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On the nucleophilic reactivity of 4,6-dichloro-5-nitrobenzofuroxan with some aliphatic and aromatic amines: selective nucleophilic substitution

Elena Chugunova,[a,b] Vincenzo Frenna,[c] Giovanni Consiglio,[d] Gabriele Micheletti,[e] Carla Boga,[e] Nurgali Akylbekov,[f] Alexander Burilov,[a,b] and Domenico Spinelli*[d]

[a] Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center, Russian Academy of Sciences, Akad. Arbuzov st. 8, 420088 Kazan, Tatarstan, Russia

[b] Laboratory of Plant Infectious Diseases, FRC Kazan Scientific Center of Russian Academy of Sciences, Lobachevskogo st. 2/31, 420111 Kazan, Tatarstan, Russia

[c] Department STEBICEF, Università di Palermo, Viale delle Scienze-Parco d'Orleans II, 90128 Palermo, Italy

[d] Department of Chemistry 'G. Ciamician' ALMA MATER STUDIORUM – Università di Bologna, Via Selmi 2, 40126 Bologna, Italy

[e] Department of Industrial Chemistry 'Toso Montanari' ALMA MATER STUDIORUM – Università di Bologna, Viale del Risorgimento 4, 40136 Bologna, Italy

[f] Korkyt Ata Kyzylorda University, Aiteke bie str., 29A, 120014 Kyzylorda, The Republic of Kazakhstan

KEYWORDS: Aromaticity Index; Benzofuroxan; Kinetics; Mayr constants; S_NAr

ABSTRACT: The reaction rates for the nucleophilic aromatic substitution of 4,6-dichloro-5-nitrobenzofuroxan **1** with eight aliphatic amines (characterized by very different basicity/nucleophilicity) and three anilines have been measured in both methanol and toluene. The obtained rates have been related with the basicity (pK_{aH} in water and K_b in benzene) or nucleophilicity (*N* Mayr constants) of the tested amines. The whole of the obtained kinetic data has furnished useful information on the high nucleophilic reactivity of benzofuroxan derivatives, that has been related essentially to two factors: the high electron-drawing ability/power of the condensed furoxan ring and the low aromatic character of the benzofuroxan system.

INTRODUCTION

Our research groups have long since focused their attention on the study of the interactions of electron-poor heterocyclic compounds (electrophiles) with electron-rich reagents (nucleophiles).[1-3]

Within this field of research, we have studied the reactions of halogenonitrothiophenes and halogenonitrobenzothiophenes with different nucleophiles, evidencing the occurrence of simple activated aromatic nucleophilic substitution (benzenoid behavior: S_NAr)[1] as well as of nucleophilic substitution with rearrangement (non-benzenoid behavior), for example in 3-bromo-2-nitrobenzothiophene.[4]

Examining the reactivity with nucleophiles of some nitrothiophenes and nitrobenzothiophenes not-containing a good leaving group (such as, halogens or sulphonyl group) we have observed different patterns of behaviour.[1a,5] For example, there can occur ring-opening reactions which produce very interesting polyfunctionalized compounds[5a] able to act as starting materials for new heterocyclization processes[1a,6] as well as for the syntheses of compounds with biological activities as antitumoral agents[7] or as L-type calcium channels blockers.[8] Moreover, some of them with arylthiolates can trigger *cine*- and *tele*-substitution processes.[5b,9]

Moreover some alkylnitrothiophenes, reacting with aliphatic amines, can cause oxidative nucleophilic substitutions of hydrogen (ONSH),[10] while polynitrothiophenes can produce π-adducts[11] and Wheland-Meisenheimer (WM) complexes with naphthalene and 1,3,5-triaminobenzenes,[12] respectively.

In this research area, some of us have recently examined the nucleophilic reactivity of some benzofuroxan derivatives, obtaining also compounds with promising biological activities.[13]

In the literature concerning the reactivity of benzofuroxans with nucleophiles, a kinetic study of Sharnin and co-workers[14] on the behavior of 5-chloro-4,6-dinitrobenzofuroxan (5-ClDNBF) with aniline showed that the chlorine atom in 5-ClDNBF is replaced a hundred times faster than in 1-chloro-2,4,6-trinitrobenzene. Consequently, furoxan cycle draws off the electrons from reaction center much stronger than a nitro group. A study on the behavior of 7-chloro-4,6-dinitrobenzofuroxan (7-ClDNBF) with different nucleophiles permitted to calculate for this compound $E_{Mayr} = -6.10^{15}$ thus including it within the electrophilic scale developed by

Mayr,[16-19] among the strongest electrophiles (for 1,3,5-trinitrobenzene E_{Mayr} = -13.19).[20]

The reactivity of some other chlorine or fluorine derivatives of 4,6-dinitrobenzofuroxan with some nitrogen, oxygen and neutral carbon nucleophiles has also been examined.[21-28]

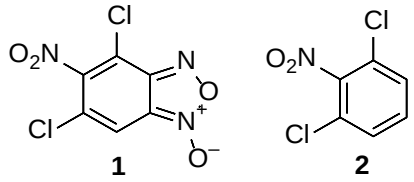
In this paper we present data on the kinetic behavior of 4,6-dichloro-5-nitrobenzofuroxan (**1**) with aliphatic and aromatic amines in two solvents with very different characteristics (methanol: ε 33; toluene: ε 2.38).[29]

In formal terms, 4,6-dichloro-5-nitrobenzofuroxan **1** (Figure 1) can be considered a derivative of 1,3-dichloro-2-nitrobenzene **2** on which, at the C_4–C_5 bond, a furoxan ring has been added. Literature data indicate that 1,3-dichloro-2-nitrobenzene (**2**) is scarcely reactive with nucleophiles, for example it reacts with amines and anilines only after treatment of the bases with sodium hydride[30] or with phenol in DMF at reflux and in the presence of potassium carbonate.[31]

These data clearly indicate that it is very less reactive of 2-nitrochlorobenzene, which is able to react with several nucleophiles in less severe experimental conditions.[32]

Literature data suggest that the addition of the furoxan ring will dramatically change the situation, because this heterocycle is a very strong electron-withdrawing system, able to activate nucleophilic aromatic substitutions.

