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PAPER

# Molecular recognition-based catalysis in nucleophilic aromatic substitution: a mechanistic study†

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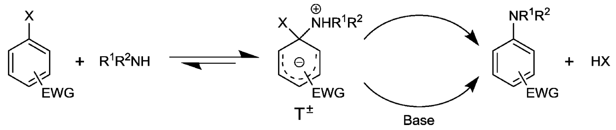
Nucleophilic aromatic substitution for nitro-activated substrates in the presence of glymes and crown ethers is reported. The kinetic study reveals the many-sided nature of the polyether-catalyzed S$_N$Ar mechanism as well as the main features affecting the course of the reaction. Thus, the process can be efficiently controlled by the catalyst through a molecular-recognition process, being also strongly dependent on the electronic structure of the substrate and, therefore, giving rise to a versatile reaction system. The kinetic model proposed herein allows quantifying the fractions of reaction proceeding through the different routes. Information on the nature of the host–guest interaction between the catalyst and the substrate will also be extracted.

## Introduction

The ability of glymes and crown ethers to bind inorganic and organic cations has allowed them to be widely used in homogeneous and heterogeneous catalysis.[1,2] Generally, these species act as catalysts either in reactions involving metal ions, salts and bases, or processes requiring substrate recognition. In this regard, ester aminolysis in aprotic solvents is one of the most reported cases in the literature.[3,4] These reactions are known to proceed through a rate-limiting breakdown of a zwitterionic tetrahedral intermediate, which is generated by the addition of a molecule of amine to the ester. In this case, glymes and crown ethers act as base catalysts through a specific host–guest interaction with the ammonium moiety of the reaction intermediate.[5–14] In order to achieve a better understanding of these molecular-recognition processes, the exploration of alternative reactions involving zwitterionic intermediates appears to be the next logical step. For this purpose, the nucleophilic aromatic substitution (S$_N$Ar) by *n*-butylamine for two different and representative nitroarenes has been studied in the presence of glymes and crown ethers. The criterion used for selecting these two nitro-activated substrates has been the highly different weight of base catalysis exhibited by these compounds in their corresponding S$_N$Ar reactions. It must be noted that the mechanism of S$_N$Ar by amines is well-established as well as the factors determining whether base catalysis is observed or not.[15–19] Scheme 1 shows the mechanism for S$_N$Ar reactions involving primary and secondary amines.[20,21]



**Scheme 1**

In this kinetic study, both the amine and the polyether act as base catalysts. Given the synthetic utility of this reaction,[15] S$_N$Ar processes constitute an ideal subject for a comprehensive mechanistic analysis. Thus, this work will provide helpful information for the elucidation of the different operating mechanisms in this process as well as the nature of the host–guest interaction between the catalyst and the substrate.

## Results

In the present work the polyether-catalyzed S$_N$Ar reaction of 1-chloro-2,4-dinitrobenzene (CDNB) and 1-fluoro-4-nitrobenzene (FNB) in chlorobenzene is reported. The presence of electron-withdrawing groups in these substrates, particularly at the *ortho* and *para* carbons, comes from the necessity of reducing the electronic density in the aromatic ring favoring the nucleophilic attack.

All the reactions have been run in the presence of crown ethers and their open-chain analogues, glymes (Table 1). In all cases *n*-butylamine has been used as the reactant nucleophile. Analogously to ester aminolysis, it is expected that these polyethers act as base catalysts facilitating the decomposition of the Meisenheimer complex during the S$_N$Ar reaction given

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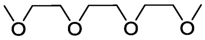
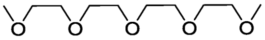
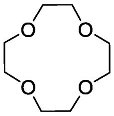
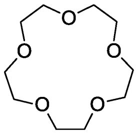
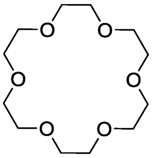
**Table 1** Polyethers employed as catalysts in the kinetic study of the CDNB and FNB $S_NAr$ reaction

| Catalyst (symbol) | Structure |
|---|---|
| Diglyme (G2) |  |
| Triglyme (G3) |  |
| Tetraglyme (G4) |  |
| Pentaglyme (G5) |  |
| 12-Crown-4 (12C4) |  |
| 15-Crown-5 (15C5) |  |
| 18-Crown-6 (18C6) |  |

that both processes show the same type of ammonium moiety in their corresponding zwitterionic addition intermediate.

Under all the experimental conditions used in this study the reaction rate for the CDNB and FNB nucleophilic aromatic substitution shows a first-order dependence on the nitro-aromatic compound concentration. Regarding the nucleophile, all the reactions exhibit a linear and quadratic dependence on the *n*-butylamine concentration and a remarkable catalytic effect as the polyether concentration is increased (see Fig. 1 and also Fig. S1–S6 and S19–S21, ESI†).

Thus, the process is governed by eqn (1).

$$k_{obs} = \alpha[BuNH_2] + \beta[BuNH_2]^2 \qquad (1)$$

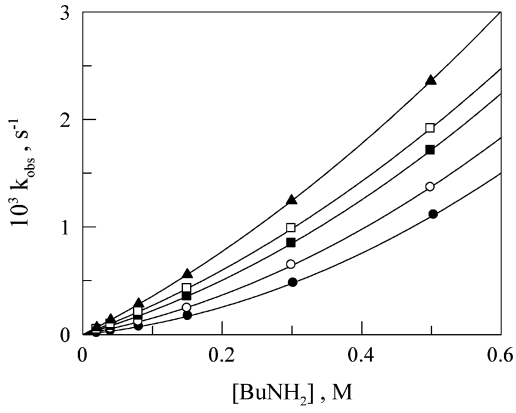


**Fig. 1** Influence of *n*-butylamine concentration on $k_{obs}$ for the $S_NAr$ reaction of 1-chloro-2,4-dinitrobenzene, $T$ = 25.0 °C, [CDNB] = $1.4 \times 10^{-4}$ M. (●) [G4] = 0 M; (○) [G4] = 0.11 M; (■) [G4] = 0.25 M; (□) [G4] = 0.35 M and (▲) [G4] = 0.55 M.

