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Pivotal role of intramolecular catalysis in the selective acetylation of alkyl amines

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Abstract

Preparation of amides by the use of esters as the "acyl donor" is less explored because they are less reactive and usually more steric demanding than conventional acid halides and anhydrides. Here, we report that 3-acetoxy-2-naphthoic acid, an aspirin analogue, can be used as a mild amine acetylating agent in ethanol at 25°C. The reaction is sensitive to steric and polar effects of the attacking amine, and the rate constants can be appropriately fitted by the Pavelich-Taft correlation. Density functional theory calculations used to study all reaction steps indicate that the *o*-carboxy group plays a pivotal role, guiding the attacking amine and accelerating the reaction. The reaction can be conveniently used for the acylation of a variety of primary and secondary amines.

KEYWORDS

acetylation, amide, chemoselectivity, kinetics, regioselectivity

1 | INTRODUCTION

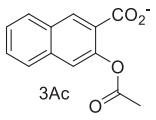
Amides are ubiquitous compounds present in the structure of drugs, biomolecules, and polymers and are usually prepared using acid anhydrides or acyl halides as the acylating agent.[1] Coupling agents, such as 1,1′-carbonyldiimidazole and *N,N′*-dicyclohexylcarbodiimide, have also been extensively employed, but such methodologies suffer from the need of a stoichiometric quantity of the external reagent. A common concern involving acylation is to avoid the reaction of other functional groups such as hydroxyl and thiol. Additionally, regioselective acylation is an important issue when dealing with di- or polyamino compounds.[2] Thus, there is a need to develop chemoselective and regioselective *N*-acylation methods.[2,3]

Some selective acylating agents have been developed and usually involve highly reactive agents bearing a transferable acyl group. For example, *N*-methoxydiacetamide was shown to acetylate primary amines in the presence of alcohols or secondary amines.[4] Similarly, *o*-substituted *N,N*-diacetylanilines were shown to be effective for acetylation of a less hindered amino group amongst more hindered amino groups.[5] Other examples include the heterocycle 3-acyl-1,3-thiazolidin-2-thione,[6] potassium acyltrifluoroborates,[7] destabilized amides,[8] and a magnetic recoverable organogel containing a *N*-hydroxysuccinimide activated ester.[9]

The reaction between amines and unactivated esters can be used to prepare amides. However, high temperature or additions of external agents are needed to accelerate the reaction. Morimoto et al[10] showed that lanthanum (III) triflate catalyze the amidation of esters, possibly through a Lewis acid carbonyl activation. Caldwell et al[11] reported that 2,2,2-trifluorethanol facilitates the condensation of unactivated ester and amines through nucleophilic catalysis by the added alcohol.

Although intramolecular catalysis is efficient and frequently observed in enzyme catalysis and in biomimetic models which include the reactions of amides and carboxylic and phosphate esters,[12–17] it is less explored in synthetic preparations. In this regard, it has been shown that *N*-acetylaminoacids can be conveniently prepared using aspirin as the acetylating agent of amino acids in

aqueous medium.[18] Here, we demonstrate that the related 3-acetoxy-2-naphthoic acid (3Ac) can be employed in the selective acetylation of primary amines in ethanol. Kinetic evidence as well as theoretical calculations supports the essential role of the neighboring carboxylate group in this reaction.



2 | EXPERIMENTAL

2.1 | Materials

All materials were purchased from Sigma Aldrich. Amines were distilled before use and kept under inert atmosphere. Ethanol was dried over molecular sieves and distilled prior to use. 3Ac was prepared as previously described.[15]

2.2 | Kinetic measurements

Reaction was monitored by UV-Vis spectrophotometry by following the appearance of 3-hydroxy-2-naphthoate (3OH) at 352 nm in closed quartz cuvettes at the desired temperature accurate to ±0.1°C. The reactions were initiated by injecting 15 μL of a stock solution of the substrate (10^{-2} mol L^{-1} in acetonitrile) into 3 mL of the solution of the amine in ethanol. The reactions were followed for at least 5 half-lives, and in all cases pseudo-first order plots were obtained. The observed rate constants k_{obs} were calculated by the nonlinear fitting of absorbance versus time plots with correlation coefficients >0.999. Second-order rate constants k_N for aminolysis were obtained from linear plots of k_{obs} against amine concentration.