Figure 1. Structures of 4,6-dichloro-5-nitrobenzofuroxan (**1**) and 1,3-dichloro-2-nitrobenzene (**2**).

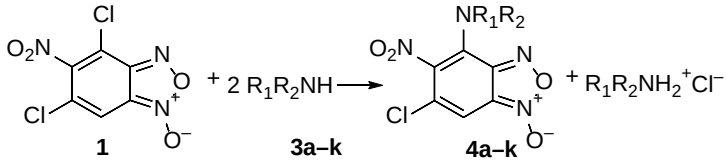


Moreover it must be remarked that benzofuroxan is characterized by a very low aromaticity (Bird aromaticity indexes of benzene, furoxan, and benzofuroxan are: 100,[33] 48.9, and 81.0, respectively;[34] perhaps the I_A for benzofuroxan represents the lowest index for a benzocondensed aromatic system reported by C. W. Bird), and this fact induce us to think that 4,6-dichloro-5-nitrobenzofuroxan could show a high reactivity with nucleophiles.

RESULTS AND DISCUSSION

In this paper we report on the reactivity of 4,6-dichloro-5-nitrobenzofuroxan (**1)** with several nitrogen nucleophiles (see Scheme 1 and Table 1) : primary (**3a-d**) and secondary aliphatic amines (acyclic and cyclic: **3e-h)** as well as primary aromatic amines (**3i-k**).

Scheme 1.



a: R_1 = $CH_3(CH_2)_2CH_2$; R_2 = H
b: R_1 = $C_6H_5CH_2$; R_2 = H
c: R_1 = $CH_3CHCH_2CH_3$; R_2 = H
d: R_1 = $(CH_3)_3CH$; R_2 = H
e: R_1 = $C_6H_5CH_2$; R_2 = CH_3
f: R_1-R_2 = -$(CH_2)_5$-
g: R_1-R_2 = -$(CH_2)_4$-
h: R_1-R_2 = -$(CH_2)_2O(CH_2)_2$-
i: R_1 = C_6H_5; R_2 = H
j: R_1 = *p*-CH_3-C_6H_4; R_2 = H
k: R_1 = *p*-CH_3O-C_6H_4; R_2 = H

Table 1. Amine abbreviations, basicity parameters,[36] and *N* Mayr's constants[37] in acetonitrile

Amine	Abbreviation	pK_{aH}	K_B	*N* Mayr's constants
3a	**BuA**	**10.75**	**110**	**15.27**
3b	**BnA**	**9.49**	**17**	**14.29**
3c	**2-BuA**	**10.56**		
3d	**t-BuA**	**10.45**		**12.35**
3e	**BnMA**	**9.03**	**153**	
3f	**PIP**	**11.12**	**4490**	**17.35**
3g	**PYR**	**11.35**	**7630**	**18.54**
3h	**MOR**	**8.45**	**70**	**15.65**
3i	**An**	**4.59**		**12.64**
3j	**Tol**	**5.08**		**13.19**
3k	**Anis**	**5.36**		**13.42**

The tested amines (Table 1) are characterized by very different basicity and nucleophilicity: anyway, as already pointed out by some of us,[35] they react with compound **1** giving rise to the replacement of only one chlorine atom (that one in position 4), even with an excess of anilines in harsh experimental conditions (excess of amines in DMSO at room temperature).[3a] We have observed the same behavior also with some aliphatic amines.[3a, 35]

Concerning basicity of amines, several years ago we measured the basicity of a number of aliphatic amines in water (K_a) and in benzene (K_b, the constant for ion-pair formation with 2,4-dinitrophenol).[36a] As a matter of fact, the basicities of six out of the eight amines examined are so available, while for the other two aliphatic amines literature data have been used[36b-d] (Table 1). Of course, the three tested aromatic amines show much lower basicity (Table 1).

Overall, a very large range of basicity values has been examined (about seven orders of magnitude in water).

Looking at nucleophilicity, the *N* Mayr constants also indicate a large range of nucleophilicity for the tested amines (in acetonitrile, *N* changes from 12.64 for aniline to 18.64 for pyrrolidine).[37]

The steric requirements of primary as compared to the bulkier secondary amines can be evaluated by the Taft substituents constants (E_s).[38]

Reactions of 4,6-dichloro-5-nitrobenzofuroxan (1) with amines.

Compound **1** with amines **3a-k** gave, both in methanol and in toluene, the expected amino derivatives **4a-k** in high yields (> 95%) as indicated by TLC and UV-VIS spectral analysis of the mixture obtained after complete reaction. The reactivity of **1** with amines has been examined in methanol and in toluene at three different temperatures in the range 293.1-313.1 K and at different concentrations of amines. The experimental data are collected in Tables A-L and M-Y of SI. As an example kinetic data in methanol at 293.1 K and in toluene at 293.6 K with morpholine at different amine concentrations are reported in Tables 2 and 3. Data in Tables show that in methanol the kinetic constants stay unchanged (within the experimental uncertainty) with increasing the amine concentration, while in toluene they show some growth.

