Amidation kinetics of succinic anhydride by amine-containing drugs

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Abstract. The reaction kinetics of succinic anhydride with amine-containing drugs benzocaine, procaine and sulfanilamide was studied. It is shown that the reaction in the initial period is autocatalytic; subsequently the amidation process is dominant, which corresponds to second order reaction type. The dependence of the reaction kinetic parameters on the properties of the medium and the structure of the amine is analyzed. Equations are given that link the value of the amidation rate constant with the characteristics of organic solvents: polarity, basicity, donor and acceptor properties.

1. Introduction
Derivatives of succinic acid, in particular, succinates, succinamides, succinimides, have various types of biological activity: antitumor, hypotensive, antispasmodic, anticonvulsant, antidiabetic, etc. [1, 2], and the reaction to obtain succinamides is often one of the main factors for drug development with directed and complex action [3]. In this regard, it is of interest to probe the fundamentals of the amidation reaction of succinic acid anhydride with pharmaceuticals containing an aromatic amino group in the structure.

The aim of the work was to study the kinetics of succinic anhydride (SAn) with sulfanilamide (SA), anestezine (benzocaine, BC) and procaine (novocaine hydrochloride, NC) interaction.

2. Experimental
In the work we used SAn of the “p” brand and pharmaceutical substances of the drugs. The purity of the starting materials was confirmed by \textsuperscript{1}H NMR and IR spectroscopy. Solvents (1,4-dioxane (DO), dimethylacetamide (DMAA), acetonitrile (AN)) were purified by distillation. Twice distilled water (bidistillate) was used for solutions containing water.

The amidation of SAn with the compounds of interest are as follows: a) benzocaine was carried out in DO, DMAA and AN; b) sulfanilamide in DO; c) procaine in a mixed solvent DO–H\textsubscript{2}O–C\textsubscript{2}H\textsubscript{5}OH (90: 5: 5 vol.%). The reactant ratio of SAn with the compounds is 1: 1 mol/mol (0.0015 mol) in the temperature range of 60–80 °C.

0.151 g of SAn was dissolved in 15 ml of solvent, 0.248 g of BC or 0.258 g of SA was subsequently added to the resulting solution and stirred until the amine was completely dissolved. An initial sample (0.5 ml) was taken. For NC, 0.409 g of anesthetic was separately dissolved in 1.5 ml of a C\textsubscript{2}H\textsubscript{5}OH–H\textsubscript{2}O mixture (1: 1 vol./vol.) and mixed with 13.5 ml of a succinic anhydride in DO solution. Each reaction
mixtures were poured into 30 ml two-necked flask equipped with a reflux condenser with a calcium chloride tube and placed in a thermostat heated to the required temperature (60, 70 or 80 °C); the reaction time counting started after 3 min. Samples (0.5 ml) were taken every 30 min for 3–5 h. The reaction progress was monitored through the content of residual drug in the reaction mixture using nitrite titration with potentiometric fixation of the equivalence point.

3. Results and discussion
It was previously established [4] that 4–{3–carboxy–propionylamino}–benzene–1–sulfonamide (succinamide SA) is the product of the interaction of SAn with SA at an equimolar reagent ratio in DO at temperatures of 60 and 90 °C. The reaction of succinic anhydride with the drugs is represented in scheme:

\[ \text{O} \text{O} + \text{NH}_2 \text{R} \rightarrow \text{O} \text{O} \text{HN} \text{R}, \]  

where R: COOCH\(_2\)CH\(_3\) (BC), COO(CH\(_2\))\(_2\)N(C\(_2\)H\(_5\))\(_2\) (NC) or SO\(_2\)NH\(_2\) (SA).

It is known that the acylation reaction of aromatic amines with anhydrides is catalyzed by acid. For dicarboxylic acid anhydrides, it is autocatalytic, since a carboxylic acid is formed for every amide generated [5]. We found that the accumulation of semi-amides (P) of all the studied drugs is characterized by the presence of an induction period (figure 1), which confirms the autocatalytic mechanism of the process.

Another consequence of the position of the carboxyl group in the immediate vicinity of the amide bond of the product of reaction (1) is the reversibility of this reaction [6], with the value of the equilibrium constant of \(K_C\) substantially affected by the basicity of the amine and solvent [7]. To exclude the contribution of the reverse reaction, according to [8], the kinetic experiment should be carried out under the condition: \([\text{Anhydride}]_0 + [\text{Amine}]_0 >> 1/K_C\). Based on the data presented in [8], for the reaction of phthalic anhydride with aniline, under the conditions of our experiment, we can expect a value of \(K_C \sim 10^4 \text{ l mol}^{-1}\). As a result of this, the condition \([\text{SAn}]_0 + [\text{Drug}]_0 = 0.2 >> 1/K_C (\sim 10^{-4})\) is fulfilled; thus, the effect of reversibility can be neglected in our study.