2.3 | Product characterization

The products from the reactions of 3Ac with dodecylamine, *N*-ethylethylenediamine, and ethanolamine were identified by GC-MS after incubating 0.6 mmol of 3Ac with 5 eq. of the respective amine in 2 mL of ethanol overnight at 25°C. Ethanol was removed in vacuo, and the residue extracted with $NaHCO_3$ 5% and ethyl acetate. Dodecylacetamide was found in the organic phase, while the more polar *N*-[2-(ethylamino)ethyl]-acetamide and *N*-(2-hydroxyethyl)-acetamide were found in the aqueous phase. In all cases, the fragmentograms were consistent with those expected for the monoacetylated products and are given in the ESI, Figures S2 to S4.

2.4 | Computational calculations

Density functional theory (DFT) calculations were performed at the B3LYP[19–22] and M06[23] with the 6-31 + G(d,p) basis set using GAUSSIAN 09 package[24] implemented in Linux operating systems. The default parameters for convergence were used; convergence on the density matrix was 10^{-9} atomic units, the threshold value for maximum displacement was 0.0018 Å, and the maximum force was 0.00045 Hartree/Bohr. Stationary points on the potential energy surface were identified by frequency calculations at 1 atm and 298.15 K. The polarizable continuum model and the solvation model density (SMD) of Truhlar and coworkers were used in all calculations.[25] The transition states (TS) were identified by their single imaginary frequencies, whereas reactants, intermediates, and products showed no imaginary frequency. Free energies of transition states and intermediates were calculated taking 3Ac and hexylamine, optimized separately, as the reference. For conversion from 1 atm standard state to 1 mol L^{-1} standard state, ΔG values were corrected by subtracting 1.90 kcal mol^{-1} to the calculated value according to an A + B → C reaction as recommended.[26]

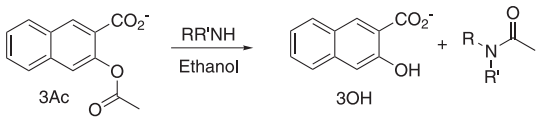
3 | RESULTS AND DISCUSSION

Reactions of amines with 3Ac, in ethanol, result in the formation of the corresponding amides and 3-hydroxy-2-naphthoate (3OH) (Scheme 1) and can be conveniently monitored by UV-Vis following the appearance of 3OH at 352 nm (typical spectral changes shown in Figure S1), allowing to calculate the observed rate constants as a function of amine concentration shown in Figure 1.

As can be seen in Figure 1, in the concentration range studied, the plots are linear, and the data can be fitted by Equation 1 with values of second-order rate constants k_N given in Table 1. The intercept k_o can be interpreted as the transesterification reaction, ie, attack of ethanol on 3Ac in the absence of amine, which is probably intramolecularly catalyzed by the neighboring carboxylate anion.

$$k_{obs} = k_0 + k_N[amine] \quad (1)$$

Because for all amines, values of k_N are considerably larger than k_o, it is clear that aminolysis is faster than