Table 2. Apparent second order kinetic constants, k_A, for the reaction of 4,6-dichloro-5-nitrobenzofuroxane **1** with morpholine at various concentrations in methanol at 293.1 K

Amine concentration	**0.00255**	**0.00510**	**0.0102**
Observed kinetic constant (l mol^{-1}s^{-1})	**0.0485**	**0.0475**	**0.0480**

Table 3. Apparent second order kinetic constants, k_A, for the reaction of 4,6-dichloro-5-nitrobenzofuroxane **1** with morpholine at various concentrations in toluene at 293.6 K

Amine concentration	**0.00255**	**0.00510**	**0.00765**	**0.0102**
Observed kinetic constant (l mol^{-1}s^{-1})	**0.0569**	**0.0582**	**0.0593**	**0.0605**

In Table 4 are reported the values of kinetic constants (recalculated from activation parameters) at 293.1 K in methanol for all of the examined amines together with the values of activation enthalpy and entropy. The measured kinetic constants cover a very wide range of reactivity going from 9.06×10^{-5} (for 2-methyl-2-propylamine) to 0.418 l mol^{-1} s^{-1} (for pyrrolidine).

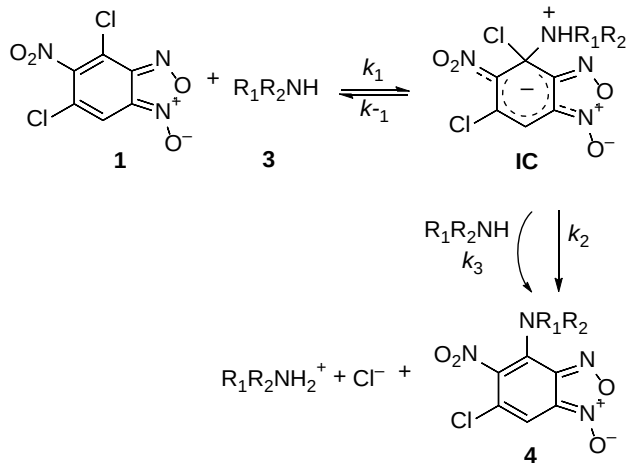
Table 4. Kinetic constants (at 293.1 K) and activation parameters for the reaction of 4.6-dichloro-5-nitro-benzofuroxan with different amines in methanol

Amine	**$10^3 k_A$** [a]	**$\Delta H^{\#}$** [b]	**$\Delta S^{\#}$** [c]
Pyrrolidine	**418**	**36.3**	**–129**
Piperidine	**288**	**36.0**	**–132**
Morpholine	**47.8**	**35.0**	**–152**
Methylbenzylamine	**50.9**	**39.1**	**–136**
Butylamine	**19.0**	**41.3**	**–137**
Benzylamine	**11.9**	**38.8**	**–149**
2-Butylamine	**3.14**	**41.2**	**–152**
t-Butylamine	**0.0906**	**45.1**	**–168**
Aniline	**4.00**	**39.0**	**–157**
p-Toluidine	**12.6**	**38.2**	**–151**
p-Anisidine	**32.5**	**37.5**	**–146**

[a] l mol^{-1} s^{-1}, values calculated by activation parameters at 293.1 K. The experimental rate constants were measured in the range 293.1-313.1 K and were accurate to within ±3%. [b]kJ mol^{-1}. At 293.1 K, the maximum error is 3 kJ mol^{-1}. [c]J K^{-1}mol^{-1}. At 293.1 K, the maximum error is 8 J K^{-1}mol^{-1}.

Looking at the reactivity in toluene it must be remembered that S_NAr reactions in apolar or low-polar solvent (such as toluene) can show different pathways, including also catalysed processes (see Scheme 2).

Scheme 2.



In fact, applying the steady state approximation to the σ-adduct intermediate (**IC**), the equation 1 can be obtained.

$$k_A = \frac{k_1(k_2 + k_3^{Am}[Am])}{k_{-1} + k_2 + k_3^{Am}[Am]} \qquad (1)$$

Similar large reactivity ranges (from 2.36×10^{-5}, for aniline, to 2.54 l mol^{-1} s^{-1}, for pyrrolidine) have been observed studying the reactivity in toluene and the relevant results are collected in Table 5. It must be remarked that with three secondary amines (benzylmethylamine, piperidine, and pyrrolidine) no catalyzed process has been observed; in contrast, a low contribution of the catalyzed pathway has been observed with morpholine and with primary (aliphatic as well as aromatic) amines: benzylamine, butylamine, 2-methyl-2-propylamine as well as aniline, *p*-toluidine, and *p*-anisidine). As a consequence kinetic data can be related to amine concentration according with the relationship: $k_A = k_0 + k_{Am}[Am]$. These results evidence that the occurrence of the 'apparent' catalyzed pathway depends by different factors and not only on their basicity.[39]

Table 5. Linear regression analysis[a] of apparent second order kinetic constants, k_A, for the reactions of 4,6-dichloro-5-nitro-benzofuroxan with different amines in toluene at 293.1 K, according to the equation $k_A = k_0 + k_{Am}[Am]$. In parentheses activation parameters

Amine	**$10^3 k_0 \pm s_0$**[a] **($\Delta H^{\#}$**[c]**, $\Delta S^{\#}$**[d]**)**	**$10^3 k_{Am} \pm s_{Am}$**[a]	**k_{Am}/k_0**	***n***	***r***