Provided that reaction (1) is irreversible autocatalytic, the kinetic equation has the form:

\[ \frac{dx}{dt} = k([\text{SAn}]_0 - x)([\text{Drug}]_0 - x) + k_A x ([\text{SAn}]_0 - x) ([\text{Drug}]_0 - x), \]  

Figure 1. Dependence of semi-amide amount on time for the reaction SAn with BC (1), SA (2), NC (3) at 80 °C. [SAn]\(_0\) = [Drug]\(_0\) = 0.1 mol/l. Solvent: 1, 2 – DO; 3 – DO–H\(_2\)O–C\(_2\)H\(_5\)OH.
where $x$ – concentration of the reaction product $P$ at time $t$; $k$ and $k_A$ – the rate constants of the non-catalytic and autocatalytic reaction flows; $[SAN]_0$, $[Drug]_0$ – initial concentrations of succinic anhydride and amine-containing drugs.

Transformation of equation (2) provided that $k \ll k_A x$ and $[SAN]_0 = [Drug]_0$, leads to the expression of the rate of $P$ formation in the form:

$$\frac{dx}{dt} = k_A x ([Drug]_0 - x)^2. \quad (3)$$

After differentiation of the variables in equation (3) and integration, we arrive at the equation:

$$\ln \frac{x}{[Drug]_0} - \ln([Drug]_0 - x) - \ln \frac{1}{([Drug]_0 - [Drug]_0^2)} + \text{const} = k_A t, \quad (4)$$

which allows us to determine the rate constant of the autocatalytic reaction flow graphically in the coordinates of the dependence:

$$\ln \frac{x}{[Drug]_0} - \ln([Drug]_0 - x) - \ln \frac{1}{([Drug]_0 - [Drug]_0^2)} = f(t) \text{ or } A = f(t). \quad (5)$$

As it turned out, the dependence in the coordinates of integral equation (5) gives a straight line, the slope of which corresponds to the rate constant $k_A$ (figure 2a). At the same time, after the induction period, the change in the amount of Drug follows second order reaction rate (figure 2b), which also allowed us to determine the rate constant of the non-catalytic reaction.

Figure 2. Dependence of «A» (a) and $1/\text{[Drug]}$ (b) on time for the reaction $SAN$ with $BC$ (1), $SA$ (2), NC (3) at $70^\circ C$. $[SAN]_0 = [Drug]_0 = 0.1 \text{ mol/l}$. Solvent: 1, 2 – DO; 3 – DO–H$_2$O–C$_2$H$_5$OH.

The values of the rate constants and reaction activation energy calculated from their dependence on the inverse temperature are presented in the Table. As can be seen, the rate constants are influenced by the nature of the substituent in the aromatic amine, which was also previously observed for the reaction of substituted anilines with other anhydrides, for example, phthalic [5] and benzoic [9].

As the basicity of the amine increases, the values of the rate constant increase, thus the rate constant of the non-catalytic reaction is affected by the basicity of the amine (figure 3). At the same time, the catalytic effect of the carboxyl group of $P$ decreases: the ratio $k_A/k$ decreases in the series: sulfanilamide $\geq$ procaine $>$ benzocaine from 29.6 to 27.8 and 17.7 respectively.
Table 1. Rate constants (80 °C) and activation energies of reaction of amine-containing drugs with succinic anhydride, found for the autocatalytic \((k_{A}, E_{A})\) and non-catalytic \((k, E)\) models

| Amine (pK\(_{a}\)[10]) | Solvent (-pK\(_{a}\) in water [8]) | \(k_{A} \cdot 10^{2}\) (l\(^{2}\)·mol\(^{-2}\)·s\(^{-1}\)) | \(k \cdot 10^{4}\) (l·mol\(^{-1}\)·s\(^{-1}\)) | \(E_{A}\) (kJ·mol\(^{-1}\)) | \(E\) (kJ·mol\(^{-1}\)) |
|------------------------|---------------------------------|---------------------------------|---------------------------------|----------------|----------------|
| AN (32.2)              |                                 | 0.60                            | 2.2                             | –              | –              |
| BC (2.51)              | DO (3.22)                      | 0.90                            | 5.1                             | 97.8           | 63.0           |
| DMAA (0.19)            |                                 | –0                             | 1.2                             | –              | –              |
| NC (2.45\(\textsuperscript{b}\)) | DO–H\(_{2}\)O–C\(_{2}\)H\(_{5}\)OH (3.85) | 1.39                           | 5.0                             | 79.3           | 25.4           |
| SA (2.08\(\textsuperscript{b}\)) | DO                            | 0.65                            | 2.2                             | 87.0           | 62.5           |

\(^{a}\) pK\(_{a}\) value is given for the amino group in the Drug aromatic rings.