SCHEME 1 Reaction of 3Ac with alkylamines affording the corresponding acetamides

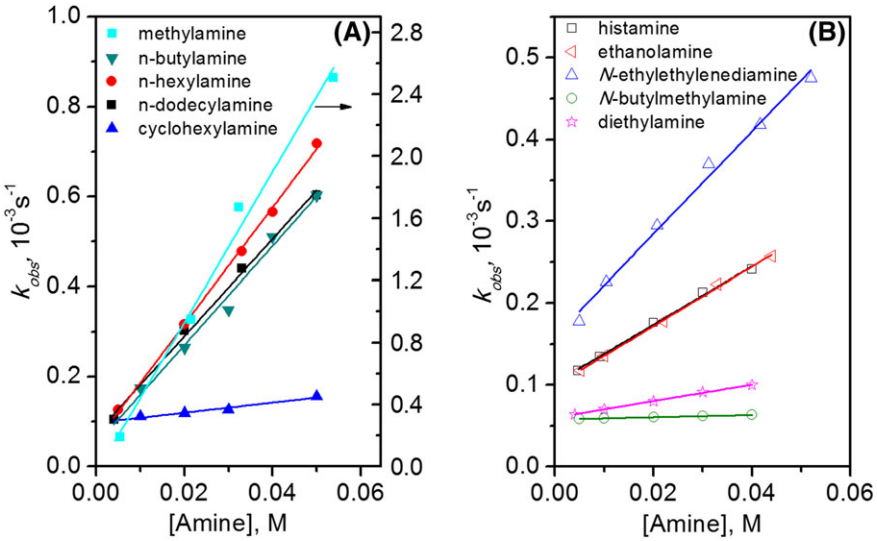


FIGURE 1 Observed rate constant as a function of amine concentration in ethanol, 25°C. Data were fitted to Equation 1. (A) Primary non-substituted alkylamines; (B) substituted and secondary amines

TABLE 1 Second-order rate constants for reactions of amines with 3-acetoxy-2-naphthoic acid at 25°C, $k_0 = 5.66 \pm 2.95 \times 10^{-5}$ s^{-1}

Amine	k_N, M^{-1} s^{-1}	σ*[a]	E_s[a]
Methylamine	$5.22 \pm 0.37 \times 10^{-2}$	0.98	2.48
Butylamine	$1.10 \pm 0.07 \times 10^{-2}$	0.85	2.09
Hexylamine	$1.30 \pm 0.03 \times 10^{-2}$	0.73	2.18
Dodecylamine	$1.08 \pm 0.05 \times 10^{-2}$	0.70	2.15
Cyclohexylamine	$1.12 \pm 0.09 \times 10^{-3}$	0.83	1.69
Diethylamine	$1.01 \pm 0.02 \times 10^{-3}$	0.29	1.10
N-methylbutylamine	$1.37 \pm 0.03 \times 10^{-4}$	0.36	0.85
Ethanolamine	$3.56 \pm 0.10 \times 10^{-3}$	NA	NA
Histamine	$3.53 \pm 0.04 \times 10^{-3}$	NA	NA
N-ethylethylenediamine	$5.99 \pm 0.14 \times 10^{-3}$	NA	NA
Triethylamine[b]	$1.54 \pm 0.04 \times 10^{-5}$		

[a]Values from Ref. 27.

[b]Second-order constant for the general base catalysis of the ethanolysis reaction.

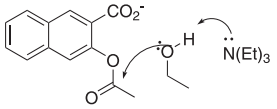
ethanolysis. It should be noted that the contribution of ethanolysis to the overall reaction depends on the concentration of amine used. For example, at 0.05 mol.L^{-1} butylamine, ethanolysis contributes to 9% of the overall reaction, while at 0.1 mol.L^{-1} it is 5% only.

As can be seen, the reaction of 3Ac with methylamine is approximately 5-fold faster than with other linear primary amines, with alkyl groups butyl, hexyl, and dodecyl. Cyclohexylamine, a hindered primary amine, reacts 10-fold slower than hexylamine and at about the same rate than diethylamine. Additionally, amines containing hydroxyl and amino groups (*N*-methylbutylamine, ethanolamine, and histamine) are slightly less reactive than the unsubstituted linear alkylamines.

It is worth mentioning that tertiary amines catalyze the degradation of 3Ac and the rate constant for the ethanolysis of 3Ac showed linear increase as a function of the concentration of triethylamine, with a rate constant 1.54×10^{-5} M^{-1} s^{-1} (data given in Figure S5 and included in Table 1). This rate constant probably corresponds to the effect of the tertiary amine acting as a general base (Scheme 2). The fact that this rate constant is considerably smaller than those determined for other amines indicates that the experimental k_N values correspond to the aminolysis reaction and that the general base catalyzed transesterification path is unimportant.