PYR[b]	**2540 ± 70 (29.5, −138)**			**3**	
PIP[b]	**992 ± 30 (28.3, −148)**			**3**	
MOR	**54.3 ± 0.1 (34.4, −152)**	**462 ± 10**	**8.5**	**4**	**0.9998**
BnMA[b]	**55.5 ± 2 (33.1, −156)**			**3**	
BuA	**7.53 ± 0.09 (39.5, −151)**	**66.0 ± 3.2**	**8.8**	**4**	**0.9988**
BnA	**2.06 ± 0.01 (46.9, −137)**	**15.8 ± 0.1**	**7.7**	**5**	**0.9999**
2-BuA	**6.47 ± 0.01 (39.6, −152)**	**46.7 ± 0.6**	**7.2**	**4**	**0.9998**
t-BuA	**0.999 ± 0.1 (43.0, −156)**	**9.42 ± 0.10**	**9.42**	**4**	**0.9998**
An	**0.0236 ± 0.0004 (53.1, −152)**	**0.0325 ± 0.0007**	**1.38**	**5**	**0.9992**
Tol	**0.0527 ± 0.0001 (53.1, −146)**	**0.162 ± 0.001**	**3.1**	**5**	**0.9999**
Anis	**0.247 ± 0.001 (48.0, −150)**	**1.20 ± 0.01**	**4.90**	**5**	**0.9999**

[a] s_0 and s_{Am} are the standard deviations of regression parameters k_0 and k_{Am}, respectively; r is the correlation coefficient; n is the number of experimental points. The confidence levels for significance of regression are all better than 99.9%. [b] Mean values. [c] kJ mol^{-1}. [d] J K^{-1}mol^{-1}.

Treatment of kinetic data.

As expected, the observed reactivities are affected by basicity/nucleophilicity and/or by steric requirements.

In fact piperidine and morpholine (two cyclic secondary amines with similar steric requirements) show a significantly different reactivity (rate ratios 6 and 18 in methanol and toluene, respectively) according to the higher basicity/nucleophilicity of piperidine with respect to morpholine (pK_{aH} 11.12 and 8.45 in water and K_b 4490 and 70 in benzene) depending on the presence of an electron-attracting oxygen atom in the morpholine ring.

Interestingly butylamine (a primary amine with the amino group linked to a primary alkyl group) and 2-methyl-2-propylamine (a primary amine with the amino group linked to a tertiary alkyl group, characterized by a large steric requirement) irrespective of the similar basicity show very different reactivity in methanol (rate ratio 200) and a significant difference also in toluene (rate ratio 7.5).

Therefore we have tried to see if a relationship could be observed between the reactivity in the S_NAr of **1** with amines in methanol and that in toluene. In Figure 2 a plot of log k values in toluene *versus* those in methanol gives an excellent correlation (*slope* 1.91 ± 0.08, r 0.996, n 6) for the following amines: primary (butylamine and benzylamine) and secondary aliphatic (both cyclic and acyclic) amines (benzylmethylamine, piperidine, pyrrolidine, and morpholine). The high value calculated for the slope agrees with the expectation that the nucleophilicity of the used amines is more able to affect the reactivity in a non-polar solvent than in a polar one. Kinetic data with aliphatic amines with high steric requirements (2-butylamine and 2-methyl-2-propylamine) do not correlate surely on account of the different solvation effects and of the different complexity of the transition states in the two solvents.[40] Moreover, also kinetic data with primary aromatic amines give a significant linear relationship (*slope* 1.24 ± 0.44, r 0.94, n 3).

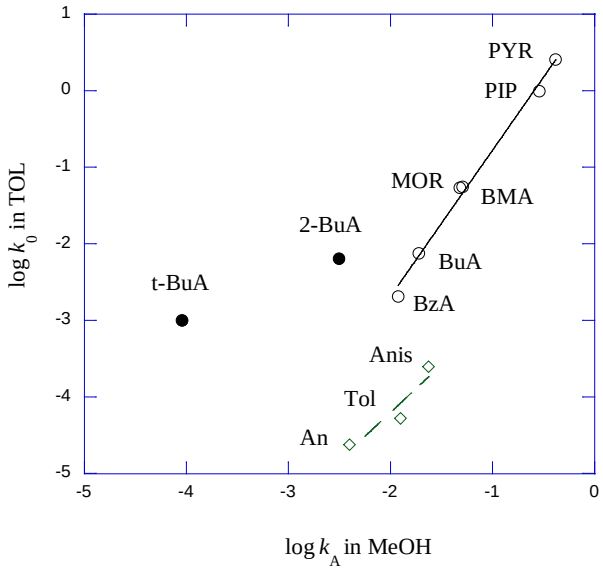


Figure 2. Plot of log k_A values in toluene *versus* those in methanol for the reactions of 4,6-dichloro-5-nitro-benzofuroxan with different amines.

Looking for a relationship between the reactivity with the different amines and their basicity [pK_{aH} (for data in methanol) or log K_b (for data in toluene)] or nucleophilicity (N Mayr constants) we have observed a series of very interesting results.

For example data relevant to secondary aliphatic amines and anilines in methanol (Figure 3) gave two separate significant relationships versus pK_{aH} (s 0.34 ± 0.09, n 4, r 0.94 and s 1.02 ± 0.020, n 3, r 0.9998), while data relevant to aliphatic primary amines do not correlate in line with the fact that they show very different steric requirements (for example consider the large difference in steric requirements between butylamine, 2-butylamine and *t*-butylamine) and probably different structures of the relevant transition states.

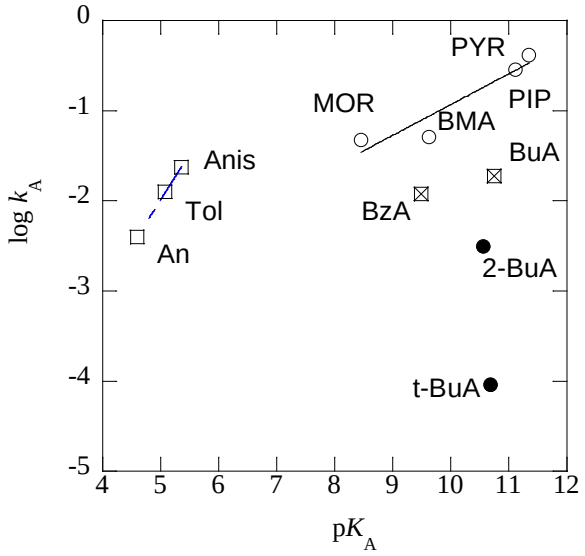


Figure 3. Plot of log k_A values at 293.1 K for the reaction of 4,6-dichloro-5-nitro-benzofuroxan with different amines in MeOH *versus* the corresponding pK_{aH} values.

