Reactivity of benzohydrazide derivatives towards acetylation reaction. Experimental and theoretical studies

Paola R. Campodónico [a,*], Margarita E. Aliaga [a], José G. Santos [b], Enrique A. Castro [b], Renato Contreras [c,*]

[a] Instituto de Ciencias, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, Código Postal 771-0162, Santiago, Chile
[b] Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 6177, Santiago, Chile
[c] Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile

ARTICLE INFO

ABSTRACT

We herein report an experimental and theoretical study on the acetylation reaction of benzohydrazide derivatives towards p-nitrophenyl acetate (NPA). The kinetic data are consistent with a stepwise mechanism with the nucleophilic attack as the rate determining step. From the theoretical analysis it is found that benzohydrazide derivatives establish intramolecular proton rearrangement. The enol form appears as the active species for nucleophilic attack. A reaction mechanism incorporating keto-enol pre-equilibria is proposed. The study is completed with a local reactivity analysis describing the most reactive centers for nucleophilic attack together with a site activation analysis describing inductive substituent effects.

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1. Introduction

Benzohydrazide and their derivatives are poly functional molecules [1,2] bearing $>C=O$, –NH– and –NH$_2$ functionalities in their structures. Therefore, we can expect these compounds to behave as ambident nucleophiles in several reactions [3]. The scarce data about their kinetics and reaction mechanisms prompted us to perform experimental and theoretical studies in order to gain insight in the corresponding reaction mechanisms towards carbonylic electrophiles, p-nitrophenyl acetate in the present case. We have shown that experimental and theoretical integrated research may become a very useful methodology to describe reaction mechanisms in organic chemistry [4].

Acetylation reactions have been studied earlier by Jencks using hydroxylamine as nucleophile [5,6]. The process may lead to two different products of reaction, depending on the nucleophilic site for electrophilic attack (at O or at N) in hydroxylamine [7]. However, the kinetics and reaction mechanisms of benzohydrazide derivatives with several acetates have not been completely documented up to date. Only few works have evaluated the reactivity of benzohydrazide derivatives in water toward the formation of carbinolamides [8]. In acetylation reactions, depending on the nature of the electrophile/nucleophile pair, two mechanisms are possible: a concerted pathway [9,10], where the nucleophile attack at the electrophilic carbon in carbonyl group occurs simultaneously with the leaving group departure within a single step. Another pos-

sibility is the interaction of the nucleophile with the electrophilic carbon that may lead to the formation of a tetrahedral intermediate, $T^\pm$, from which the leaving group detaches. This mechanism will be referred to as stepwise [9,11].

In this work, we report on the kinetics of the acetylation reaction of benzohydrazide derivatives towards 4-nitrophenyl acetate (NPA) (see Scheme 1). The kinetic data are then rationalized by using theoretical tools that include the calculation of the potential energy surface (PES). Some stationary points located at the PES are then subjected to theoretical analysis to establish global nucleophilicity of benzohydrazides and their local reactivity patterns (identification of active sites in the molecule towards nucleophilic attack). The aim of this study is threefold: first of all the kinetic measurements [12] are used to obtain useful information about the reaction mechanism using Brönsted type-plot in terms of the observed rate coefficients and available pKa values [13]. Secondly, the exploration of the PES adds useful information about the presence of keto-enol pre-equilibria in the proposed reaction mechanism, and finally, a local reactivity analysis may assist the identification of nucleophilic site of reactions.
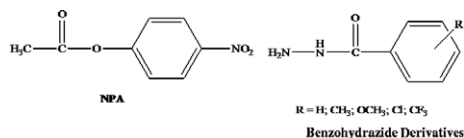
2. Results and discussion

The rate law obtained for the reactions studied is given by Eqs. (1) and (2), where P, S and N represent the product (4-nitrophenoxide anion), the substrate (NPA) and the nucleophile (benzohydrazide derivatives), respectively.

$$\frac{d[P]}{dt} = k_{obsd}[S] \tag{1}$$

where

Scheme 1. General structures of benzohydrazide derivatives and *p*-nitrophenyl acetate (NPA) considered in this study.