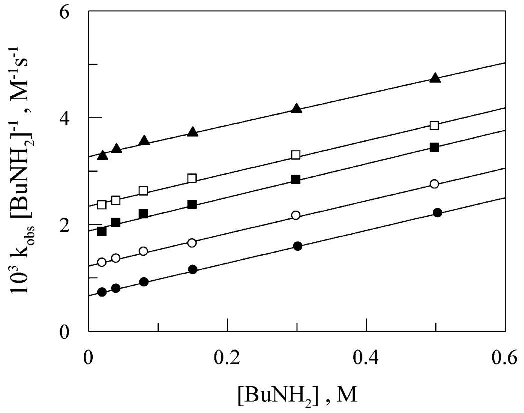


**Fig. 2** Influence of *n*-butylamine concentration on $k_{obs}$/[$BuNH_2$] (eqn (2)) for the $S_NAr$ reaction of 1-chloro-2,4-dinitrobenzene, $T$ = 25.0 °C, [CDNB] = $1.4 \times 10^{-4}$ M. (●) [G4] = 0 M; (○) [G4] = 0.11 M; (■) [G4] = 0.25 M; (□) [G4] = 0.35 M and (▲) [G4] = 0.55 M.

where $k_{obs}$ denotes the observed rate constant for the $S_NAr$ reaction. This linear and quadratic dependence can be confirmed by linearizing eqn (1) to eqn (2):

$$\frac{k_{obs}}{[BuNH_2]} = \alpha + \beta[BuNH_2] \qquad (2)$$

Fig. 2 shows how eqn (2) fits the experimental data (see also Fig. S7–S12 and S22–S24, ESI†). As a result, this dual kinetic behavior can be clearly confirmed, which suggests the possibility of different operating mechanisms in this process.

From the intercepts and slopes in Fig. 2, values for $\alpha$ and $\beta$ in the absence and presence of catalysts can be obtained for the CDNB $S_NAr$ reaction. By plotting these parameters against the catalyst concentration for every set of data, Fig. 3 is obtained.

As shown in Fig. 3, $\alpha$ exhibits a linear dependence on the catalyst concentration while $\beta$ remains constant despite the variation in the polyether concentration. This behavior is observed for all glymes and crown ethers tested in this work (see Fig. S13–S18, ESI†).[22] Accordingly, these rate constants can be expressed as $\alpha = k_A + k_C$[catalyst] and $\beta = k_B$. Thus, the rate equation for CDNB $S_NAr$ reaction (eqn (1)) can be rewritten as eqn (3):

$$k_{obs} = k_A[BuNH_2] + k_B[BuNH_2]^2 + k_C[BuNH_2][catalyst] \qquad (3)$$

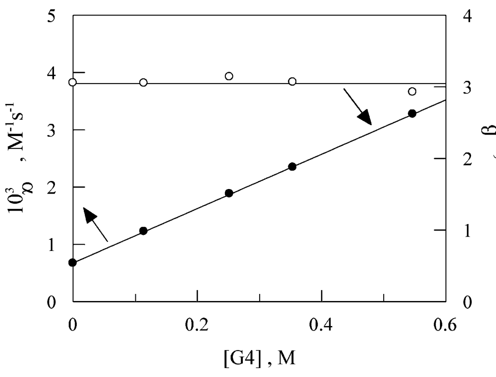


**Fig. 3** Influence of G4 concentration on the $\alpha$ and $\beta$ terms (eqn (2)) for the $S_NAr$ reaction of 1-chloro-2,4-dinitrobenzene. (●) $\alpha$ and (○) $\beta$.

**Table 2** Macroscopic rate constants for the CDNB $S_NAr$ by *n*-butylamine in the presence of different polyethers, $T = 25.0$ °C

| Catalyst | $10^4\ k_A/M^{-1}\ s^{-1}$ | $10^3\ k_B/M^{-2}\ s^{-1}$ | $10^3\ k_C/M^{-2}\ s^{-1}$ |
|---|---|---|---|
| G2 | 6.5 0.2 | 2.9 0.1 | 1.4 0.1 |
| G3 | 7.0 0.3 | 2.9 0.1 | 3.2 0.1 |
| G4 | 6.8 0.1 | 3.0 0.1 | 4.7 0.1 |
| G5 | 7.0 0.1 | 3.2 0.2 | 5.2 0.1 |
| 12C4 | 6.8 0.1 | 3.1 0.1 | 2.3 0.1 |
| 15C5 | 6.6 0.1 | 3.2 0.2 | 3.2 0.1 |
| 18C6 | 6.7 0.3 | 2.9 0.2 | 4.1 0.1 |

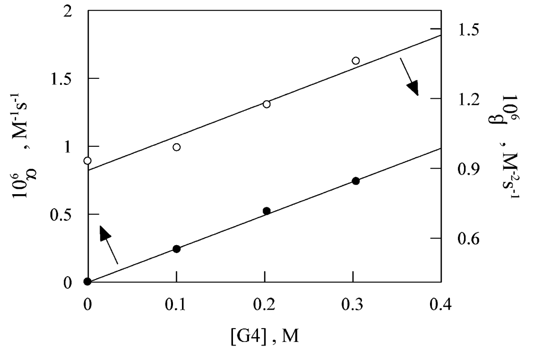


**Fig. 4** Influence of G4 concentration on the $\alpha$ and $\beta$ terms (eqn (2)) for the $S_NAr$ reaction of 1-fluoro-4-nitrobenzene. (●) $\alpha$ and (○) $\beta$.

Table 2 shows the values for the CDNB macroscopic rate constants. These parameters are obtained from the intercepts and slopes in Fig. 3 and Fig. S13–S18 (ESI†).

The same procedure is followed to determine the rate equation for the FNB $S_NAr$ reaction. By plotting $\alpha$ and $\beta$ values against the polyether concentration, Fig. 4 is obtained.

