4-X-phenyl)thiazoles **2a-g** in the range 2.0×10^{-4}–1.0×10^{-1} mol dm^{-3}. In all realized experiment, the rates data were found to be reproducible to 2–3%.

2.3. Computational methods

All calculations were performed with the Gaussian 03 suite of programs. Geometry optimizations were performed on **2a-g** *in vacuo* with density functional theory (DFT) using B3LYP exchange correlation functional, together with the standard 6-31G(d) basis set. Frequency calculations were performed on the optimized geometries using the same level of theory.

3. Results and discussion

3.1. Ambident reactivity of 2-amino-4-arylthiazoles **2a-g** toward DNBF **1**

3.1.1. Kinetics of complexation reactions of DNBF **1** with 2-amino-4-(4-X-phenyl)thiazole **2a-f**

The kinetic study was realized under the conditions of the experiments pseudo-first order in which the concentration of 4-substitutedphenyl-2-aminothiazole **2a-f** in excess over DNBF **1** substrate concentration. Experiments were performed by directly mixing a solution of 3×10^{-5} mol/dm^3 of DNBF with the solution of 2-amino-4-arylthiazole with concentrations in the range of ([**2a-f**]$_o$ = 2.0×10^{-4}–1.0×10^{-1} mol/dm^3). As described in Scheme 1, the rates of reactions, were recorded at 20 °C in acetonitrile, following the formation of the resulting σ -adducts by spectrophotometric method. The formation of σ -adduct **3** characterized by λ_{max} = 482 nm was studied by mixing in acetonitrile a solutions of 2-amino-4-(4-X-phenyl)thiazole **2a-f** with DNBF **1** solution (Scheme 1), where neither the electrophilic (DNBF **1** ; λ_{max} = 418 nm) nor nucleophilic partners have a notable absorption. Figs. S1–S6 (*c. f.* Supporting Information) shows the UV–Vis spectra for the progressive formation of σ -adduct **3a-f**. In all reactions, we observed only one time of relaxation (see Experimental Section, Figs. (S1′)–(S6′)), related to formation of the anionic C-adducts **3(a-f)-H** at divers concentrations of 2-amino-4-(4-X-phenyl)thiazole **2a-f**.

The reaction of 2-amino-4-(4-X-phenyl)thiazole **2a-f** with DNBF **1** obeyed kinetics with first-order. Thus, from the equation $\ln(A_\infty - A_t) = -k_{obsd}\, t + \ln(A_\infty - A_o)$, pseudo-first order rate constants (k_{obsd}) have been determined, where A_o represent the initial absorbance while A_t represent the absorbance at time t (s) and A_∞ stands for absorbance at infinite dilution. The use of integration method by plotting $\ln(A_\infty - A_t)$ vs. time, allowed us to collect kinetic data relating coupling reaction. Linear plots were obtained for DNBF **1** with constant concentration and a different concentrations of 2-amino-4-(4-X-phenyl)thiazole **2a-f**. These straight lines plots indicate that the reaction is first-order (Figs. (S1′)–(S6′) (*c.f.* Supporting Information)), which was defined through the first-order rate constant integral equation. Tables S1–S6 (*c.f.* Supporting Information) summarizes the values of k_{obsd}.

As shown in Scheme 1, the rearomatization of thiazole ring of the intermediate ZH ± (Wheland-Meisenheimer) can be accounted to proceed via : (i) the recovery of the π -aromatic character of the thiazole ring spontaneously via rearomatization of Wheland-Meisenheimer ZH ± by expulsion of a proton, thus, binding of excess of **2a-f** to the amino group of adducts **2a-f** or the parent thiazole occurred instantaneously, to give **3(a-f)-H**, or **3a-f**, respectively. The latter behavior is similar to the situation in case of the DNBF/aniline system [15,23]. (ii) solvent-assisted pathway (k_2), however, the assistance of acetonitrile as a solvent is not reasonable pathway in this situation, as concluded from the relative values of pK_a of acetonitrile ($pK_a \sim -10$) [40] and aminothiazole in H_2O. (iii) base-catalyzed process involving the parent aminothiazole as the effective catalyst (k_3[**2a-f**]$_o$). Indeed, Bug has suggested that the nitronate or N-oxide functionalities of the resulting anionic σ -adducts might also act as base catalysts to promote the deprotonation of ZH ±. While this proposal is consistent with the fact that such functionalities exhibit a much higher basicity in dipolar solvents than in aqueous solution [41]. However, under our experimental conditions, the σ -adducts concentration cannot exceed the very low concentration ($\leq 3 \times 10^{-5}$ M) that of DNBF. Thus, the observed first-order rate constant (k_{obsd}) for the formation of **3a-f** can be expressed by assuming that low concentration of the zwitterions ZH ± as follows:

$$k_{obsd} = \frac{k_1^{DNBF} k_2 [2a-f]_o}{k_{-1} + k_2 + k_3 [2a-f]_o} + \frac{k_1^{DNBF} k_3 [2a-f]_o^2}{k_{-1} + k_2 + k_3 [2a-f]_o} \qquad (1)$$