Table 1
Values of pKa for the conjugate acids, rate nucleophilic attack constant (k_N) with NPA, Hammett substituent constant (σ) and HOMO energy (ε_{HOMO}) of benzohydrazide derivatives.

Benzohydrazides	pKa[a]	k_N[a,b] (s^{-1} M^{-1})	σ	ε_{HOMO}(eV)
Substituent				
4-OCH$_3$	3.46	3.30×10^{-3}	−0.27	−8.53
4-CH$_3$	3.40	3.10×10^{-3}	−0.17	−8.90
H	3.00	2.60×10^{-3}	0.00	−9.17
4-Cl	2.80	2.30×10^{-3}	0.23	−9.30
4-CF$_3$	2.71	2.00×10^{-3}	0.54	−9.70
(*)4-OCF$_3$	–	2.04×10^{-3}	0.35	−9.67
(*)3-NO$_2$	–	1.74×10^{-3}	0.71	−10.00
(*)4-CN	–	1.91×10^{-3}	0.66	−9.80

[a] pKa and k_N values were determined in aqueous solution, at 25.0 °C, ionic strength 0.2 M (KCl).
[b] Predicted values of nucleophilic attack constant marked with (*) were obtained from Eq. (3).
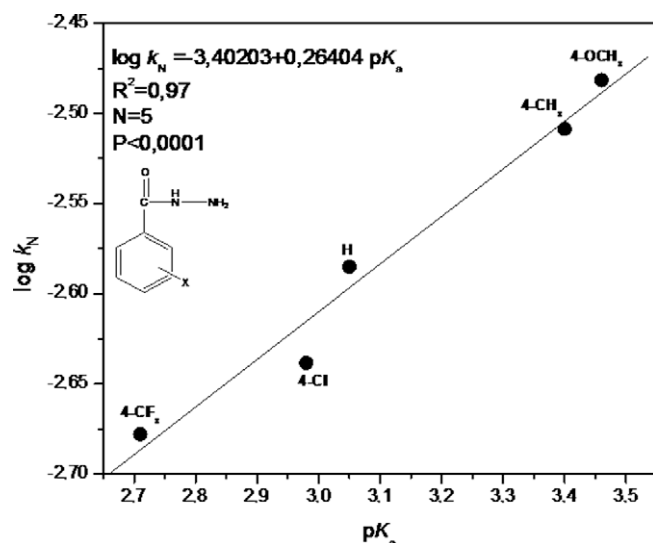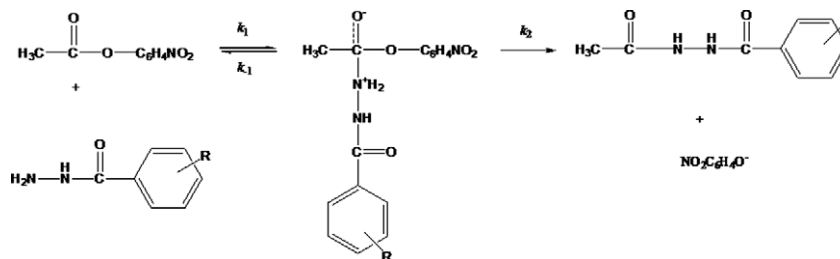

Fig. 1. Brönsted-type plot for the reactions of benzohydrazide derivatives with NPA in aqueous solution, at 25.0 °C, ionic strength 0.2 M (KCl).