In Fig. 4, the FNB $S_NAr$ reaction also exhibits a linear dependence of $\alpha$ on the catalyst concentration. However, in contrast to the CDNB $S_NAr$ reaction, $\beta$ does not remain constant but increases linearly as the polyether concentration is increased (see also Fig. S25 and S26, ESI†). Therefore, $\alpha$ and $\beta$ for the FNB $S_NAr$ reaction can be reformulated as $\alpha = k_C[\text{catalyst}]$ (it must be noted that no intercept is observed in the absence of catalysts) and $\beta = k_B + k_D[\text{catalyst}]$. As a result, the rate equation for the FNB $S_NAr$ reaction can be expressed as eqn (4):

$$k_{obs} = k_B[BuNH_2]^2 + k_C[BuNH_2][\text{catalyst}] + k_D[BuNH_2]^2[\text{catalyst}] \quad (4)$$

Table 3 shows the values for the FNB macroscopic rate constants. These parameters are obtained from the intercepts and slopes in Fig. 4 and Fig. S25 and S26 (ESI†).

Taking into account these results, a more general kinetic law for polyether-catalyzed $S_NAr$ can be proposed. This rate equation is given by eqn (5):

**Table 3** Macroscopic rate constants for the FNB $S_NAr$ by *n*-butylamine in the presence of different polyethers, $T = 25.0$ °C

| Catalyst | $10^7\ k_B/M^{-1}\ s^{-1}$ | $10^6\ k_C/M^{-2}\ s^{-1}$ | $10^6\ k_D/M^{-2}\ s^{-1}$ |
|---|---|---|---|
| G4 | 8.9 0.2 | 2.5 0.1 | 1.1 0.1 |
| G5 | 9.0 0.1 | 3.0 0.1 | 1.3 0.1 |
| 18C6 | 9.3 0.2 | 1.1 0.1 | 1.1 0.1 |

$$k_{obs} = k_A[BuNH_2] + k_B[BuNH_2]^2 + k_C[BuNH_2][\text{catalyst}] + k_D[BuNH_2]^2[\text{catalyst}] \quad (5)$$

Eqn (5) accounts for the experimental results found for the CDNB and FNB nucleophilic aromatic substitution reactions. Thus, while the CDNB $S_NAr$ reaction is governed by the rate constants $k_A$, $k_B$ and $k_C$ (eqn (3)), the kinetic behavior for the FNB reaction is controlled by $k_B$, $k_C$ and $k_D$ (eqn (4)). All these observations point to the existence of two differentiated operating mechanisms for the CDNB and FNB $S_NAr$ reactions or at least, a common mechanism where the relative weight of the different paths is markedly different.

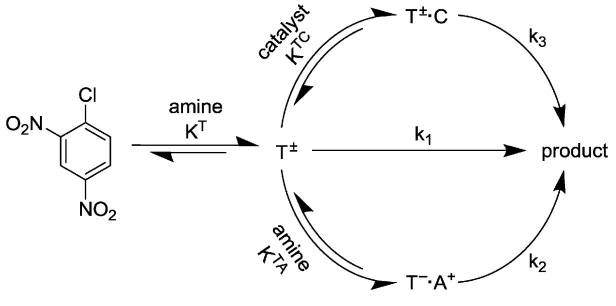
## Discussion

### 1. Polyether-catalyzed $S_NAr$ reaction of 1-chloro-2,4-dinitrobenzene

From eqn (3), a mechanism for the CDNB $S_NAr$ reaction with *n*-butylamine in the presence of polyethers can be proposed (Scheme 2).

Thus, this reaction would proceed through an initial attack of *n*-butylamine at the nucleofuge-bearing carbon atom of CDNB to generate a zwitterionic Meisenheimer complex. The existence of this σ-complex tetrahedral intermediate (from now on simply referred to as $T^{\pm}$) has been widely reported in the literature.[18,19] In the absence of catalysts, this addition intermediate may lead to the final product both spontaneously ($k_1$ route) and assisted by another molecule of amine ($k_2$ route). The latter process would take place through a stepwise mechanism. As can be observed, the existence of a $T^{\pm}$–amine complex is proposed. This complex will be referred to as $T^{-}{\cdot}A^{+}$ given that $T^{\pm}$ is more acidic (1–2 p$K_a$ units) than the butylammonium ion and, therefore, it is unlikely the formation of a complex between $T^{\pm}$ and an amine molecule not involving a proton transfer. In the presence of added polyethers, as proposed by Hogan and Gandour[8] for aminolysis reactions, the formation of a complex between the intermediate and the catalyst ($T^{\pm}{\cdot}C$) is suggested. Such a complex would evolve directly into the final product through a rate-limiting decomposition ($k_3$ route).

It must be noted that the different reaction pathways of the mechanisms shown in Scheme 2 are accounted for in eqn (3). On one hand, the catalyst-independent terms of this expression show a linear and quadratic dependence on the amine concentration. These terms would correspond to the spontaneous and amine-assisted decomposition of the tetrahedral intermediate, respectively. On the other hand, the catalyst-dependent term