Analysis of the amine structure effect on the kinetics of reaction (1) showed that the presence of an electron-withdrawing substituent at the para-position of the nucleophile reduces the rate constant. Thus, the sensitivity parameter of the Hammett equation for the reaction of SAn with benzocaine is characterized by a large negative value (–4.44).

Our results (table 1) confirm the significant effect of the solvent on the amidation kinetics, noted earlier in the literature [8], a striking example of which is the absence of autocatalysis during the reaction in the amide solvent. In assessing the influence of the medium on the reaction rate (1), a generalizing approach was applied [11], taking into account various aspects of the solvent – reagent interaction:

\[
\lg k = \lg k_{0} + a_{1} \frac{n^{2} - 1}{n^{2} + 2} + a_{2} \frac{\varepsilon - 1}{2\varepsilon + 1} + a_{3} E + a_{4} B, \tag{6}
\]

where \(k_{0}\) – reaction rate constant in the gas phase; \(n, \varepsilon, E, B\) – refractive index, dielectric constant, acidity, basicity of the solvent respectively; \(a_{1}\) and \(a_{2}\) are constants that take into account the sensitivity of the reaction to the influence of nonspecific solvation (polarizability and polarity of the solvent); \(a_{3}\) and \(a_{4}\) are constants that take into account the sensitivity of the reaction to the influence of specific solvation (electrophilicity and nucleophilicity of the medium).

The possibility of correlation between the found values of \(\lg k\) and \(\lg k_{A}\) for amines with close pK\(_{a}\) (BC, NC) and the parameters included in equation (6) was considered (the values of \(n, \varepsilon, E, B\) for the mixed solvent were calculated by the additivity principle [12]). Such an assessment showed that the such solvent properties as polarity \((\varepsilon - 1)/(2\varepsilon + 1)\), acidity \(E\) and basicity \(B\) significantly affects the rate constant of the SAn amidation \((\lg k)\). In the framework of the three-factor model, the following equation is obtained that describes the effects of the medium during the interaction of succinic anhydride with BC and NC in four solvents:

Figure 3. Dependence of \(k\) (1) and \(k_{A}\) (2) values for SAn amidation reaction on amine basicity (DO, 80 °C).
\[
\lg k = -4.83 - 1.50 \frac{\varepsilon - 1}{2\varepsilon + 1} + 0.27E + 0.003B.
\] (7)

For \(\lg k_A\) the correlation equation has the form:
\[
\lg k_A = -4.82 + 2.95 \frac{\varepsilon - 1}{2\varepsilon + 1} - 0.092E + 0.011B.
\] (8)

From the form of equations (7) and (8) it follows that the contributions of polarity and acidity are “opposite-directional”. A comparative assessment shows that the electrophilicity of the medium makes a greater contribution to the value of \(k\), while the polarity of the solvent and the nucleophilic component of the specific solvation mainly affect \(k_A\).

Taking into account the approach proposed by the authors of [13], we considered the effect of specific solvation on the reaction rate constant (1), expressed in terms of the donor and acceptor properties of the solvent by the equation:
\[
\lg k = b_0 + b_1DN + b_2AN,
\] (9)

where \(b_0, b_1, b_2\) – constants taking into account the influence of donor–acceptor properties of the solvent on the reaction rate constant; DN, AN – donor and acceptor number of the solvent on the Gutmann scale.

The solution of equation (9) showed that \(b_1 \approx b_2\) (similar to that found in [13]), which allows us to write:
\[
\lg k = b_0 + b(DN + AN) = b_0 + bY.
\] (10)

For the non-catalytic reaction of SAn with BC, equation (10) has the form:
\[
\lg k = -2.27 - 0.0405Y, \quad r^2 = 0.99.
\] (11)

Despite the significant role of the solvent basicity in amide formation in [8], the influence of this factor in our experiment turned out to be negligible, possibly due to the smaller number of solvents involved.

The results obtained indicate that the solvent properties and the nature of the substituent in the aromatic amine have a cooperative effect on the kinetics of amidation of SAn with amine-containing drugs, which should be taken into account when preparing correlation equations for calculating the rate constants of the catalytic and non-catalytic reaction flows.

The found values of the activation energy of the autocatalytic process (table 1) are quite close for all drugs, which logically follows from the nature of the reaction centers. The activation energy of the non-catalytic reaction is lower and coincides for BC and SA in DO, which can also be a consequence of the reaction of amines with close \(pK_a\) in one solvent. A sharp decrease in \(E\) in a mixed solvent is most likely due to the role of polar solvents in proton transfer. This fact additionally indicates a significant influence of the medium on the kinetics of the studied processes.

4. Conclusion

Thus, the previously described features of the amidation of dicarboxylic acid anhydrides with aromatic amines are valid in the case of the reaction of succinic anhydride with amine-containing drugs in organic solvents, which can be used to select optimal conditions for the production of biologically active succinamides.

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