The sensitivity of the reaction to polar and steric effects was examined applying the Taft equation (Equation 2), where the parameters δ and ρ^* indicate how sensitive these reactions are to steric and electronic effects. Values of the used polar substituent constant σ^* and steric substituent constant E_s are given in Table 1 (the methyl group is taken as reference). Figure 2 shows a plot of the experimental versus calculated values obtained using Equation 2 and a multilinear regression routine. The calculated ρ^* value is −1.39 which indicates that electron donation through sigma bonds is important, while the value for δ is 1.92, indicating that the reaction center is more sterically crowded than that for hydrolysis of methyl esters.[28] Thus, the reaction is largely influenced by steric and electronic effects, being fast for linear primary amines.

$$\log\left(\frac{k_N}{k_{Me}}\right) = \rho^* \sigma^* + \delta E_s \quad (2)$$



SCHEME 2 Triethylamine catalyzed ethanolysis of 3Ac

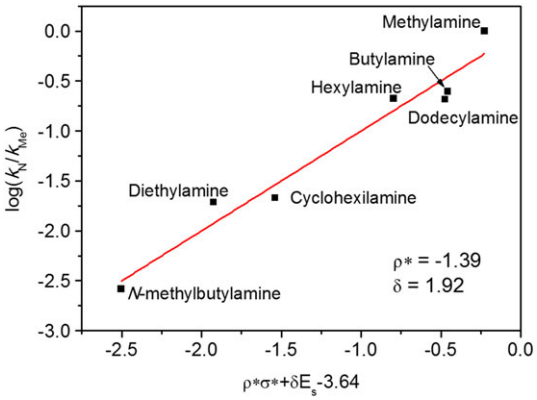


FIGURE 2 Pavelich-Taft plot for aminolysis of 3-acetoxy-2-naphthoic acid in ethanol at 25°C

3.1 | Effect of the *o*-carboxylate group

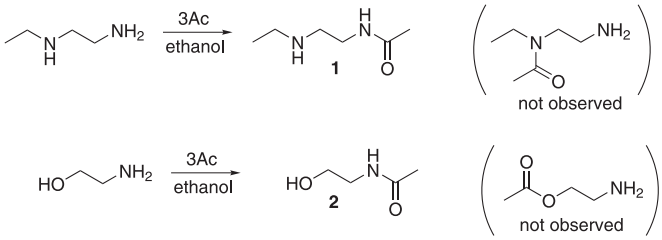
Aspirin is a classic example of rate enhancement due to the intramolecular assistance by the carboxylate group acting as a general base.[29] Similarly, the effect of the carboxylate group on 3Ac was evaluated by comparing the aminolysis rate of 3Ac with that of 2-naphthylacetate (2AcN) under the same experimental conditions. Values of k_N for hexylamine and *N*-methylbutylamine are 1.15×10^{-3} M^{-1} s^{-1} and 2.13×10^{-4} M^{-1} s^{-1}, respectively (data in Figure S6 of the ESI) indicating that aminolysis of 3Ac is faster than that of 2AcN. Additionally, the observed rate enhancement is larger for hexylamine, indicating that the neighboring group participation is more efficient for the less crowded amines. The fact that both primary and secondary amines react faster with 3Ac than 2AcN lends credence to the intramolecular assistance of the carboxylate group. These results indicate that the carboxylate group in 3Ac is directly involved in these reactions, in accordance with previous observations that hydrolysis of 3Ac anion involves intramolecular general base catalysis and is faster than that of 2AcN at neutral pH.[15]

3.2 | Selectivity to monoacetylated products

From the Pavelich-Taft analysis, it is clear that steric effects play a crucial role in the aminolysis of 3Ac. Thus, products from the reaction of *N*-ethylethylenediamine were analyzed by GC-MS in order to evaluate the regioselectivity of the reaction to the primary center. As depicted in Scheme 3, only *N*-[2-(ethylamino)ethyl]-acetamide 1 was detected, indicating excellent regioselectivity to acetylation of primary amines. Similarly, reaction of 3Ac with ethanolamine yields only *N*-acetylethanolamine 2, demonstrating good chemoselectivity in the presence of hydroxyl group.