Kinetic data in toluene (Figure 4) appear very interesting. As a matter of fact now the k_0 values, i.e. the kinetic constants concerning the uncatalyzed process of all aliphatic secondary and primary (with low steric requirement) amines, gave a good unique relationship *versus* log K_B (*slope* 1.14 ± 0.14, *r* 0.972, *n* 6).

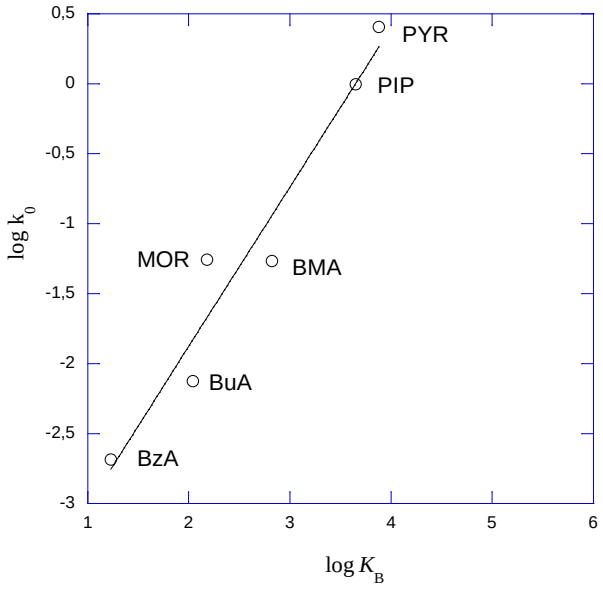


Figure 4. Plot of log k_0 values at 293.1 K for the reaction of 4,6-dichloro-5-nitro-benzofuroxan with different amines in toluene *versus* the corresponding log K_B values of amines.

As expected, plots *versus* the *N* Mayr constants (in acetonitrile) largely appears the most interesting one, in fact these constants of nucleophiles give a picture of the electronic and steric effects/interactions occurring in the nucleophilic process much more near to reality of a nucleophilic aromatic substitution than pK_{aH} and K_b values. We have not been able to find in literature the *N* Mayr constant concerning methylbenzylamine (a secondary amine) and 2-butylamine (a primary amine with a significant steric requirement).

Considering the other nine nucleophiles (both aliphatic and aromatic) we have obtained interesting results quite different in the two solvents (Figures 5 and 6), finding two relationships for kinetic data in methanol one for aliphatic (*s* 0.38 ± 0.05, *r* 0.975, *n* 5) and another for aromatic amines (*s* 0.86 ± 0.31, *r* 0.96, *n* 3), and in contrast a good unique relationship in toluene (*s* 0.88 ± 0.06, *r* 0.995, *n* 8). Interestingly in both solvents kinetic data for *t*-butylamine, *id est* for the primary amine characterized by the highest steric requirement, do not correlate with *N* Mayr constants.

Looking at data in methanol we have found different sensibility to *N* Mayr constants of the two lots of amines: higher in the aromatic amines (*s* 0.86) than in the aliphatic ones (slope 0.38). Then a comparison between the relationships in the two solvents indicate a larger effect in toluene than in methanol, in line with the fact that used Mayr constants have been collected in acetonitrile, that is a solvent more similar to methanol than to toluene (compare, for example, the dielectric constants, ε values, for the three solvents considered: 33, 2.38, 38).[29]

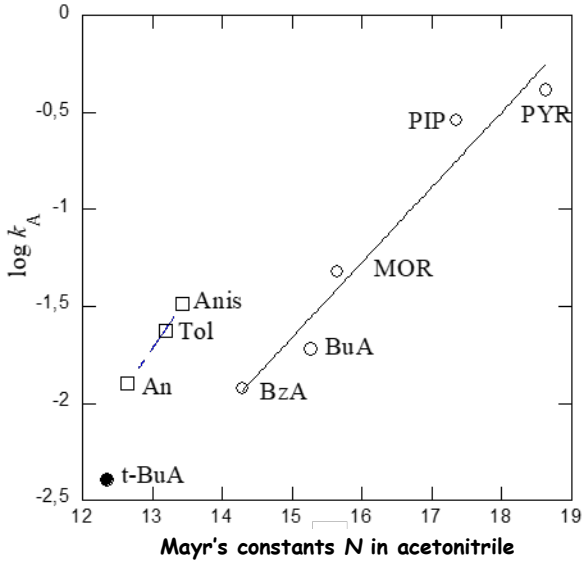


Figure 5. Plot of log k_A for the reaction of 4,6-dichloro-5-nitro-benzofuroxan with different amines in MeOH *versus* *N* Mayr constants.

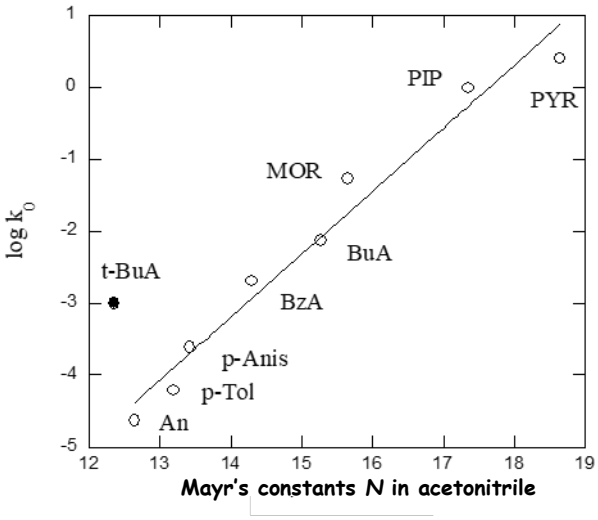


Figure 6. Plot of log k_A for the reaction of 4,6-dichloro-5-nitrobenzofuroxan with different amines in toluene *versus N* Mayr nucleophylic constants.