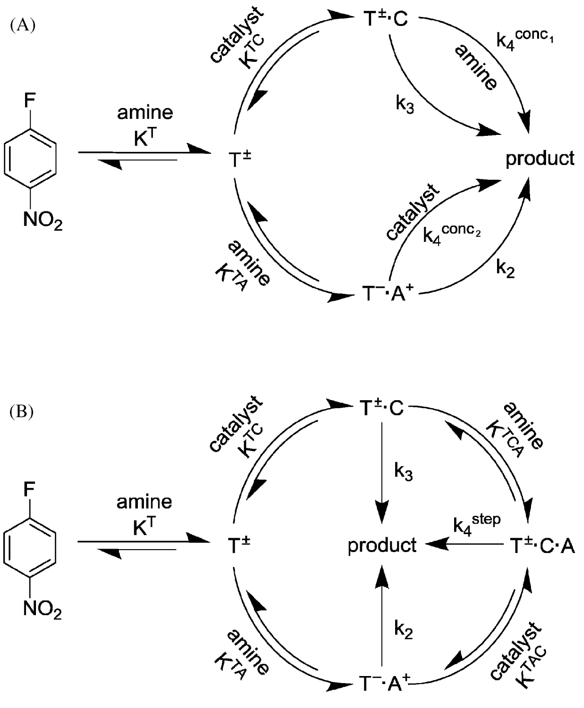
**Scheme 2**

would be ascribed to the rate-limiting decomposition of the $T^{\pm}{\cdot}C$ complex. According to this model, the empirical constants previously determined ($k_A$, $k_B$ and $k_C$) can be redefined as a function of microscopic parameters. Thus, $k_A = K^T k_1$, $k_B = K^T K^{TA} k_2$ and $k_C = K^T K^{TC} k_3$, where $K^T$, $K^{TA}$ and $K^{TC}$ are the equilibrium constants for the formation of the $T^{\pm}$, $T^{-}{\cdot}A^{+}$ and $T^{\pm}{\cdot}C$ complexes, respectively, and $k_1$, $k_2$ and $k_3$ are the intrinsic reactivity constants for the CDNB $S_NAr$ reaction.

## 2. Polyether-catalyzed $S_NAr$ reaction of 1-fluoro-4-nitrobenzene

Taking into account the kinetic law shown in eqn (4) the following reaction mechanisms for the FNB $S_NAr$ may be suggested (Scheme 3).

Analogously to CDNB, the FNB $S_NAr$ reaction proceeds through a nucleophilic attack at the nucleofuge-bearing carbon generating a tetrahedral intermediate. In the absence of catalysts, this intermediate would lead to the final product through a stepwise amine-promoted decomposition ($k_2$ route). However, unlike CDNB, the rate law for the FNB $S_NAr$ reaction shows no linear dependence on the amine concentration in the catalyst-independent term (eqn (4)). Therefore, a spontaneous breakdown of the addition intermediate can be ruled out. In the presence of polyethers several are the possibilities. On one hand, as concerted mechanisms, the amine-assisted decomposition of the $T^{\pm}{\cdot}C$ complex and/or the polyether-promoted breakdown of the $T^{-}{\cdot}A^{+}$ species are proposed ($k_4$ routes in Scheme 3A). On the other hand, and assuming a stepwise nature of such pathways, the formation of a $T^{\pm}$–catalyst–amine species ($T^{\pm}{\cdot}C{\cdot}A$) is postulated. This complex would arise from the association of $T^{\pm}{\cdot}C$ to a molecule of amine and/or the binding of $T^{-}{\cdot}A^{+}$ to a molecule of polyether (see discussion in Section 3). Either way, the reaction would proceed through a rate-limiting decomposition of the $T^{\pm}{\cdot}C{\cdot}A$ complex ($k_4$ route in Scheme 3B). Concerted or stepwise, the amine-assisted decomposition of $T^{\pm}{\cdot}C$ and the polyether-promoted breakdown of the $T^{-}{\cdot}A^{+}$ intermediate must be considered since they both are kinetically undistinguishable. It must be also noted that the very existence of the $k_4$ route supports the postulated formation of the $T^{\pm}{\cdot}C$ and/or $T^{-}{\cdot}A^{+}$ complex, since a concerted trimolecular process between the Meisenheimer complex, the catalyst and the amine is highly unlikely.



Scheme 3

The different reaction pathways considered in Scheme 3 are accounted for in eqn (4). On one hand, the catalyst-independent term shows exclusively a quadratic dependence on the amine concentration. This term would correspond to the amine-assisted breakdown of $T^{\pm}$. On the other hand, the catalyst-dependent terms show both linear and quadratic dependence on the amine concentration. The first can be ascribed to the spontaneous decomposition of the $T^{\pm}{\cdot}C$ complex. The latter can be attributed to the amine-promoted decomposition of the $T^{\pm}{\cdot}C$ complex and/or the polyether-promoted decomposition of the $T^{-}{\cdot}A^{+}$ complex. As pointed out in eqn (4), the FNB nucleophilic aromatic substitution is governed by the macroscopic rate constants $k_B$, $k_C$ and $k_D$. According to this kinetic model, such constants can be redefined as a function of microscopic parameters. Thus, $k_B = K^T K^{TA} k_2$, $k_C = K^T K^{TC} k_3$, $k_D = K^T K^{TC} k_4^{conc_1}$ and/or $k_D = K^T K^{TA} k_4^{conc_2}$ or $k_D = K^T K^{TC} K^{TCA} k_4^{step}$ and/or $k_D = K^T K^{TA} K^{TAC} k_4^{step}$, where $K^T$, $K^{TA}$, $K^{TC}$ and $K^{TCA/TAC}$ are the equilibrium constants for the formation of the $T^{\pm}$, $T^{-}{\cdot}A^{+}$, $T^{\pm}{\cdot}C$ and $T^{\pm}{\cdot}C{\cdot}A$ complexes, respectively, and $k_2$, $k_3$ and $k_4$ are the intrinsic rate constants for the FNB $S_NAr$ reaction.

## 3. Nature of the polyether catalysis on $S_NAr$ reactions

In order to elucidate the nature of the observed catalysis, a systematic comparison of the catalytic efficacies of glymes and crown ethers is required. This analysis will allow us to identify the best catalyst structure for the reaction as well as understand the mechanism of the host–guest interaction between the polyether and the substrate.

Crown ethers are generally known to be better complexing agents than glymes,[1] and might therefore be expected to be better $S_NAr$ catalysts as well. However, as shown in Table 2, glyme catalysis exhibits an inverse macrocyclic effect, *i.e.*, open-chain polyethers are better catalysts than the corresponding macrocyclic polyethers. This behavior enables a close analogy between $S_NAr$ and ester aminolysis reactions, since the latter also undergo catalysis in the presence of phase transfer agents when carried out in aprotic solvents.[5,6] In this case, catalysis arises from the binding of polyethers to the ammonium ion part of the tetrahedral intermediate formed by the attack of the amine at the ester carbonyl group. The binding interaction accelerates the decomposition of $T^{\pm}$ by breaking the stabilization of the uncomplexed zwitterionic intermediate and as a result, facilitating the expulsion of the leaving group. In view of the fact that the same type of ammonium moiety is present in the addition intermediate of $S_NAr$ reactions with amines, it may be assumed that glymes and crown ethers act in a similar way to that found in ester aminolysis.