3.3 | Computational calculations

To gain a deeper understanding of the role of the carboxylate group of 3Ac on the aminolysis reactions, we performed DFT calculations at the SMD/B3LYP/6-31 + G(d,p) in ethanol. Using hexylamine as the selected amine, 3 transition states were found which are given in Figure 3. A better understating of the reaction can be visualized by following the intrinsic reaction coordinate IRC as shown in Figure 4, while the most important interatomic distances are given in Table 2. The structure of reactions shown in Figure 3 corresponds to the structure found at IRC = −7 $amu^{1/2}$.bohr in the reverse direction starting from TS1. In this structure, the NH_2 group is 2.73 Å from the ester carbon (N···C1) while the CO_2^-···H-NHR interatomic distance (O3···H) is 2.05 Å. On going from Reactants to TS1, the amine approaches C1 accompanied by the decrease of O3-H interatomic distance. The intermediate species found can be characterized as a tetrahedral addition intermediate where the carbonyl ester group is 1.56 Å from the naphthoate leaving group (C1-O2) and 1.61 Å (C1-N) from the attacking amino group. The intermediate also shows a longer C1-O1 bond length (1.27 Å versus 1.22 Å in 3Ac) and pyramidal geometry (O2-C1-O1-CH_3 dihedral angle is 109.3° versus 179.9° in 3Ac). The breakdown of the intermediate occurs through TS2 and the most important structural variation in this step is the elongation of C1-O2 and decrease of N-C1 and C1-O1, as well as a steady decrease in O3-H1 interatomic distance. Optimization of the last point in the forward direction from TS2 leads to a charged complex in which the charged amide group interacts with the carboxylate moiety. Finally, the last reaction step involves proton transfer from the charged amide to the carboxylate group in TS3 (O3-H1 = 1.34 Å and N-H = 1.19 Å) along with elongation of O2-C1 interatomic distance. This step is followed by the intramolecular



SCHEME 3 Aminolysis of 3Ac with *N*-ethylethylenediamine and ethanolamine

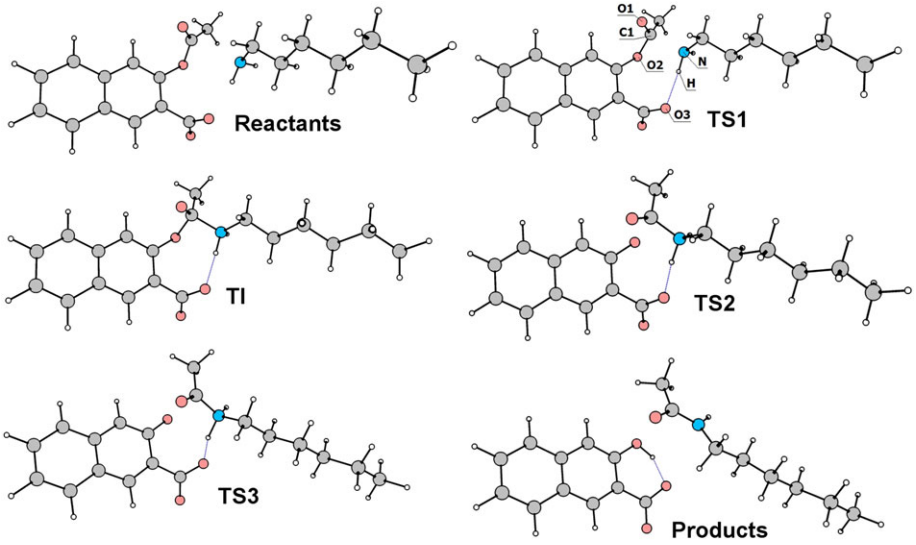


FIGURE 3 Calculated structures of Reactants, TS1, TI, TS2, TS3, and Products optimized at the SMD/B3LYP/6-31 + G(d,p) level. Reactants correspond to the structure found at IRC = −7.5 amu $^{1/2}$.bohr from TS1 in the reverse direction, while Products is found at IRC = 13.5 amu $^{1/2}$.bohr starting from TS3 in the forward direction

