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Deuterium Exchange of the α-Methylene Group Protons in the Quinazolones. III. Environment Influence on the Exchange Rate

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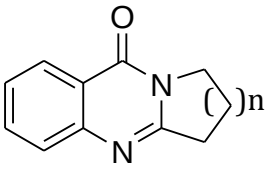
Abstract: By ^{1}H NMR spectroscopy methods the exchange process of α-methylene group protons of deoxyvasicinone by deuterium atoms in the medium of CD_3OD+NaOH and CD_3OD+CD_3COOD depending on NaOH concentration and temperature of the solution and CD_3COOD have been investigated. It was shown that NaOH and CD_3COOD have exchange initiator character, and their effect on the concentration are linear to D-exchange rate. The exponential dependence on temperature allowed us to determine the potential barrier of the initiation of the D- exchange process for deoxyvasicinone in the CD_3COOD.

INTRODUCTION

Tricyclic quinazoline derivatives, which were isolated from plants *Peganum harmala* (deoxyvasicinone, 1) and *Mackinlaya sp.* (Mackinazolinone, 2) are widely used in the some field of the medicine [Tulyaganov,1979; Fitzgerald et al., 1966]. Together with that, these compounds react with electrophilic and nuclephilic reagents on benzene ring and/or activated methylene group in α -position. Earlier, we studied different substitution reaction (mono- and dibromination) and condensation (electrophilic addition-elimination with aldehydes, formylation by Vilsmeier–Haack reagent) reactions and etc. [Shakhidoyatov and Elmuradov, 2014; Abdurazakov et al., 2013; Nasrullayev et al., 2012; Turdibaev et al., 2011; Elmuradov et al., 2010, 2011; Belovodskiy et al., 2010; Abdurazakov et al., 2009].

In continuation of the work begun in [Shakhidoyatov et al., 2014] (exchange of the α - methylene protons of quinazolones on deuterium atoms in the medium of CD_3OD+NaOH and CD_3COOD) in the present work we investigated the dependence of the exchange process on environmental conditions: the concentration and temperature of exchange initiators. In the works [Shakhidoyatov et al., 2014; Levkovich et al., 2013; Levkovich et al., 2015], it was observed that the D-exchange is well in an alkaline solution of methanol and/or acetic acid, but in pure CD_3OD was very slow or even not at all observed.

For mackinazolinone (**2**) in CD_3OD semi-exchange time of H-9 protons was about 1000 hours, and in the case of deoxyvasicinone and 7- or 8-membered homologues with polymethylene rings D- exchange process is at all not detected:



1, n=1
2, n=2
3, n=3
4, n=4

The presence of NaOH, $(C_2H_5)_3N$ or CD_3COOD in methanol initiated D-exchange in all the 4 homologues - deoxyvasicinone (**1**), mackinazolinone (**2**) and 7- or 8-membered homologues (**3**,**4**) with polymethylene cycles.

MATERIALS AND METHODS

Starting compounds were synthesized according the literature procedures [Shakhidoyatov and Elmuradov, 2014; Abdurazakov et al., 2013; Belovodskiy et al., 2010]. Mps were measured on a Boethius and MEL-TEMP apparatus manufactured by Barnstead International (USA) and were uncorrected. Solvents were purified by standard procedures. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with a RVO-64 ROT VAC Evaporator at reduced pressure.
To register ^{1}H NMR spectra were taken sample deoxyvasicinone about 4.0 - 5.0 mg. and dissolved in 0.5 cm^3 of CD_3OD + NaOH or CD_3COOD. ^{1}H NMR spectra were recorded on a spectrometer NMR UNITY 400+ (Varian) with an operating frequency of 400 MHz. Hexamethyldisiloxcane (HMDSO) was used as internal standard, chemical shift δ of ^{1}H was recorded in ppm.

The quantity of the proton signal of H-9 was measured by the integrated signal intensity with respect to H-10 and H-11. When measuring of the concentration dependences the temperature of the sample was kept in the range of 21-23°C. At

temperature measurements a temperature value is set with an accuracy of 0.5°C.

RESULTS AND DISCUSSION

In the present work for determination of the role of NaOH in the initiation of the D-exchange process of deoxyvasicinone was studied the exchange rate dependence on the concentration of NaOH. For the numerical evaluation of the exchange speed (T½) it was measured semi- exchange time of N-9 protons on deuterium atoms. In the work [Levkovich et al., 2016] it was shown, that although in this case T½ is not conventional physical constant of the process, however, quite reliably can serve as a measure of the exchange process speed (signal decay of H-9 protons is different from the exponential function and therefore T½ cannot be considered as constant of the process time, such notion be defined as a common half-life [Levkovich et al., 2016]). Concentration of NaOH in CD_3OD was varied in the range 0.062-4.00 mg / ml with six-step double concentration measurement. The obtained schedule dependencies are shown in Fig.1.