**(a) Catalysis by glymes.** A clear evidence for the analogous kinetic behavior of ester aminolysis and $S_NAr$ reactions is presented in Fig. 5. In this plot it is shown how the per oxygen

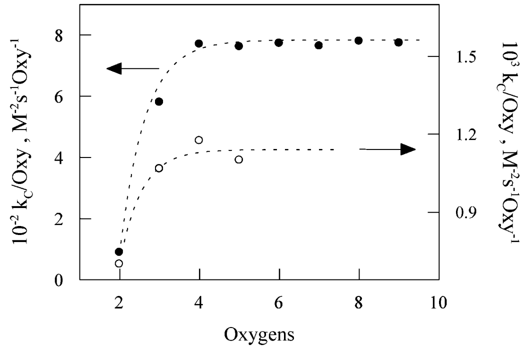


**Fig. 5** Per oxygen catalytic rate constant, $k_C$/Oxy, *vs.* number of oxygens per glyme molecule. (●) Aminolysis of *p*-nitrophenyl acetate by *n*-butylamine;[13] (○) $S_NAr$ of 1-chloro-2,4-dinitrobenzene by *n*-butylamine.

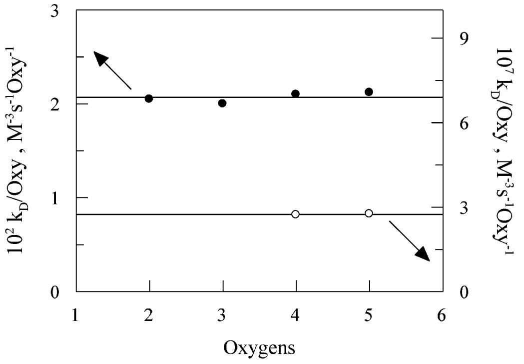


**Fig. 6** Per oxygen catalytic rate constant, $k_D$/Oxy, *vs.* number of oxygens per glyme molecule. (●) Aminolysis of *p*-nitrophenyl acetate by *n*-butylamine;[13] (○) $S_NAr$ of 1-fluoro-4-nitrobenzene by *n*-butylamine.

catalytic rate constant for both reactions increases as the number of oxygens per glyme molecule increases. The profiles seem to level off at four oxygens, and successive oxygens would only contribute to the catalysis in a statistical manner.

From this profile, the $-(CH_2OCH_2)_4-$ subunit is identified as the optimal segment for catalysis of ester aminolysis. This catalytic effect implies a specific host–guest interaction between the glyme and the tetrahedral intermediate in such a way that four oxygens donate electron density to stabilize the ammonium moiety of $T^{\pm}$. Thus, the formation of a doubly bifurcated hydrogen-bonded catalyst–substrate complex is proposed. Since a similar catalytic profile is found for the CDNB $S_NAr$ reaction, the existence of a four-point recognition of the secondary ammonium ion of the zwitterionic intermediate for this kind of processes may be also suggested. In this respect, Scheme 4 shows a tentative transition structure where this kind of host–guest interaction takes place. Hence, a glyme with more than four O atoms would only use four oxygens in order to catalyze the $S_NAr$ reaction. Further interactions between $T^{\pm}$ and glymes have been discussed in the literature.[9]

Due to the low reaction rate of the FNB $S_NAr$ reaction (half-life times on the order of weeks and months) only a reduced set of experiments on this substrate is shown. However, it must be noted that similar values were obtained for the per oxygen catalytic rate constant, $k_C$/Oxy, in the presence of G4 and G5 glymes: $(6.2 \pm 0.1) \times 10^{-7}$ $M^{-2}$ $s^{-1}$ and $(6.0 \pm 0.2) \times 10^{-7}$ $M^{-2}$ $s^{-1}$, respectively. These results support the idea of a doubly bifurcated hydrogen-bonded polyether–substrate interaction.

Regarding the polyether-promoted decomposition of the $T^{-}\cdot A^{+}$ complex (and/or the amine-promoted breakdown of the $T^{\pm}\cdot C$ complex) an analogy between nucleophilic aromatic substitution and ester aminolysis can be also drawn. Thus, for *p*-nitrophenyl acetate aminolysis the $k_D$/Oxy ratio remains constant with an increasing glyme length (Fig. 6). In spite of the lack of experimental data, the FNB $S_NAr$ reaction seems to show a similar trend for $k_D$/Oxy than that found in ester aminolysis.

This behavior is consistent with the formation of a single bifurcated hydrogen-bonded glyme–substrate association (Scheme 5) since one of the two protons of the ammonium moiety must be free to be abstracted by a base, *i.e.*, an amine molecule.

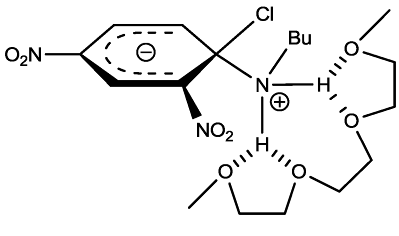
**(b) Catalysis by crown ethers.** In Fig. 7 it is shown how the per oxygen catalytic rate constant for the CDNB $S_NAr$ reaction increases as the number of oxygens per crown ether molecule increases. This catalytic profile starts to level off at five oxygen atoms. The same tendency is observed for aminolysis of *p*-nitrophenyl acetate.

In this case, a mechanism where 12C4 binds the two ammonium protons of the intermediate is proposed. This interaction would consist in one simple and two bifurcated hydrogen bonds (Scheme 6A). Thus, 12C4 would bind the reaction intermediate through three oxygen atoms. On the other hand, 15C5 and 18C6 would give rise to a doubly bifurcated hydrogen-bonded polyether–substrate association (Scheme 6B and C). Both crown ethers would make use of four oxygen atoms in order to stabilize the zwitterionic intermediate.