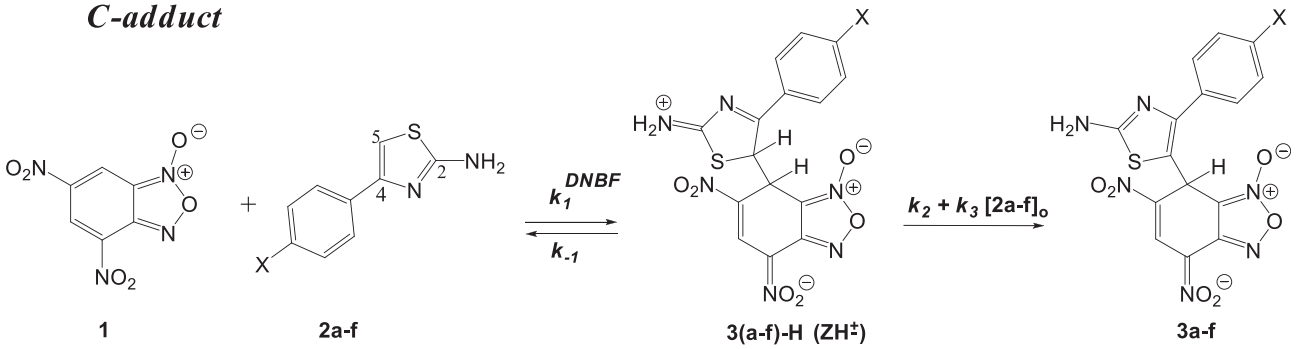
Obaviously, a good straight line with zero intercept was found when the values of k_{obsd} were plotted versus the concentration of aminothiazole derivatives as shown in Fig. 1. This behavior indicates that the assumption of the base catalyzed pathway is not working in the second step of Scheme 1. Thus, Eq. (1) could be simplified to the form of Eq. (2):

$$k_{obsd} = \frac{k_1^{DNBF} k_2}{k_{-1} + k_2} [2a-f]_o = k_1^{DNBF} [2a-f]_o \qquad (2)$$

making the determination of the second-order rate constant k_1^{DNBF} from the slopes of the observed first-order rate constant (k_{obsd}) versus the concentration of aminothiazoles [**2a-f**]$_o$ plots straightforward (Fig. 1).

3.1.2. Kinetics of complexation reaction of DNBF **1** with 2-amino-5-methyl-4-phenyl thiazole **2g**

The complexation have been achieved by simple mixing of the solution of 2-amino-5-methyl-4-phenylthiazole solution



(a) ; X = NH_2 ; **(b)** ; X = OMe ; **(c)** ; X = Me ; **(d)** ; X = H ; **(e)** ; X = F ; **(f)** ; X = Cl

Scheme 1 Reaction of 2-amino-4-arylthiazoles **2a-f** with 4,6-dinitrobenzofuroxan (**1**).