CONCLUSIONS

The whole of the kinetic data collected in this work, allows us to draw some interesting considerations.

4,6-Dichloro-5-nitrobenzofuroxan **1** shows a very large reactivity with the tested nitrogen nucleophiles and this result appears very interesting and seems depending on different factors.

In fact, looking at its structure we can presume that the presence of the two chlorine atoms at C_4 and C_6 will constrain the nitrogroup at C_5 out of the plane of the carbocyclic system lowering its ability to activate nucleophilic substitutions. This idea is validated by the behavior of 1,3-dichloro-2-nitrobenzene with nucleophiles. In this compound the presence of a second chlorine in *meta* position would be able to increase the reactivity with nucleophiles with respect to 2-nitrochlorobenzene because of the electron-attracting effect of the *meta*-chlorine atom (σ_m +0.373), *viceversa* the opposite occurs,[41] clearly indicating the occurrence of a kind of secondary steric effect able to affect its nucleophilic reactivity. Moreover we would like to evidence that in 1,3-dichloro-2-nitrobenzene, considering the nucleophilic substitution, the two chlorine atoms are 'equivalent'.

In line with the fact that the behavior (very low reactivity) of 1,3-dichloro-2-nitrobenzene with nucleophiles depends on the rotation out of plane of the carbocyclic ring of the nitro group (then unable to exert in a complete way its electron-withdrawing ability) another very interesting datum can be remembered. 1,3-Dichloro-2,5-dinitrobenzene reacts with piperidine giving 1-(2,6-dichloro-4-nitrophenyl)piperidine:[42] that is the substitution of the nitrogroup linked at C-2 occurs and not that of one of the two chlorine atoms, once more again confirming the rotation of the nitro group, then not able to activate the substitution of a chlorine atom. This interpretation of the previous data is in line with the data concerning the reactivity of 2,5-dinitrochlorobenzene: it reacts with nitrogen nucleophiles giving the expected substitution of the chlorine[43] thus confirming that the unexpected behavior of 1,3-dichloro-2,5-dinitrobenzene depends 'only' by the non-planarity of the nitrogroup.

Therefore, the behavior with nucleophiles of 4,6-dichloro-5-nitrobenzofuroxan (**1)** can be understood considering the following factors. First of discussing its nucleophilic reactivity it must be remarked that in it the two chlorine atoms are not equivalent and that only that one linked at C-4 is substituted by nucleophiles, in line with the fact that C-4 is linked by a 'double' bond to C-5, on which the electron-withdrawing nitrogroup is present (*viceversa* chlorine on C-6 is on a carbon atom linked to C-5 by a 'single' bond). Therefore this peculiar behavior seems strictly linked to the non-aromatic character of the benzocondensed ring that behaves essentially as ciclohexadiene system: this fact is well in line with the already remembered low aromatic character of benzofuroxan (Bird aromaticity index 81**)**.

Looking at the factors affecting the reactivity of 4,6-dichloro-5-nitrobenzofuroxan (**1)** surely must be considered the very strong electron-withdrawing power of the furoxan ring: we 'can' say that it is much more efficient of a nitrogroup in activating the reactivity with nucleophiles of 4-chlorine atom, as already pointed out by Sharnin and co-workers.[14]

We think that another relevant factor must be considered to understand the high reactivity with nucleophiles of 4,6-dichloro-5-nitrobenzofuroxan (**1)**: the low aromatic character of the benzofuroxan.

It is well known that halogen derivatives of benzene can react with nucleophiles (giving a S_NAr process) only if one or more strong electron-withdrawing groups are present in the ring and this fact has been related to the otherwise too high activation energy in large part depending on the destabilization linked to the formation of intermediates which have loss a large part of the resonance stabilization characteristic of the aromatic starting substrates. In line with this point of view some years ago, comparing the reactivity in ethanol of 4-nitrobromobenzene[44], 2-bromo-5-nitrothiophene,[45] 2-bromo-5-nitroselenophene[46] and 2-bromo-5-nitrofuran[47] with piperidine we have evidenced that there is a relationship between reactivity and aromatic character of the studied substrates[1a] (I_A for the four aromatic systems are 100, 81.5, 73, 53, respectively)[33] as shown in figure 7.

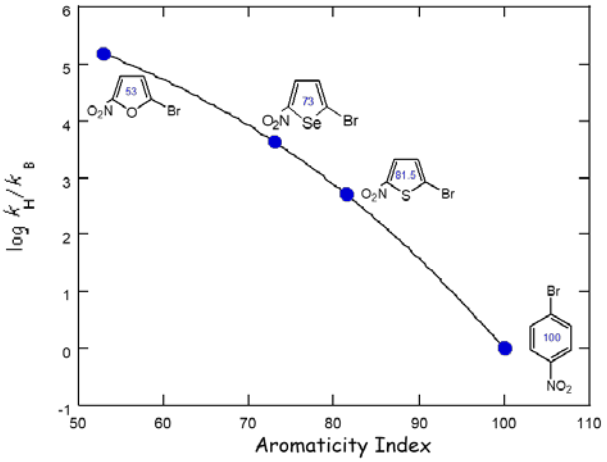


Figure 7. Logarithmic plot of the reactivity in piperidinodebromination (ethanol, at 293.1 K) of 4-nitrobromobenzene, 2-bromo-5-nitrothiophene, 2-bromo-5-nitroselenophene, and 2-bromo-5-nitrofurane *versus* Bird aromaticity indexes.