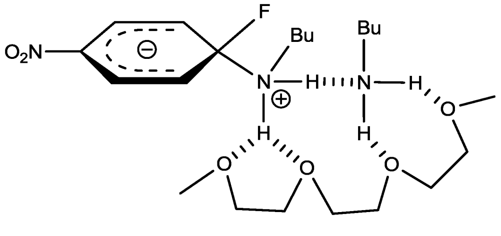
According to these results, crown ether-catalyzed nucleophilic aromatic substitution would proceed through the same mechanism than that found for ester aminolysis.

## 4. Influence of the substrate on the polyether-catalyzed $S_NAr$ mechanism

The observation of polyether catalysis for the CDNB and FNB nucleophilic aromatic substitution reactions points to a rate-limiting decomposition of the $S_NAr$ Meisenheimer complex.



**Scheme 4**



**Scheme 5**

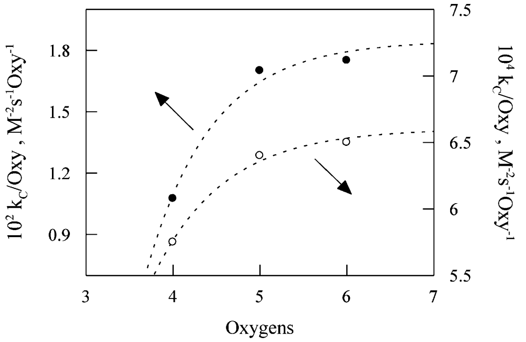
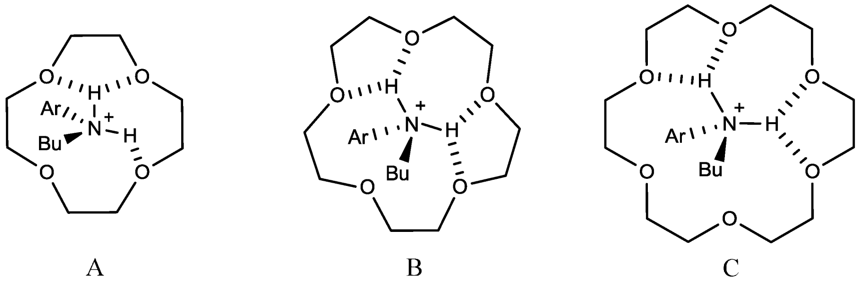


**Fig. 7** Per oxygen catalytic rate constant, $k_C$/Oxy, *vs.* number of oxygens per crown ether molecule. (●) Aminolysis of *p*-nitrophenyl acetate by *n*-butylamine;[13] (○) $S_NAr$ of 1-chloro-2,4-dinitrobenzene by *n*-butylamine.

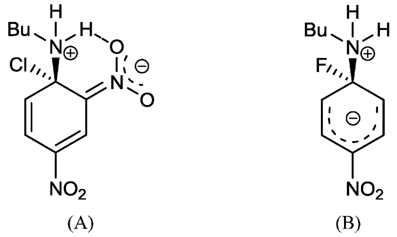
Even though glymes and crown ethers are much weaker bases than amines, they exhibit a similar ability to act as base catalysts despite their p$K_a$ differences (see $k_B$ and $k_C$ values in Table 2). In this regard, it has been reported that for ester aminolysis in aprotic solvents the catalytic abilities of oxygen bases are enhanced relative to those of nitrogen bases.[4] Thus, the catalytic efficacy of the bases would be correlated with their hydrogen-bonding capacity rather than their aqueous basicity. This behavior can be extrapolated to $S_NAr$ reactions where the same type of polyether–ammonium moiety interaction can take place.

Major differences between the CDNB and FNB $S_NAr$ reactions can be observed by analyzing mechanisms shown in Schemes 2 and 3. Thus, the CDNB $S_NAr$ reaction shows a pathway where the $T^{\pm}$ intermediate evolves spontaneously into the final product ($k_1$ route). Conversely, the assistance of an amine molecule to the zwitterionic intermediate becomes essential for the FNB $S_NAr$ reaction. The ability of the tetrahedral intermediate of CDNB to decompose without further support may be due to two different factors. First, the better leaving group present in CDNB compared to FNB will decrease the energy of the reaction intermediate facilitating the spontaneous breakdown. Second, and based on previous works,[23,24] the ability of the Meisenheimer complex of CDNB to collapse without the participation of the polyether may also be attributed to the presence of the nitro group at the *ortho* carbon of the aromatic ring. In this respect, Nudelman *et al.* reported a detailed semiempirical study on σ-complexes derived from the reaction of fluorobenzene, *o*- and *p*-fluoronitrobenzene with ammonia. Their results show the importance of the hydrogen bond between the *ortho*-nitro group and the ammonium proton. On one hand, this attractive interaction makes the *ortho*-nitro derivatives being more reactive than the *para*-isomers in their reaction with amines. On the other hand, the hydrogen bond decreases the energy of the reaction intermediate promoting the spontaneous collapse (Scheme 7A). Additional evidence in favor of this hydrogen bond stabilization was provided by the same authors.[25] On studying the *o*- and *p*-fluoronitrobenzene $S_NAr$ with amines, an $o:p$ ratio of 444 for the reaction rates in toluene is obtained. The magnitude of this value indicates the higher stability of the intermediate σ-complex in the *ortho*-isomer. In addition, possible steric effects due to the presence of the nitro group at the *ortho* carbon can be ruled out. In the absence of catalysts, the much higher reactivity of CDNB than that found for FNB supports these statements. Accordingly, the presence of a poorer leaving group in FNB and the lack of a nitro group at the *ortho* carbon of its aromatic ring (Scheme 7B) would justify the absence of a non-supported decomposition of $T^{\pm}$ for the FNB $S_NAr$ reaction.