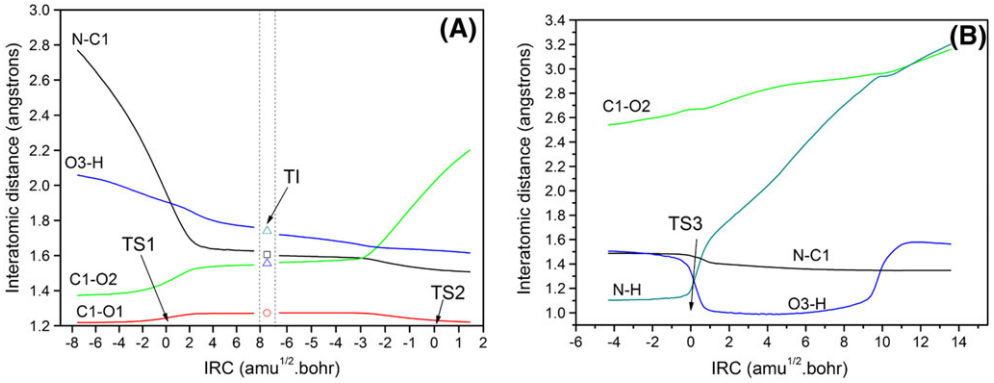


FIGURE 4 (A) Evolution of interatomic distances for reaction of 3Ac with hexylamine calculated by following the IRC starting from TS1 (left) and TS2 (right). Also given are the interatomic distances for the intermediate formed. (B) IRC plot calculated for TS3 in the forward and reverse directions. All calculations performed at the SMD/B3LYP/6-31 + G(d,p) level. Numerations according to TS2 in Figure 3

TABLE 2 Selected distances (Å) for optimized structures involved in the reaction of 3Ac and hexylamine calculated at the SMD/B3LYP/6-31 + G(d,p) level. Numbering according to TS2 in Figure 3

Structure	C1-O1	C1-O2	C1-N	O3-H	N-H
Reactant[a]	1.22	1.36	2.73	2.05	1.02
TS1	1.24	1.45	1.96	1.90	1.03
TI	1.27	1.56	1.61	1.74	1.05
TS2	1.23	2.02	1.52	1.63	1.07
TS3	1.22	2.67	1.47	1.34	1.19
Products[b]	1.25	3.16	1.35	1.53	-

[a]Corresponds to the structure found at IRC = -7.5 amu$^{1/2}$.bohr by following the IRC from TS1 in the reverse direction.

[b]Corresponds to the structure found at IRC = 13.5 amu$^{1/2}$.bohr by following the IRC from TS3 in the forward direction.

proton transfer from O3 to O2 giving 3OH and *N*-hexylacetamide as shown in Products in Figure 4B.

The DFT calculations indicate that breakdown of TI through TS2 is rate determining, and the calculated activation free energy obtained at the SMD/B3LYP/6-31 + G(d,p) is 23.86 kcal.mol^{-1}, slightly higher than the experimental value of 20.5 kcal.mol^{-1} determined by the Eyring plot (graph given in Figure S7 of the ESI). The Minnesota functional M06[23] was also used to model this reaction, and similar geometries were obtained, while the calculated activation free energy for TS2 falls to 20.72 kcal.mol^{-1}, largely improving the agreement with the experimental value. It should be noted that although calculations indicate formation of a tetrahedral intermediate, the free energy differences among all stationary points were found to be small (within 3 kcal.mol^{-1}). It is

therefore likely that the reaction proceeds in a concerted rather than in stepwise fashion.

4 | CONCLUSIONS

The use of 3Ac as a mild amine acetylating agent was examined, and the reactions proved to be sensitive to steric and polar effects of the attacking nucleophile. Aminolysis of 3Ac is somewhat faster than the corresponding reactions with 2-naphthylacetate, which is most probably due to the intramolecular assistance of the carboxylate group. This hypothesis is supported by DFT calculations which indicate that the *o*-carboxy group plays a pivotal role, guiding the attacking amine and accelerating the reaction. The reaction of 3Ac can be used for the selective acetylation of primary amino groups in diamines as well in amino alcohols, and we are in the process of examining the wider scope of this intramolecularly catalyzed reaction.

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SUPPORTING INFORMATION

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