IR SPECTROSCOPIC STUDY OF INTERACTIONS IN THE ACETALDEHYDE-DOPAMINE-UNITHIOL TERNARY SYSTEM

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IR spectroscopy has been used for the first comparative study of the kinetics of reaction of dopamine with acetaldehyde in the presence and absence of unithiol (sodium salt of 2,3-dimercapto-1-propanesulfonic acid, DMPS), a vicinal dithioglycol. Based on the analysis of these reactions, it is concluded that the rate of interaction between acetaldehyde and dopamine decreases significantly in the presence of unithiol, which is a new kind of pharmacological activity for unithiol. This property of unithiol allows it to be recommended for further investigation aimed at the development of a new remedy capable of inhibiting the development of alcohol addiction.

The leading biochemical theory of the development of alcohol dependency (alcoholism, chronic alcoholism) is based on the psychotropic activity of the products from reaction of acetaldehyde with several biogenic amines that are derivatives of phenylalanine (dopamine, noradrenaline, etc.) and tryptophan (serotonin etc.). The products (tetrahydroisoquinolines, betacarbolines) are capable of activating opiate receptors in the brain [1]. Alcohol intoxication is accompanied categorically by the formation of aldehyde (AA), for the binding of which vicinal dithiols (VD) were proposed [2]. In particular, the AA concentration can be decreased by administration of VD such as unithiol (sodium salt of 2,3-dimercapto-1-propanesulfonic acid). We have previously studied the kinetics of the reaction of AA and unithiol [3]. The question of whether VD are capable of affecting the course of the reactions of acetaldehyde with the aforementioned amines and, therefore, whether this effect can inhibit or block the development of alcohol dependency remains open. Dopamine (DP) was selected as the biogenic amine and unithiol (Ut), as the VD, for the purposes of the study. Considering that AA reacts vigorously with Ut (47% of the carbonyl groups disappear in the first hour) [3], it can be assumed that adding Ut to

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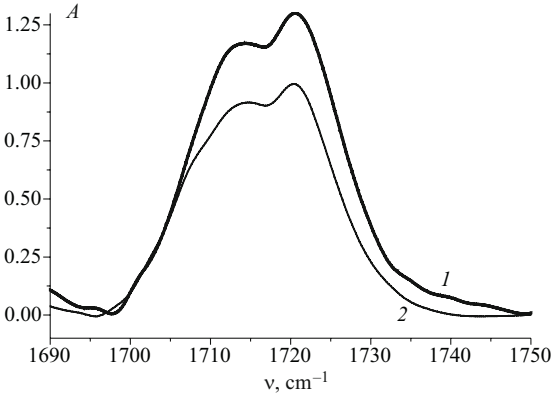

Fig. 1. Spectra of AA (*1*) and AA-DP (10:1) (*2*) in aqueous alcohol.

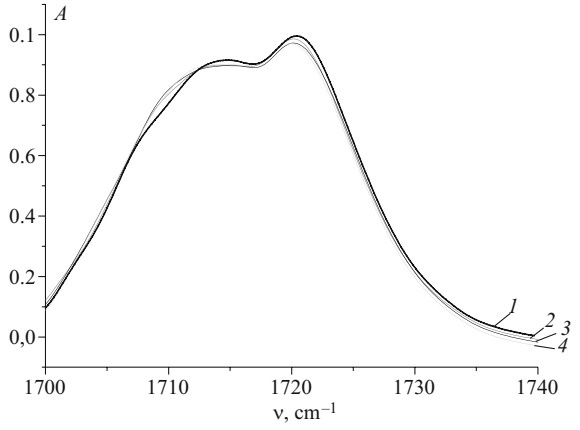

Fig. 2. Change of AA-DP (10:1) spectrum during the first hour of reaction: 5 min (*1*), 20 (*2*), 35 (*3*), and 50 (*4*).