According to Schemes 2 and 3, another major difference between the CDNB and FNB $S_NAr$ mechanisms can be observed, which is the formation and breakdown of the $T^{\pm}\cdot$C·A rate-limiting structure found in the FNB $S_NAr$ reaction. The absence of this route in the CDNB $S_NAr$ reaction can be considered as expected taking into account the different experimental evidence found previously. In this regard, by using eqn (3) and (4) and data shown in Tables 2 and 3 the fraction of polyether-catalyzed $S_NAr$ reaction can be calculated (Fig. 8). Thus, taking $T$ = 25.0 °C, [$BuNH_2$] = 0.1 M, [G4] = 0.1 M and [$(O_2N)_xAr–L$] = $1.5 \times 10^{-4}$ M as reaction conditions, it can be estimated that only 30% of the CDNB $S_NAr$ reaction is catalyzed by the glyme intervention. Under the same conditions, 75% of the FNB $S_NAr$ reaction occurs with the involvement of polyethers. These results show how variable the significance of the polyether catalysis depending on the substrate structure can be. Hence, the remarkable stabilization of $T^{\pm}$ in the CDNB $S_NAr$ reaction compared to FNB favors the route where no polyether is involved, while the high energy barrier for the spontaneous decomposition of $T^{\pm}$ in the FNB $S_NAr$ reaction inhibits this process, promoting the reaction pathways where glymes and crown ethers catalyze the formation of the final product. Therefore, the absence of a route in the CDNB $S_NAr$ reaction where $T^{\pm}\cdot$C·A is formed and evolves into the final product can be justified on the basis of the existence of a lower energy reaction pathway. This may decrease the need for the polyether catalyst favoring alternative and probably less energy demanding pathways.



**Scheme 6**

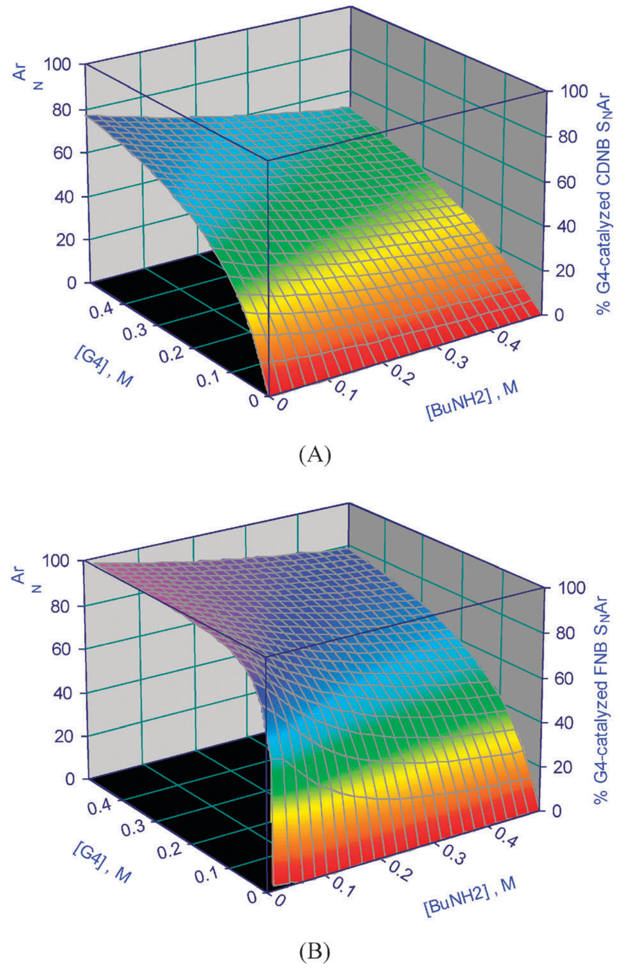


(A) (B)

**Scheme 7**

At this point, combining Schemes 2 and 3, a general mechanism for the polyether-catalyzed $S_NAr$ reaction with amines in aprotic solvents can be obtained (Scheme 8). Both CDNB and FNB will contribute to the overall reaction mechanism.

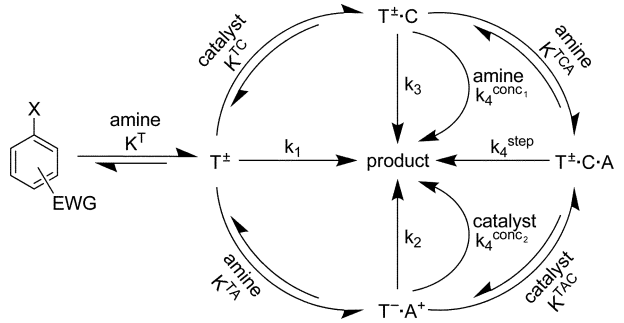
On one hand, CDNB and FNB show common reaction pathways through which $S_NAr$ takes place. These routes are the amine-promoted breakdown of $T^{\pm}$ ($k_2$ route) and the spontaneous decomposition of $T^{\pm}{\cdot}C$ ($k_3$ route). On the other hand, each substrate shows a distinctive reaction pathway to give rise to the final product. Thus, while only the CDNB $S_NAr$ reaction shows a spontaneous decomposition of $T^{\pm}$ ($k_1$ route), the formation of a $T^{\pm}{\cdot}C{\cdot}A$ rate-limiting structure and its subsequent collapse ($k_4$ route) is exclusive of the FNB $S_NAr$ reaction. Besides, an additional route involving a reaction between the substrate and an amine–catalyst precomplex could be suggested. Such preassociation would modify the charge distribution of the amine giving rise to a more reactive nucleophile. However, this possibility may be ruled out in view of previous works.[10,11] In this regard, when formation of $T^{\pm}$ in ester aminolysis becomes rate-limiting, the reaction rate is not affected by the presence of added-crown ethers. This absence of catalysis points to the participation of a non-precomplexed nucleophile in the reaction process. Hence, an association between $T^{\pm}$ and C·A to yield $T^{\pm}{\cdot}C{\cdot}A$ may also be excluded.