Therefore being the benzofuroxan characterized by a very low aromatic character we can suppose that this factor is 'fundamental' in determining the high reactivity of 4,6-dichloro-5-nitrobenzofuroxan **1** with nitrogen nucleophiles that we have observed.

In conclusion we can say that the high reactivity of 4,6-dichloro-5-nitrobenzofuroxan **1** with nucleophiles depends by the combination of two factors: 1) the high electron-withdrawing power of the furoxan ring; 2) the low aromatic character of the benzofuroxan system.

The whole of these two factors makes 4,6-dichloro-5-nitrobenzofuroxan **1** reactive about as 2,4-dinitrochlorobenzene (**5**) with nucleophiles, for example with piperidine in methanol.[48] This fact occurs notwithstanding the above mentioned secondary steric effect, which prevents to nitro group at C-5 to exert at the better its activating effect on

the nucleophilic substitution, thus confirming the relevance of the above discussed factors.

EXPERIMENTAL

General. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AVANCE 400 spectrometer (Bruker BioSpin, Rheinstetten, Germany) operating at 400 MHz (for ^{1}H NMR) and 100.56 MHz (for ^{13}C NMR). Chemical shifts were measured in δ (ppm) with reference to the solvent (δ= 7.26 ppm and 77.00 ppm for $CDCl_3$, for ^{1}H and ^{13}C NMR, respectively). IR spectra were recorded on a UR-20 spectrometer in the 400–3600 cm^{-1} range in KBr. Elemental analysis was performed on a CHNS-O Elemental Analyser EuroEA3028-HT-OM (EuroVector S.p.A., Milan, Italy). The melting points were determined in glass capillaries on a Stuart SMP 10 instrument.

The following compounds were prepared according with the literature procedures indicated: 4,6-dichloro-5-nitrobenzofuroxan **1**,[3a] 4-(benzylamino)-6-chloro-5-nitrobenzofuroxan **4b**,[3a] 6-chloro-5-nitro-4-(piperidin-1-yl)benzofuroxan **4f**,[49] 6-chloro-4-morpholino-5-nitrobenzofuroxan **4h**,[3a] 6-chloro-5-nitro-4-(phenylamino)benzofuroxan **4i**,[49] 6-chloro-5-nitro-4-((4-methoxyphenyl)amino)benzofuroxan **4k**.[49]

Kinetic Measurements

The kinetics have been followed spectrophotometrically as previously described by measuring the formation of **3a**–**k** at the wavelengths of the maxima of their absorbance by using a UV-Vis spectrophotometer Beckman_Coulter DU 800 apparatus equipped with a Peltier devise. It works using a Kaleidagraph program, which gives directly the values constants. In every instance, the experimental kinetic constants have been obtained with correlation coefficient ≥ 0.9997. The concentrations used were 2.00×10^{-4} mol dm^{-3} for substrates and those reported in Tables A-L and M-Y for amines. The used wavelengths and log ε values are shown in Tables A-L and M-Y. The rate constants are accurate to within ± 3%. Experimental second-order kinetic constants are reported in Tables A-L and M-Y.

Reaction between 4,6-dichloro-5-nitrobenzofuroxan (1) and amines. To a solution of 4,6-dichloro-5-nitrobenzofuroxan **(1)** (0.0008 mol) in 5 mL of methanol or toluene at room temperature was added a solution of amine **3** (0.0016 mol) in 5 mL of methanol or toluene. The reaction was carried out at room temperature and under magnetic stirring, and the conversion was monitored through TLC analysis (eluent: toluene:ethyl acetate, 2:1). After 2-4 h the the solvent was removed in vacuum, the residue was washed with cold water (100 mL) and dried under vacuum (0.06 mm Hg) at 40 °C to constant weight.

4-(Butylamino)-6-chloro-5-nitrobenzo[*c*][1,2,5]oxadiazole 1-oxide (4a). 0.225 g (98 %), dark red powder, Mp: 112-113 °C. IR (*v*, cm^{-1}): 685 (CCl), 1331 (NO_2 symm), 1532 (NO_2 asymm), 1624 (furoxan ring), 3075 (C^7H), 3445 (NH). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.35 (br. s, 1H), 6.63 (s, 1H), 4.04-4.10 (m, 2H), 1.74-1.82 (m, 2H), 1.49 (dd, 3H, *J* = 14.80 Hz, *J* = 7.42 Hz), 1.01 (t, 3H, *J* = 7.35 Hz). ^{13}C{^{1}H} NMR (100.56 MHz, $CDCl_3$), δ (ppm): 147.4, 138.4, 129.9, 127.0, 112.7, 99.4, 47.2, 32.2, 19.8, 13.6. Anal. calcd (%) for $C_{10}H_{11}ClN_4O_4$: C 41.90; H 3.87; Cl 12.37; N 19.54. Found: C 41.95; H 3.81; Cl 12.32; N 19.59.