$$k_{obsd} = k_0 + k_N[\text{free nucleophile}] \tag{2}$$

Pseudo-first-order rate constants (k_{obsd}) obtained under nucleophile excess for all the reactions obey Eq. (2), where k_0 and k_N are the rate coefficients for solvolysis and aminolysis of the substrate, respectively. The values of both coefficients show no dependence on pH within the range employed. These values were obtained as the slope and intercept, respectively, of linear plots of k_{obsd} against the free nucleophile concentration ([free nucleophile]) at constant pH. For the studied reactions, k_0 values were much smaller than the corresponding term related to aminolysis (k_N [free nucleophile] in Eq. (2)). The values of k_N for the reactions of NPA with benzohydrazide derivatives as well as the available pKa values [13] are shown in Table 1. Fig. 1 shows the Brönsted-type plot for the reactions of benzohydrazide derivatives with NPA. The plot is linear with slope $\beta = 0.26$, which is consistent with β values associated with stepwise mechanism that proceed through a zwitterionic tetrahedral intermediate (T$^\pm$) [14]. In this reaction the nucleophilic attack is the rate determining step (see Scheme 2) [15,16]. Based on the reported pKa values [13] and the kinetic data obtained in this work it is possible to postulate at first glance that the nucleophilic site of reaction corresponds to the nitrogen atom of the terminal amine on the benzohydrazide structure (see Scheme 1). Note that Fig. 1 shows a fair enhancement in nucleophilicity due to the presence of the electron releasing groups –CH$_3$ and –OCH$_3$ at *p*-position of the aromatic ring. Note also that a fair nucleophilic deactivation induced by the presence of electron withdrawing groups –Cl and –CF$_3$ is also observed. In order to generalize this result for other known substituents, we plotted the values of log k_N vs. the Hammett substituent constant (σ) [17,18]. The result of such a comparison is depicted in Fig. 2, and the corresponding data are displayed in Table 1. The Hammett plots for the reactions of benzohydrazide derivatives with NPA gives a straight lines with slope $\rho = -0.27$.

In order to rationalize the experimental results and with the object of assisting in a more complete description of the reaction mechanism involved, we performed a theoretical analysis. We first calculated the potential energy surface (PES) for the reaction of the title compounds towards NPA at HF/6-311G(d,p) level of theory using the GAUSSIAN 03 package of programs [19]. The transition state structures located for the unsubstituted benzohydrazide strongly suggested the presence of a keto-enol pre-equilibrium. The energy barrier separating the keto-enol tautomers was computed to be 34 kcal/mol in the gas phase. This figure may become smaller when corrected by solvation effects, but in any case is a substantial energy barrier. This result suggests that prior to the nucleophilic attack, a tautomeric barrier must be surmounted, and that this barrier may act as an effective bottleneck for the reaction. This argument may explain in part the low response to substituent effects reflected in the values of rate coefficients experimentally recorded for the series of benzohydrazide evaluated in this work. The results based on the analysis of the PES also suggest that the enol form would be the active nucleophilic species. Theoretical values of global nucleophilicity may be readily obtained by representing this

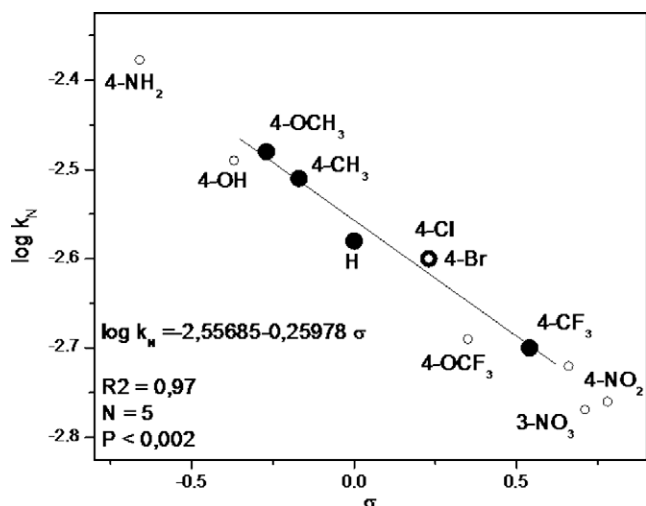**Scheme 2.** Possible reaction mechanism for acetylation of benzohydrazide derivatives.