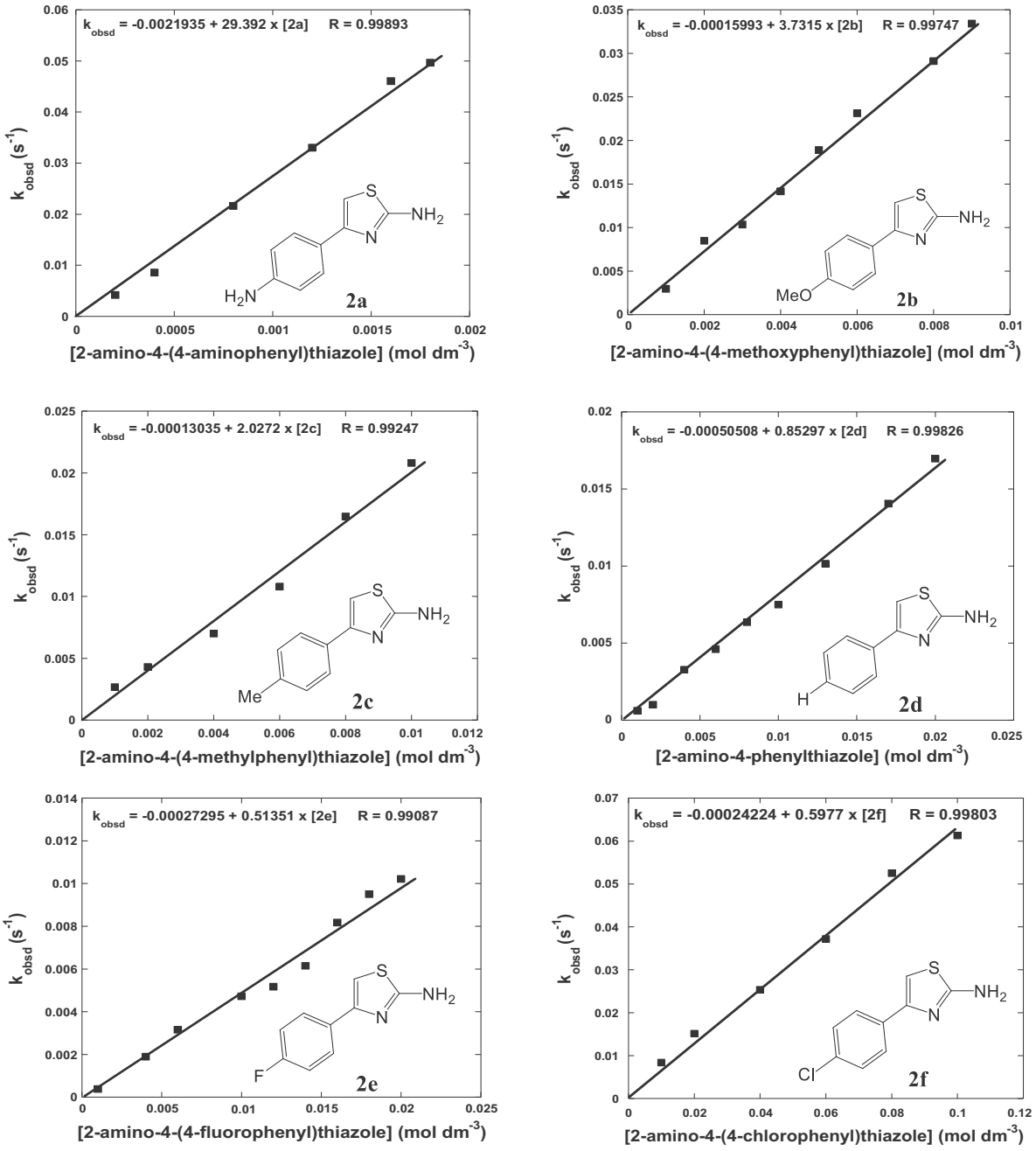


Fig. 1 Effect of concentration of 2-amino-4-(4-X-phenyl)thiazole **2a-f** substituted at C-5 on k_{obsd} of adducts **3a-f** in acetonitrile.

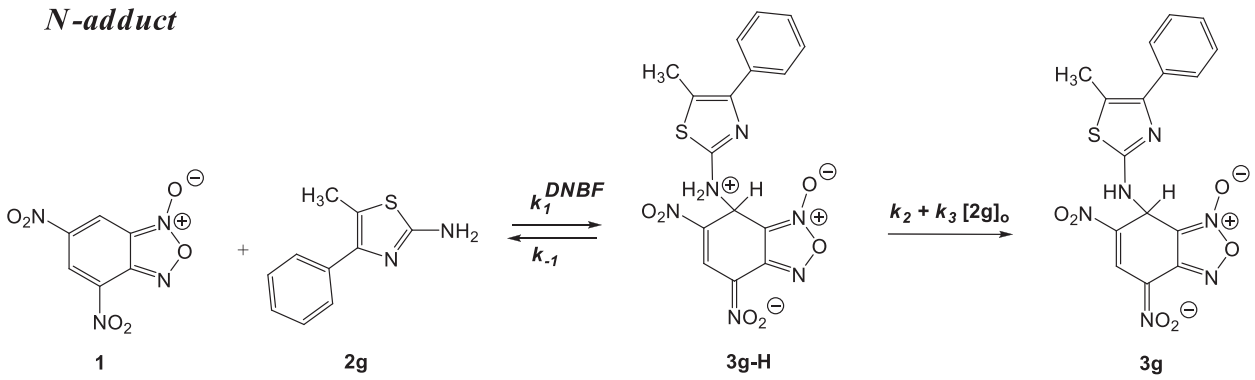
([**2g**]$_o$ = 1.0 × 10^{-3}–1.0 × 10^{-2} mol dm^{-3}) with DNBF (3 × 10^{-5} mol dm^{-3}). As shown in Figs. (S7, S7′) (see Experimental Section), only one relaxation time was obtained corresponding to the formation of N-adduct **3g** through Scheme 2.

Plotting the k_{obsd} values for formation of adducts **3g-H** versus the concentration of thiazole **2g** gave a straight line relationship passing through the origin. Therefore, the formation of the intermediates **3g-H** is rate-limiting in Scheme 2, due to the strong acidity of the negatively charged DNBF group which thermodynamically favors the proton transfer step [12,28,42]. Thus, k_{obsd} is given by Eq. (3) in a simple form. As shown in Fig. 2 k_1^{DNBF} = 8.97 dm^3 mol^{-1} s^{-1}. could be readily obtained from the slope.

$$k_{obsd} = k_1^{DNBF}[2g]_o \quad (3)$$

3.2. Structure-reactivity relationship: Substituent effect

Examination of the rate constants (k_1^{DNBF}) relative to the couplings of of 2-amino-4-(4-X-phenyl)thiazoles **2a-f** with DNBF **1** (values obtained in acetonitrile solution, see Table 1) reveals that the obtained rates relative to this complexation reactions have been found remarkably sensitive to the inductive electronic effects of the substituents X in the aminothiazole moiety. Fig. 3 show that a straight line was obtained by plotting the values of log k_1 versus the appropriate Hammett σ_{para} [43]. Deviation from linear behavior in Hammett plot in



Scheme 2 Reaction of 2-amino-5-methyl-4-phenylthiazole **2g** with 4,6-dinitrobenzofuroxan (**1**).