4-(*Sec*-butylamino)-6-chloro-5-nitrobenzo[*c*][1,2,5]oxadiazole 1-oxide (4c). 0.220 g (96 %), Orange powder. Mp: 112-113 °C. IR (*v*, cm^{-1}): 684 (CCl), 1321 (NO_2 symm), 1561 (NO_2 asymm), 1621 (furoxan ring), 3083 (C^7H), 3314 (NH). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.20 (br. s, 1H), 6.65 (s, 1H), 4.84 (dt, 1H, *J* = 6.4, *J* = 15.1 Hz), 1.69-1.79 (m, 2H), 1.40 (d, 3H, *J* = 6.4 Hz), 1.04 (t, 3H, *J* = 7.4 Hz). ^{13}C{^{1}H} NMR (100.56 MHz, $CDCl_3$), δ (ppm): 147.0, 137.7, 129.9, 127.2, 112.8, 99.4, 54.4, 30.8, 21.3, 10.2. Anal. calcd (%) for $C_{10}H_{11}ClN_4O_4$: C 41.90; H 3.87; Cl 12.37; N 19.54. Found: C 41.94; H 3.83; Cl 12.35; N 19.59.

4-(*Tert*-butylamino)-6-chloro-5-nitrobenzo[*c*][1,2,5]oxadiazole 1-oxide (4d). 0.216 g (95 %), Red powder. Mp: 91-92 °C. IR (*v*, cm^{-1}): 649 (CCl), 1294 (NO_2 symm), 1565 (NO_2 asymm), 1627 (furoxan ring), 3087 (C^7H), 3313 (NH). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.99 (br. s, 1H), 6.69 (s, 1H), 1.64 (s, 9H). ^{13}C{^{1}H} NMR (100.56 MHz, $CDCl_3$) δ (ppm): 146.3, 136.6, 130.7, 129.4, 113.4, 100.4, 56.7, 30.3. Anal. calcd (%) for $C_{10}H_{11}ClN_4O_4$: C 41.90; H 3.87; Cl 12.37; N 19.54. Found: C 41.95; H 3.83; Cl 12.32; N 19.59.

4-(Benzyl(methyl)amino)-6-chloro-5-nitrobenzo[*c*][1,2,5]oxadiazole 1-oxide (4e). 0.258 g (96 %), Orange powder. Mp: 104.9-105.0 °C. IR (*v*, cm^{-1}): 744 (CCl), 1339 (NO_2 symm), 1524 (NO_2 asymm), 1621 (furoxan ring), 3069 (H_{ap}), 3443 (NH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.31-7.40 (m, 5H), 6.89 (s, 1H), 5.03 (s, 2H), 3.00 (s, 3H). ^{13}C{^{1}H} NMR (100.56 MHz, $CDCl_3$) δ (ppm): 149.1, 136.1, 135.9, 135.7, 128.9, 128.3, 128.2, 127.9, 113.6, 101.5, 59.4, 39.3. Anal. calcd (%) for $C_{14}H_{11}ClN_4O_4$: C 50.24; H 3.31; Cl 10.59; N 16.74. Found: C 50.29; H 3.37; Cl 10.52; N 16.72.

6-Chloro-5-nitro-4-(pyrrolidin-1-yl)benzo[*c*][1,2,5]oxadiazole 1-oxide (4g). 0.225 g (99 %), Red powder. Mp: 172-175 °C. IR (*v*, cm^{-1}): 682 (CCl), 1337 (NO_2 symm), 1550 (NO_2 asymm), 1619 (furoxan ring), 3074 (C^7H). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.59 (s, 1H), 3.83 (t, 4H, *J* = 6.4 Hz), 2.07 (t, 4H, *J* = 6.5 Hz). ^{13}C{^{1}H} NMR (100.56 MHz $CDCl_3$) δ (ppm): 149.0, 132.9, 130.8, 129.1, 113.8, 96.9, 52.2, 25.7. Anal. calcd (%) for $C_{10}H_9ClN_4O_4$: C 42.19; H 3.19; Cl 12.45; N 19.68. Found: C 42.12; H 3.15; Cl 12.47; N 19.61.

6-Chloro-5-nitro-4-(*p*-tolylamino)benzo[*c*][1,2,5]oxadiazole 1-oxide (**4j).** 0.256 g (99 %), Purple powder. Mp: 168-169 °C. IR (*v*, cm^{-1}): 649 (CCl), 1361 (NO_2, symm), 1559 (NO_2, asymm), 1620 (furoxan ring), 3040 (C^7H), 3442 (NH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.71 (s, 1H), 7.22 (d, 2H, *J* = 8.3 Hz), 7.16 (d, 2H, *J* = 8.3 Hz), 6.86 (s, 1H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (100.56 MHz, $CDCl_3$) δ (ppm): 146.3, 138.1, 134.8, 133.6, 130.0, 128.7, 124.9, 123.2, 112.9, 101.9, 21.2. Anal. calcd (%) for $C_{13}H_9ClN_4O_4$: C 48.69; H 2.83; Cl 11.06; N 17.47. Found: C 48.68; H 2.87; Cl 11.01; N 17.45.

ASSOCIATED CONTENT

Supporting Information. Rate constants and activation parameters. ^{1}H and ^{13}C{^{1}H} NMR spectra of new compounds. "This material is available free of charge via the Internet at http://pubs.acs.org."

AUTHOR INFORMATION

Corresponding Author

*Domenico Spinelli, Department of Chemistry 'G. Ciamician' ALMA MATER STUDIORUM – Università di Bologna, Via Selmi 2, 40126 Bologna, Italy E-mail address: domenico.spinelli@unibo.it Tel.: 00393487733265.

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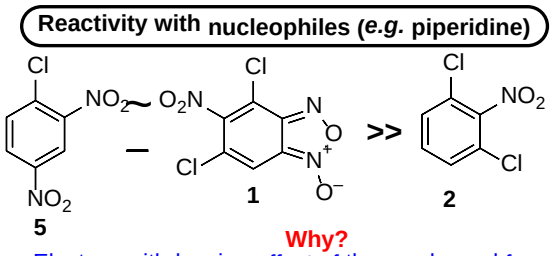

Why?

1) Electron-withdrawing effect of the condensed furoxan ring

2) Low aromaticity of the benzofuroxan ring