Fig. 2. Hammett-type plot for the reactions of benzohydrazide derivatives with NPA and other benzohydrazides not experimentally evaluated.
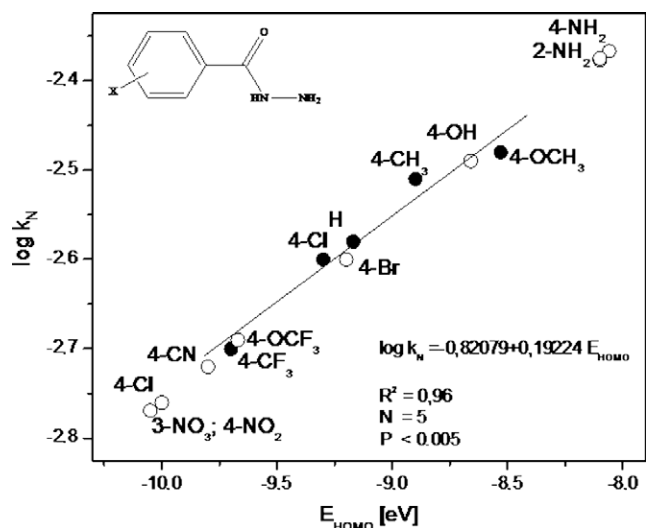

Fig. 3. Relationships between k_N and ε_{HOMO} for benzohydrazide derivatives.

property by the value of the HOMO energy level [20]. In order to validate this reactivity index, a comparison between the measured rate coefficients and the corresponding ε_{HOMO} values was performed. The result of such a comparison is depicted in Fig. 3. The resulting regression equation is:

$$\log k_N = -0.74327 + 0.20162\varepsilon_{HOMO}; \quad R = 0.975 \tag{3}$$

From this equation, the rate coefficient for the nucleophilic attack k_N may be predicted from the knowledge of the energy of the HOMO orbital. These values are compiled in Table 1. In the ab-

sence of experimental values for compounds marked with (*) in Table 1, the reliability of the predictions made from Eq. (3) may be reinforced by using the empirical Hammett's rules about substituent effects [17,18]. Note that in Table 1, the k_N values for the reactions of benzohydrazide derivatives with NPA also suggests extremely moderate activation/deactivation patterns induced by chemical substitution. One of the possible reasons to observe marginal changes in the rate coefficients for this series of benzohydrazide derivatives may be traced to their approximately similar pKa values and also to the presence of keto-enol pre-equilibria. Based on these results the reaction pathway sketched in Scheme 3 may be proposed. The proposed mechanism is consistent with the following kinetic law:

$$k_{obsd} = \frac{K}{K+1} x \frac{k_1 k_2}{k_1 + k_2} \tag{4}$$

where K is the equilibrium constant for the keto-enol tautomerism. In deriving the rate law written in Eq. (4) we have made the following approximations: we have first assumed a keto-enol pre-equilibrium described by the constant K; next we considered a second equilibrium involving reactants and a tetrahedral intermediate (see Scheme 3). If the enol form is the nucleophilic active species, then we can assume $K \gg 1$, and the first term becomes a constant α says:

$$\alpha = \frac{K}{K+1} \tag{5}$$

and k_N can be expressed as:

$$k_N = \alpha k_1 k_2 / (k_1 + k_2) \tag{6}$$

This rate law is consistent with a stepwise mechanism that proceed through a zwitterionic tetrahedral intermediate ($T^{\pm}$) with the nucleophilic attack as the rate determining step (see Fig. 1 and Scheme 3) [15,16]. Finally, in order to reinforce our hypothesis that the enol form is the proximate nucleophile, and that the nucleophilic center is the terminal N_3 atom we performed a simple calculation of the local nucleophilicity at the O_1, N_2 and N_3 sites (see Scheme 3 for atom numbering). Local nucleophilicity is readily obtained from the global nucleophilicity value by multiplying it by the nucleophilic Fukui function [20]. The result of this simple calculation yields values of local nucleophilicity at O_1, N_2 and N_3: −0.0240 eV; −0.0064 eV; and −0.0366 eV for the keto form respectively and the enhanced values of −0.4649 eV; −1.9092 eV and −2.1210 eV respectively for the enol tautomer. During the process of review, one reviewer called our attention on the possible additional sites of reactions in ambient nucleophiles. This problem is related to the charge/orbital control of chemical reactions [21]. We performed a Mulliken population analysis to assess the atomic charge at centres O_1, N_2 and N_3 of the keto and enol tautomers. The results are: $q(O_1) = -0.469e$, $q(N_2) = -0.398e$ and $q(N_2) = -0.373e$ for the keto form and $q(O_1) = -0.416e$, $q(N_2) = -0.270e$ and $q(N_2) = -0.381e$ for the enol form. Because globally speaking the enol form is more reactive than the keto form we may conclude that the reaction is orbital controlled and driven by the nucleo-
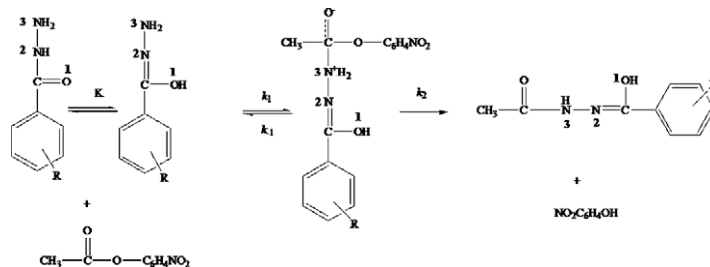
Scheme 3. Postulated reaction mechanism incorporating tautomeric equilibria for acetylation of benzohydrazide derivatives.

philic Fukui function, namely, $f_k^-(O_1) = 0.003$, $f_k^-(N_2) = 0.001$ and $f_k^-(N_2) = 0.004$ for the keto form and $f_k^-(O_1) = 0.051$, $f_k^-(N_2) = 0.208$ and $q(N_2) = 0.231$ for the enol form. These results reinforce the hypothesis based on experimental data that the nucleophilic site is the terminal N_3 atom (see Scheme 3 for atom numbering). This result also explain the low response in the rate coefficients to inductive substituent effects: the marginal activation/deactivation patterns induced by electron releasing and electron withdrawing substituents may be traced to the fact that being the terminal N_3 site the active nucleophilic center for these reactions, substituent at p-positions in the ring are too much far from the site of reaction at N_3. Substituent effects should be more important at the carbonyl site but after the results obtained here they should have relevant effects on the keto-enol tautomerism, not at the nucleophilic attack stage of the reaction.

The product analysis for the reaction between 4-nitrophenyl acetate and benzohydrazide in the same experimental conditions corresponded to 4-nitrophenolate anion and the corresponding diacylhydrazine, thereby reinforcing the theoretical prediction. The identification of the products was achieved by comparison of the UV–vis and HPLC spectra after completion of the reactions with those of authentic samples of 4-nitrophenol and diacylhydrazine in accord to Scheme 3. The latter was synthesized as reported previously by Carlsen and Jorgensen protocol [22].

3. Concluding remarks

The reaction of a series of benzohydrazide derivatives towards p-nitrophenyl acetate have been both kinetically and theoretically studied. The kinetic data are consistent with a stepwise mechanism with the nucleophilic attack as the rate determining step. From the theoretical analysis it is found that benzohydrazide derivatives establish intramolecular proton rearrangement. The enol form appears as the active species for nucleophilic attack and this result consistently explain the low response in the reaction rate coefficients to inductive substituent effects. A reaction mechanism incorporating keto-enol pre-equilibria is proposed. The study is completed with a local reactivity analysis describing the most reactive centers for nucleophilic attack, and the predicted selectivity was confirmed by products study.

Acknowledgements

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