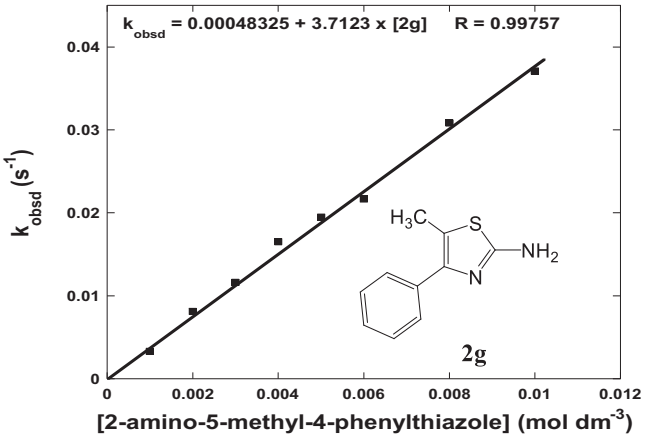


Fig. 2 Effect of the concentration of 2-amino-5-methyl-4-phenylthiazole **2g** on k_{obsd} of the DNBF adduct **3g** at T = 20 °C in acetonitrile.

Fig. 3 could be noticed in case of substrates having a Cl in the phenyl moiety. We assume that resonance stabilization of the thiazoles in the ground state (GS) is a reason for the deviation observed in Hammett plot for X = Cl.

The value of ρ obtained from the slope of the log k_1^{DNBF} versus σ_{para} is −2.4 for the five 2-amino-4-(4-X-phenyl) thiazoles **2a-e** (Fig. 3), the ρ value indicate the significant effect of positive charge at the N-atom of amino group bonded to the thiazole ring in the transition state of formation of the intermediate ZH±. Linear free energy relationship indicates in this case that all couplings reactions follow similar mechanistic pathway.

To examine the validity of the above assumption, the Yukawa-Tsuno equation is applied. The values of r in Eq. (4) represents the resonance demand of the coupling site or the extent of resonance contribution. On the other hand, the term ($\sigma^+ - \sigma_{para}$) is the resonance substituent constant that measures the capacity for π -delocalization of the π -electron donor substituent (see Table S8 in Supporting information) [44–47]. In order to account for the kinetic values obtained from solvolysis of benzylic moieties, in which a positive charge develops partially in the transition state (TS) Eq. (4) was derived [44–47]. Recently, it have shown that Eq. (4) is also highly effective in elucidation of ambiguities in the reaction mechanism, for electrophilic and nucleophilic substitution reactions [48].

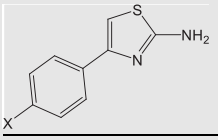
$$\log\frac{k_1^X}{k_1^H} = \rho\left[\sigma_p + r\left(\sigma_p^+ - \sigma_p\right)\right] \quad (4)$$

As shown in Fig. S8 (see Supporting Information), the Yukawa-Tsuno plots exhibit excellent linear correlations with ρ^X = 1.35 and r = 0.59 for the reactions of DNBF with 2-amino-4-(4-X-phenyl) thiazoles **2a-f**. Such linearity indicates that the nonlinear Hammett plots are not attributed to a change in rate determining step (RDS) but due to stabilization of the substrates having an electron-donating group (EDG) via resonance interactions.

*3.3. Assessing the carbon and nitrogen nucleophilicity of 2-Amino-4-arylthiazoles **2a-g**: Mayr equation*

Assessing the nucleophilic character of 2-Amino-4-arylthiazoles **2a-g** could be achieved by using Mayr approach which could describe the rates of various electrophile–nucleophile combinations using three parameters as shown in

Table 1 Second-order rate constants k_1^{DNBF} ($mol^{-1}dm^3\ s^{-1}$) for coupling of the DNBF 1 with the 2-amino-4-(4-X-phenyl)thiazoles 2a-f in acetonitrile at 20 °C and Hammett constant corresponding to substituent in *para*-position σ_p.