(A)

(B)

**Fig. 8** Fraction of polyether-catalyzed $S_NAr$ reaction calculated through eqn (3) and data shown in Table 2, and eqn (4) and data shown in Table 3 for the CDNB $S_NAr$ (A) and FNB $S_NAr$ (B) reactions, respectively. Data range: $[BuNH_2]$ = 0 to 0.5 M; [G4] = 0 to 0.5 M.



**Scheme 8**

The obtained results show the critical influence of the electronic structure of the substrate on the $S_NAr$ reaction mechanism. Accordingly, depending on the nature of the substrate the amine : catalyst ratio can be altered in order to increase in a controlled manner the overall reaction rate by modifying the balance among the mentioned operating mechanisms. The kinetic model proposed herein also allows quantifying the fraction of reaction proceeding through the different reaction routes.

## Conclusions

Nucleophilic aromatic substitution for nitro-activated substrates in the presence of glymes and crown ethers has been reported. This kinetic study reveals the multipathway character of the polyether-catalyzed $S_NAr$ reaction. In this regard, the substrate structure defines the nature of the reaction mechanism giving rise to a versatile process. Thus, depending on the electronic properties of the nitro-activated compound different reaction routes have been found. On the other hand, it has been observed that the formation of the final product can be efficiently accelerated either by the presence of glymes or crown ethers, being identified the $-(CH_2OCH_2)_4-$ subunit as the optimal segment for catalysis.

## Experimental section

All chemicals were of the highest commercially available purity and were used as supplied. Kinetic experiments were conducted in chlorobenzene at 25 °C. All rates were measured using a 8453 Agilent diode array UV-Vis spectrophotometer monitoring the formation of the final product at 350 and 375 nm for the CDNB and FNB $S_NAr$ reactions, respectively. Typical nitro-activated substrate concentrations were $[(O_2N)_xAr–L] = (1.3–1.5) \times 10^{-4}$ M. Amine, glyme and crown ether concentrations were always in large excess over the nitroaromatic compound, ensuring pseudo-first-order conditions. The absorbance–time data always fitted the first-order integrated equation satisfactorily and the observed rate constant, $k_{obs}$, was found to be reproducible within a precision of about 3% or better. As expected, under all the experimental conditions the corresponding amino-substituted product was observed.

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## References

1 G. W. Gokel and O. Murillo, *Compr. Supramol. Chem.*, 1996, **1**, 1–33.
2 J. S. Bradshaw, R. M. Izatt, A. V. Bordunov, C. Y. Zhu and J. K. Hathaway, *Compr. Supramol. Chem.*, 1996, **1**, 35–95.
3 F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, 1972, **94**, 3824–3829.
4 C.-W. Su and J. W. Watson, *J. Am. Chem. Soc.*, 1974, **96**, 1854–1857.
5 R. D. Gandour, D. A. Walker, A. Nayak and G. R. Newkome, *J. Am. Chem. Soc.*, 1978, **100**, 3608–3609.
6 J. C. Hogan and R. D. Gandour, *J. Am. Chem. Soc.*, 1980, **102**, 2865–2866.
7 H. Zipse, L. H. Wang and K. N. Houk, *Liebigs Ann.*, 1996, 1511–1522.
8 J. C. Hogan and R. D. Gandour, *J. Org. Chem.*, 1991, **56**, 2821–2826.
9 J. C. Hogan and R. D. Gandour, *J. Org. Chem.*, 1992, **57**, 55–61.
10 A. B. Maude and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1995, 691–696.
11 A. B. Maude and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1997, 179–183.
12 N. Basilio, L. García-Río, J. R. Leis, J. C. Mejuto and M. Pérez-Lorenzo, *Chem. Commun.*, 2005, 3817–3819.
13 N. Basilio, L. García-Río, J. C. Mejuto and M. Pérez-Lorenzo, *J. Org. Chem.*, 2006, **71**, 4280–4285.
14 H. J. Koh, K. L. Han and I. Lee, *J. Org. Chem.*, 1999, **64**, 4783–4789.
15 F. Terrier, *Nucleophilic Aromatic Displacement*, Wiley, New York, 1991.
16 M. R. Crampton, T. A. Emokpae, C. Isanbor, A. S. Batsanov, J. A. K. Howard and R. Mondal, *Eur. J. Org. Chem.*, 2006, 1222–1230.
17 M. Barra, H. R. de Rossi and E. B. de Vargas, *J. Org. Chem.*, 1987, **52**, 5004–5008.
18 J. F. Bunnett, *Quart. Rev. (London)*, 1958, **12**, 1–16.
19 C. F. Bernasconi, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, 1973, **3**, 33–63.
20 It must be noted that only the $\sigma^X$ adduct is depicted in this scheme. In this regard, in halonitroarenes contrary to esters, amines as well as other nucleophiles can be added in few positions to yield the corresponding $\sigma^H$ adducts.[21] Since a hydride anion cannot depart in a spontaneous reaction, whereas this addition is a reversible process, dissociation of the initially formed $\sigma^H$ adducts followed by slower addition in the halogen position results in the formation of the $\sigma^X$ adducts that finally provide the products of the $S_NAr$. Thus, substitution of hydrogen will be the primary fast process whereas the conventional $S_NAr$ of halogen will be a slower secondary process which, therefore, will be subjected to polyether catalysis.
21 M. Mąkosza, *Chem. Soc. Rev.*, 2010, **39**, 2855–2868 and references therein.
22 According to these experimental results, medium effects on the rate constant due to the increasing polyether concentration can be ruled out. A change in the polarity of chlorobenzene would be evidenced through an upward curvature in the plot of $\alpha$ against polyether concentration.
23 C. F. Bernasconi and R. H. de Rossi, *J. Org. Chem.*, 1974, **41**, 44.
24 N. S. Nudelman and P. MacCormack, *Tetrahedron*, 1984, **40**, 4227–4235.
25 N. S. Nudelman and S. Cerdeira, *J. Chem. Soc., Perkin Trans. 2*, 1986, 695–698.