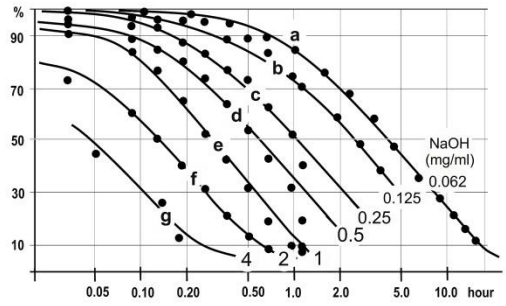


Fig.1. Flowing kinetics of D- exchange of α -methylene protons deoxyvasicinone in CD_3OD+NaOH at different concentrations of alkali. The case ***a*** corresponds to a molar ratio of NaOH: deoxyvasicinone= 0.032:1,and in the case ***g*** - 2: 1.

Even at a concentration of NaOH 0.062 mg/ml of deoxyvasicinone and 9.4 mg/ml semi- exchange time was only approximately 4 hours, while in pure CD_3OD exchange process was not observed even at 1000 hours. Noteworthy ramp exchange rate with increasing concentration of NaOH. Each doubling the alkali concentration (graphics **a→ b→**….**→g**) semi- exchange speed (V=1/T½) increased by ~ 30%. That is clearly expressed for deoxyvasicinone direct proportion:

$$1 / T½ = 0.3 * C (NaOH (mg/ml))$$

The dependence of the D-exchange rate of deoxyvasicinone concentration in a concentration range from 8.0 to 40.0 mg/ml was not found. Thus, the direct proportion indicates, that NaOH is the initiator of the process, and not involved in any chemical conversion.

A similar experiment of mackinazolinone when added CD_3COOD to CD_3OD also led to a linear dependence on the concentration of acetic acid. The molar ratio of CD_3COOD mackinazolinone was in the range from 2.4: 1 to 34.0: 1.

$$1/T½ = 0.01*C (CD_3COOD (mg/ml))$$

D- exchange rate dependence on deoxyvasicinone concentration, as in the previous case, is not detected.

In a separate series of experiments for initiation of D-exchange in methanol were added D_2O and HCl. However, these additives to D- exchange failed. Hence just excess of protons or hydroxyl groups increase the acidity does not lead to the initiation of the process. Apparently molecules of NaOH and CD_3COOD with deoxyvasicinone form the specific dynamic formation. The result of this is the exchange of protons by deuterium atoms. These formations (MC - molecular complexes) must be short-term (dynamic). If a MC strong enough and long-lived, depending on the concentration of the initiators exchange rate would have to occur nonlinearity - the saturation point C (initiator) : C (deoxyvasicinone) = 1:1.

Another important parameter of the environment is a temperature. Temperature dependence of D-exchange rate for deoxyvasicinone was observed in CD_3COOD in the temperature range 20-100°C.

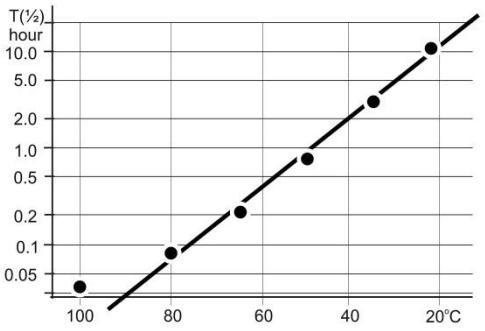


Fig.2. The dependence of the D- exchange rate of α -methylene protons of deoxyvasicinone in CD_3COOD on the solution temperature.

Semi- exchange time T½ in the experiment illustrated in Fig.2., and in the range from 10 hours (T=22°C) to about 2.5 minutes (T=100°C). The graphics Fig.2. clear well-defined relationship: at every step (ΔT≈15°C) temperature changes during semi- exchange varied ≈3 times. This indicates a well-defined exponential dependence, from which it can reliably determine the potential barrier of the activation D- exchange process as:

E_{init} ≈18 kcal/mol

From well-defined semi-logarithmic relationship (Fig.2) deviated only one point: T=100°C, T½=2

min. However, such a great speed of the process leading to the complexity of experimental measurements T½, which could lead to an experimental measurement errors.

CONCLUSION

In the pure methanol D-exchange does not take place or it is very slow. To activate the process requires a certain initiators forming with deoxyvasicinone molecules dynamic complexes. In the present case it was a molecule of NaOH or CD_3COOD. However, the initiators may make other compounds. For example in [Shakhidoyatov et al., 2014], a D-exchange in the presence of $(C_2H_5)_3N$, but proceeding with much less efficiency than in NaOH.

Initiation barrier of deoxyvasicinone in CD_3COOD was ≈18 kcal/mol, which leads to a substantial depending of the rate on the temperature in the range of room temperature.

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