	X = NH_2	X = OMe	X = Me	X = H	X = F	X = Cl
log k_1^{DNBF}/mol dm^{-3} s^{-1}	1.468	0.572	0.307	−0.069	−0.289	−0.223
σ_p	−0.66	−0.28	−0.17	0.00	0.06	0.23

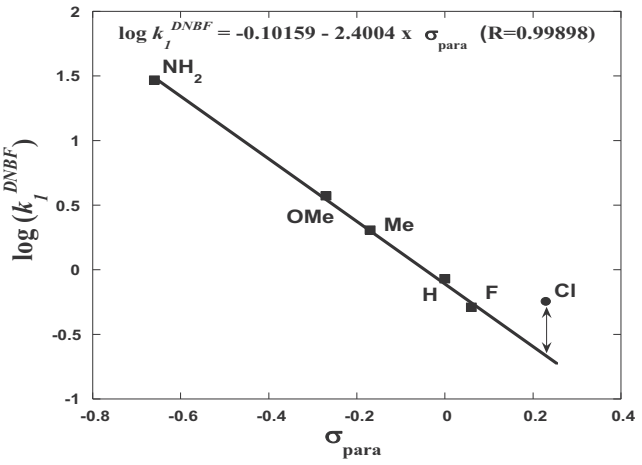


Fig. 3 Hammett plots log k_1 = f (σ_p) for the reactions of DNBF **1** with 2-amino-4-(4-X-phenyl)thiazoles **2a-f** in MeCN at 20 °C.

Eq. (5) [49–51]. According the Eq. (5), two general scales have been described one of electrophilicity (E) and one of nucleophilicity (N). These scales are useful in predicting the reactivity [41,52–54].

$$\log k = s(N + E) \quad (5)$$

E parameter measures the strength of the electrophile while the N and s parameters characterize the sensitivity of the nucleophile.

Based on Eq. (5), E and N scales cover a reactivity range of nearly thirty orders of magnitude and used to assess the reactivity of various electrophiles or nucleophiles. Among the different nucleophiles that have been studied, enamines which have been classified by on the N scale, it was found that the corresponding s parameter does not differ much with the enamine structure ($0.79 < s < 1.03$) [55]. Thus, by combination of the average value of $s = 0.90$ with the value of E recently determined for DNBF ($E = -5.22$), it is possible to get approximate the values of N for 2-amino-4-(4-X-phenyl) thiazole **2a-f** through Eq. (5), in which the log k_1 values refer to our kinetic measurements (k_1) obtained from coupling reactions of DNBF **1** with aminothiazoles **2a-f** in acetonitrile. On the other hand, previous studies allowed Mayr to classify aliphatic and aromatic amine on the N scale and s parameter does not vary much with the primary amine structure ($0.6 < s < 0.75$) [56–58]. Thus, combination of the average value of $s = 0.70$ with the value of E for DNBF ($E = -5.22$), it is possible to get approximate the N values for 2-amino-5-methyl-4-phenyl thiazole **2g** through Eq. (5), in which the values of log k_1 refer to the kinetic measurements (k_1) obtained from coupling reaction of DNBF **1** with 2-amino-5-methyl-4-phenyl thiazole **2g** in acetonitrile. The obtained N values are given in Table 2.

The quantitative ranking of our 2-amino-4-arylthiazoles **2a-g** on the nucleophilicity scale (N) (Fig. 4) allows to locate their nucleophilic behavior and so permit to compare their reactivity with analogous compounds previously classified in the scale. The obtained experimental N values of **2a-f** shows that the nucleophilicity increase with the nature of substituent in phenyl moiety following the order $NH_2 > OMe > Me > H > Cl > F$.

The addition of one benzo group of 2-aminothiazole ($N = 5.56$) to give 2-amino-4-phenyl thiazole **2d** ($N = 5.14$) decrease his nucleophilicity strength by approx. 0.5 order of magnitude. Interestingly, The nucleophilicity value determined for 2-amino-4-(4-aminophenyl) thiazole **2a** ($N = 6.85$) is comparable to 2-amino-4-methylthiazole ($N = 6.80$), similar observation was detected for 2-amino-4-(4-methylphenyl) thiazole **2c** ($N = 5.56$) and 2-aminothiazole ($N = 5.56$), as well as for 4-(pyren-1-yl)thiazol-2-amine ($N = 5.39$) when replacing phenyl fragment by pyrenyl on the thiazole moiety [36].

The experimental N values of 2-amino-5-methyl-4-phenyl thiazole **2g** ($N = 6.03$) and 2-amino-4,5-dimethyl thiazole ($N = 6.42$) shows that the substitution of one methyl group by benzo group to give **2g** decrease his nucleophilicity strength by approx. 0.5 order of magnitude.

The nucleophilicity of **2a** ($N = 6.85$) compare very clearly with that of the compound of 2-methylindole ($N = 6.91$) and otherwise to approach that of benzotriazole ($N = 7.69$) but found lower than that of other aromatic amines such as 4-amino-3,5-dibromo-pyridine, aniline and anilines derivates or aliphatic amines such as butylamine, hydrazine,... as shown in Fig. 4.

