TECHNOLOGICAL FEATURES OF THE REACTION OF α-TOCOPHEROL ACETYLATION

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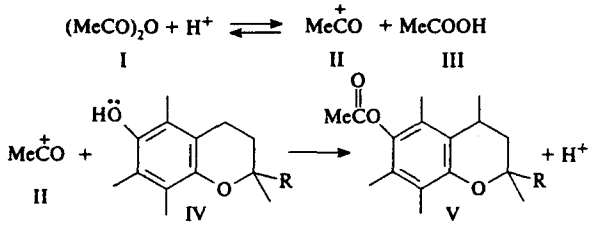
The process of α-tocopherol acetylation is widely used in the production of synthetic vitamin E [1]. This is related to the fact that introduction of the acetyl group into the molecule of α-tocopherol markedly increases its stability with respect to long-term storage and oxidation, while not affecting the physiological activity.

The reaction of α-tocopherol acetylation with acetic anhydride, catalyzed by Brönstedt or Lewis acids, proceeds according to the scheme of electrophilic substitution:



$R = C_{16}H_{33}$

Hydrogen ion – the catalyst – interacts with acetic anhydride (I) to generate a carbocation (II). The latter attacks the nucleophilic center of α-tocopherol (IV) to yield the acetyl derivative (V), while the liberated hydrogen ion enters a new interaction with compound I to form electrophilic particle II, after which this catalytic cycle is multiply repeated. An excess of acetic anhydride (1.5 – 2.0 times the stoichiometric amount) and an increase in the concentration (or the strength) of acid are factors favoring the generation of carbocations and, hence, accelerating the acetylation process. The same positive trend is provided by the removal of acetic acid from the reaction zone, for example, with the aid of pyridine.

The reaction enthalpy, estimated from the heats of combustion of the reaction products and initial substances, amounts to 16.7 kcal / mole. Since the reaction is exothermal, it is necessary to select an optimum temperature profile: a high temperature (about 100°C) advantageous in the initial stage, for the system far from equilibrium, should be gradually decreased to 40 – 50°C by the end of the process.

Using a combination of the above factors allows, in principle, the process to be conducted so as to obtain α-tocopherol acetate with a nearly quantitative yield. However, this is not the case in practice where the final product always contains a certain proportion of free α-tocopherol.

The maximum allowable percentage of α-tocopherol in the commercial vitamin E acetate, as stipulated by the pharmacopoeias of various countries, may vary, for example, from 0.5% in Japan to 1.0% (Great Britain), 2.0% (Germany and Yugoslavia), and 3.0% (Russia).

Thus, the maximum content of free α-tocopherol is allowed by the State Pharmacopoeia in Russia, and the minimum in Japan. Note that an excess content of free α-tocopherol in the final product (α-tocopherol acetate) reduces its quality and decreases the maximum storage duration.

Therefore, it would be important to elucidate the reasons for α-tocopherol accumulation in the final product. The possible factors may include incomplete conversion during the acetylation process, reversibility of the reaction, and / or the thermal decomposition of α-tocopherol acetate in the final process stages (d stillation of unreacted acetic aldehyde, vacuum distillation c f the product).

The thermal decomposition of α-tocopherol acetate may proceed with the formation of α-tocopherol and ketene:

$$V \rightarrow IV + CH_2{=}C{=}O.$$

Calculation of the isobaric potential of this reaction under standard conditions and at a temperature of 200°C [2] yields $\Delta G^{:0}_{298}$ + 26 kcal / mole and $\Delta G^{:0}_{473}$ + 21 kcal / mole. The positive values of the isobaric potential indicate that, from the standpoint of thermodynamics, no decomposition of compound V with the formation of compound IV may take place under the conditions studied (i.e., at 25 – 200°C).

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TABLE 1. Kinetics of α-Tocopherol Acetylation

Process parameter	Temperature, °C		
	60	80	100
k_1, liter/(mole · min)	0.955	1.45	1.75
$K_{eq} = k_1 / k_2$	738.0	177.0	50.1
ΔG_T^0, cal / mole	−4370	−3631	−2899

In order to study the other possible ways of α-tocopherol accumulation in the reaction mass, we have studied the kinetics of acetylation:

$$\text{I} + \text{IV} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{V} + \text{III}$$

Because the α-tocopherol acetylation is a fast reaction, the variation of composition of the reaction mixture was monitored by the quantitative TLC on Silufol plates with densitometric analysis of the chromatograms (ERI-65 optical densitometer). The process kinetics were studied at various temperatures (60, 80, and 100°C), a constant concentration of the catalyst (sulfuric acid), and a working ratio of the catalyst and acetic anhydride concentrations varying within $1 \times 10^{-3} - 1 \times 10^{-2}$ mole / mole. Computer processing of the experimental data gave the following equation of the α-tocopherol acetylation rate (valid under the conditions indicated above and the I / IV ratio from 1.0 to 2.0 mole / mole):

$$r_{ac} = k_1(a-x)(b-x) - k_2x^2,$$

where k_1 and k_2 are the rate constants of the forward and reverse reactions, a and b are the initial concentrations of compounds I and IV, respectively, and x is the current concentration of the final products V and III (all concentrations expressed in M).

The values of the rate constants for the forward reaction k_1, equilibrium constant K_{eq}, and isobaric potential ΔG_T^0 for the three temperatures studied are listed in Table 1.

As is seen from Table 1, the reaction of α-tocopherol acetylation is virtually irreversible in the range of conditions studied. As the temperature grows, the rate constant of the forward reaction k_1 increases and the equilibrium constant K_{eq} drops (i.e., the process is exothermal, $\Delta H < 0$). The latter circumstance merits special attention, because the drop of the K_{eq} value with increasing temperature is related to an increase in the isobaric potential ΔG_T^0. Assuming that the reaction enthalpy and the heat capacities of the initial and final substances are independent of the temperature, we obtained the following temperature dependence of the isobaric potential:

$$\Delta G_T^0 = -16.317 + 35.87T.$$

This relationship indicates that the reaction becomes reversible ($\Delta G_T^0 = 0$) at 455K (182°C) and may be even inverted at temperature above this value, since the isobaric potential would become positive.

Thus, we may conclude that the accumulation of free tocopherol in the final product (vitamin E acetate) is related to the reversible character of the acetylation reaction at high temperatures. Therefore, the duration of thermal action upon α-tocopherol acetate must be sufficiently short to avoid establishing the undesired equilibrium. This very condition (the so-called "retarded" equilibrium) must be used as a basis for obtaining high-purity α-tocopherol acetate with the minimum possible content of free α-tocopherol.

REFERENCES

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