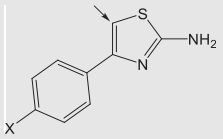
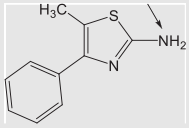
3.4. Computational studies: analysis of the global Electrophilicity/Nucleophilicity reactivity indexes

The density functional theory (DFT) in the last four decades affords various indices to rationalize and understand chemical structure. The concepts that emerge from this theory have also been widely used to generate a general approach to the description of chemical reactivity [59]. Thus, structures of 2-amino-4-arylthiazoles **2a-g** in this work were minimized according with the parameters described. A frontier molecular orbital (FMO) analysis was performed in order to predict reactivity. The calculated Frontier orbital energies E_{HOMO} and E_{LUMO} for 2-amino-4-arylthiazoles **2a-g** are collected in Table 3. Moreover, theoretical quantitative scales have shown to be powerful means in the rationalization of the reactivity of wide variety of chemical species. These scales become a desirable tool as they can be used to justify the electronic aspects of reactivity, selectivity, and their variations induced by field effects due to conformational changes or arising from chemical substitution.

Many global and local reactivity descriptors, defined within the density functional theory (DFT), have been anticipated and have shown to be very useful in the study and interpretation of reactivity in polar reactions. Well-known among these reactivity indices, we can cite chemical potential μ, chemical hardness η and global electrophilicity ω. Both quantities of electronic chemical potential μ and chemical hardness η are obtained from one-electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu = (\varepsilon_H + \varepsilon_L)/2$ and $\eta = (\varepsilon_L - \varepsilon_H)$, respectively [60]. Calculated values *of* μ and η are presented in Table 3.

In this context, the electrophilicity index (ω) has shown to be a powerful theoretical mean to predict the electrophilic behavior [61,62]. Indeed, ω index measure the stabilization in energy when a molecule acquires from environment a supplementary electronic charge. For this reason, the electrophilicity index takes into account both the propensity of the molecule to acquire an additional electronic charge, and the resistance of the system to exchange charge with the environment. Thus,

Table 2 The Positioning of 2-amino-4-arylthiazoles Structures on the Nucleophilicity Scale.

Aminothiazoles			k_1 dm^3 mol^{-1} s^{-1}	N
(2a)		X = NH_2	29.39	6.85[a]
(2b)		X = OMe	3.73	5.86[a]
(2c)		X = Me	2.03	5.56[a]
(2d)		X = H	8.53×10^{-1}	5.14[a]
(2e)		X = F	5.13×10^{-1}	4.90[a]
(2f)		X = Cl	5.98×10^{-1}	4.97[a]
(2g)			3.71	6.03[b]

The k_1 values for the coupling of 2-amino-4-arylthiazoles structures with DNBF (E = −5.22) in acetonitrile; T = 20 °C. (a) Approximate N values through rearrangement of Eq. (5) into N = (log (k_1)/s) − E with s = 0.9. (b) Approximate N values through rearrangement of Eq. (5) into N = (log (k_1)/s) − E with s = 0.7.

ω is given by the following simple Eq. (6) in terms of the electronic chemical potential (μ) and the chemical hardness (η).

$$\omega = \mu^2/2\eta \tag{6}$$

The data summarized in Table 3 reveals that the 2-amino-4-arylthiazoles **2a-g** due to the moderate value of their ω ($1.102 < \omega < 1.294$) act as good nucleophiles. It is important to mention that a recently study of a set of organic molecules, allowed to classify these molecules as strong, $\omega > 1.5$ eV, moderate, $0.8 < \omega < 1.5$ eV, and marginal electrophiles $\omega < 0.8$ eV.

Following the electrophilicity ω index approach and in order to equate with the general notion that "more is better", recently, Gázquez et al. [63,64] have proposed new reactivity index and have defined the electroaccepting (Eq. (7)), ω^+, and electrodonating (Eq. (8)), ω^-, powers as,

$$\omega+ = \frac{A^2}{2(I-A)} \tag{7}$$

$$\omega- = \frac{I^2}{2(I-A)} \tag{8}$$

where ω^+ represents the measure of the propensity of a given system to accept charge, whereas, ω^- is the propensity to donate charge. It is important to mention here that a greater ω^+ value of a system reflects to a better capability of accepting charge, whereas a smaller value of ω^+ corresponds to a better electron donor. Both quantities are calculated by employing the vertical ionization energy I and electron affinity A and collected in Table 3.

Note that according to these definitions and as mentioned in Table 3 the 2-amino-4-(4-aminophenyl)thiazole **2a** is the molecule with the more capability to donate charge.

Recently, a simplest approach in order to have a different descriptor to give further information about the nucleophilicity have proposed [64,65]. Based on this idea, an empirical (relative) nucleophilicity index (N) have introduced, relating the nucleophilicity with the highest occupied molecular orbital (HOMO) energy obtained within the Kohn–Sham scheme [66], and defined as

$$N = E_{HOMO}(eV) - -E_{HOMO(TCE)}(eV) \tag{9}$$

where tetracyanoethylene (TCE) was taken as reference, because it presents the lowest HOMO energy in a long series of organic molecules.

A subsequent study involving a wide series of substituted alkenes compounds, as well as substituted aromatic compounds and simple nucleophilic molecules, supported and approved the usefulness of the nucleophilicity N index in the nucleophilicity model [67]. In this latter study, such a model allowed to classify organic molecules as strong, $N > 3.00$ eV, moderate, 2.00 eV $< N < 3.00$ eV, and marginal nucleophiles, $N < 2.00$ eV.

By examining the nucleophilicity descriptor N for these compounds calculated using Eq. (9) (Table 3), we found that the 2-amino-4-arylthiazoles **2a** ($N = 3.425$ eV), **2b** ($N = 3.129$ eV) and **2c** ($N = 3.029$ eV) represent the best nucleophiles of this series with nucleophilicity N value >3.00 eV.

Next we have calculated the nucleophilicity on the basis of the assumption of Chattaraj et al. that electrophilicity and nucleophilicity are inversely related to each other [68]. The suggested nucleophilicity parameter has been described as the multiplicative inverse of the electrophilicity index (ω) [69] and denoted as

$$N' = 1/\omega \tag{10}$$

In that same sense, Roy et al. have proposed the nucleophilicity index, N'', as the inverse of the electrodonating ω^- power [70]. In addition, since the nucleophilicity index obtained as $1/\omega^-$ was below 1 [63,70], the nucleophilicity N'' index have lately defined as

$$N'' = ((1/\omega^-) \times 10) \tag{11}$$

As shown in Table 3, calculated N' and N'' follows the same order that as that found for the corresponding nucleophilicity N descriptor. Thus, a comparison of the values obtained using three nucleophilicity models, nucleophilicity N values with that the inverse of the electrophilicity powers, N', and Roy's N'' values, shows a reasonable agreement. Therefore, the combining effect of the two groups amino and aryl on thiazole is well established by the three-nucleophilicity models. It is interesting to note that N values obtained using three nucleophilicity models from Eqs. ((9)–(11)) correlate well with the corresponding experimental Mayr's (Fig. 5). Thus, in view of these results,

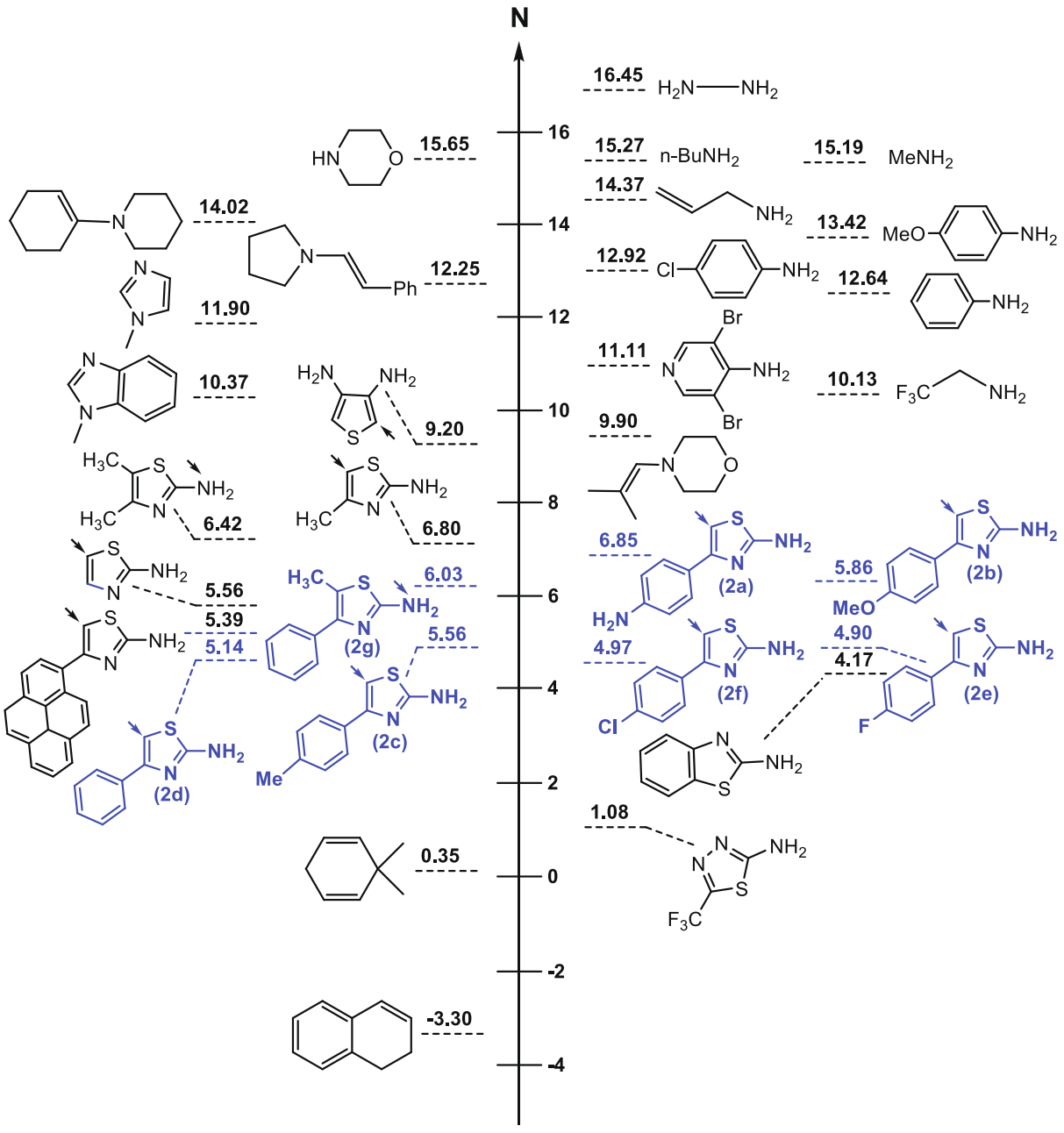


Fig. 4 The ranking of 2-aminothiazoles derivatives **2a-g** on the N scale, as defined by Mayr et al.

it is expected that any model of nucleophilicity described in this work can be used to represent with reasonably manner this property.

4. Conclusion

The enaminic character of 2-amino-4-arylthiazoles is assessed through their nucleophilic reactivity with superelectophilic 4,6-dinitrobenzofuroxan. By applying the common approach electrophilicity/nucleophilicity improved by Mayer and coworkers. (2003), the *N*-parameters that determine the nucleophilic-reactivity of the substituted-aminothiazoles in acetonitrile were determined by kinetic investigations of σ-complexation reactions involving DNBF as the reference electrophile. This finding present major interest, since this allows us to extend the applicability of Mayr equation to σ-complexation processes implying neutral-electrophiles and thus, it broadens markedly the field of coupling reactions which can be predicted with 4,6-dinitrobenzofuroxans. The electrophilic/nucleophilic character of a series of 2-amino-4-arylthiazoles has been studied using DFT calculations. The global electrophilicity pattern of of 2-amino-4-arylthiazoles involved in the complexation reactions has been quantitatively established in terms of the electrophilicity ω index. The global nucleophilicity values (*N*) of molecules used in this work has been calculated by using three different methods. Analysis of

Table 3 The Frontier orbital energies, global properties and global electrophilicity/nucleophilicity indices values for 2-amino-4-arylthiazoles **2a-g**.[a,b]

Reactants	ε_H	ε_L	μ	η	ω	ω^+	ω^-	N	N'	N''
2a	−8.0978	−0.2302	−4.1642	7.8676	1.102	0.00337	4.167	3.425	0.907	2.400
2b	−8.3936	−0.3037	−4.3486	8.0899	1.169	0.00570	4.354	3.129	0.855	2.297
2c	−8.4937	−0.3257	−4.4099	8.1680	1.190	0.00649	4.416	3.029	0.840	2.264
2d	−8.6083	−0.3360	−4.4722	8.2722	1.209	0.00683	4.479	2.914	0.827	2.233
2e	−8.6606	−0.5072	−4.5840	8.1533	1.288	0.01577	4.600	2.862	0.776	2.174
2f	−8.6674	−0.5173	−4.5925	8.1501	1.294	0.01642	4.609	2.855	0.772	2.170
2g	−8.5806	−0.3175	−4.4491	8.2630	1.198	0.00610	4.455	2.942	0.835	2.245

[a] Frontier orbital energies, electronic chemical potential μ, chemical hardness η and global electrophilicities/nucleophilicities indices ω, ω^+, ω^-, N, N', N'' in eV as defined by Eqs. ((6)–(11)); See the text for definitions.

[b] All computations were carried out with the Gaussian 03 suite of programs. Calculations based on the method of DFT were performed using the B3LYP exchange correlation functional, together with the standard 6-31G basis set.

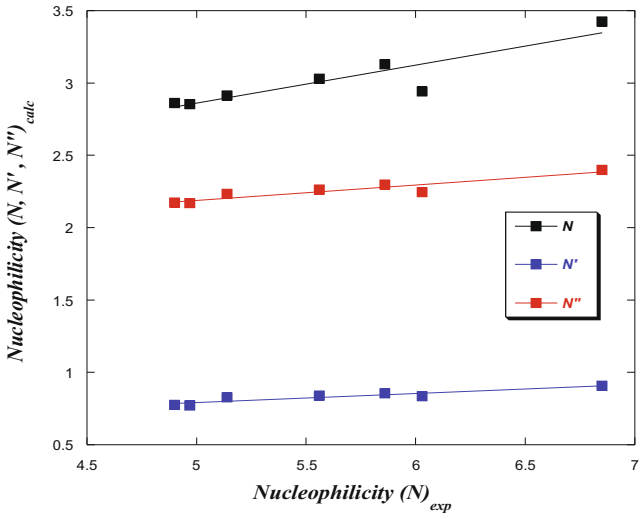


Fig. 5 Relationship between calculated gas-phase nucleophilicity *N*, *N′ and N″* values (in eV) for a series of 2-amino-4-arylthiazoles **2a-g** obtained from Eqs. (9)–(11) and those obtained experimentally from Mayr equation Eq. (5)). See the text for details.

the reactivity indexes based on the based on frontier molecular orbitals explains the reactivity of these species in reactions and has been found to correlate well with the experimental results.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jscs.2020.08.004.

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