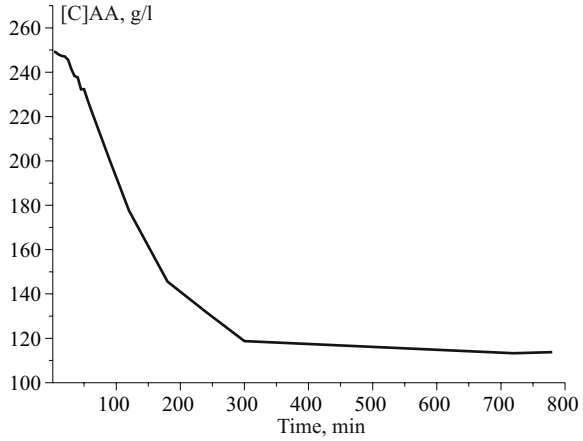

Fig. 3. Kinetics of change of AA concentration in AA-DP (10:1).

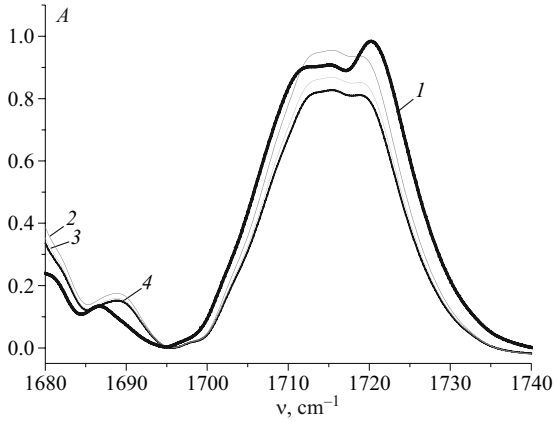

Fig. 4. Change of spectrum of AA-DP (10:1) mixture after reaction for 1 h (*1*), 2 (*2*), 5 (*3*), and 15 (*4*).

the AA-DP system will result in binding of AA by Ut and, as a result, prevention of the reaction of AA with DP. We did not find literature reports on the course of the reaction in the ternary system catecholamine-aldehyde-VD. Herein the reaction in the ternary system AA-DP-Ut is studied for the first time. The condensation of aldehydes and aromatic amines to form tetrahydroisoquinolines has been well studied [4]. We used IR-Fourier spectroscopy first to study the kinetics of the reaction of AA and DP to form methyldihydroxytetrahydroisoquinoline (MDHTHIQ) and then to study the effect of Ut on the course of this reaction.

EXPERIMENTAL PART

We used AA (99%, Sigma-Aldrich), DP (3-hydroxytyramine hydrochloride, 98.5%, Fluka), and Ut (sodium 2,3-dimercaptopropanesulfonic acid, DMPS, Farmstandart-Oktyabr', RF, 5% aqueous solution in ampuls). Tables 1 and 2 and the text give the incubation conditions. All measurements were made under normal conditions in aqueous alcohol solutions in CaF_2 spectral cuvettes. Solid samples of DP

TABLE 1. Concentration of AA in AA-DP Mixture (10:1) as a Function of Reaction Time

No.	Time, min	*D*	[C] AA	
			M	g/L
1	3	0.997	5.667	249.33
2	5	0.996	5.661	249.10
3	10	0.992	5.638	248.09
4	15	0.989	5.621	247.32
5	20	0.988	5.615	247.07
6	25	0.982	5.581	245.56
7	30	0.971	5.485	241.34
8	35	0.959	5.417	238.36
9	40	0.956	5.400	237.60
10	45	0.949	5.360	235.86
11	50	0.935	5.281	232.36
12	55	0.917	5.179	227.89
13	60	0.900	5.083	223.65
14	90	0.806	4.552	200.29
15	120	0.715	4.038	177.67
16	180	0.586	3.309	145.62
17	240	0.531	2.998	131.93
18	300	0.478	2.699	118.74
19	720	0.456	2.574	113.29
20	780	0.457	2.580	113.52

TABLE 2. Concentration of AA in AA-DP-Ut Mixture (10:1:10) as a Function of Reaction Time

No.	Time, min	*D*	[C] AA	
			M	g/L
1	5	0.659	2.833	124.65
2	10	0.651	2.798	123.14
3	15	0.646	2.777	122.17
4	20	0.599	2.575	113.30
5	25	0.574	2.468	108.57
6	30	0.572	2.459	108.21
7	35	0.563	2.420	106.49
8	40	0.560	2.407	105.91
9	45	0.558	2.398	105.53
10	60	0.563	2.419	106.46
11	90	0.567	2.436	107.19
12	135	0.577	2.479	109.07
13	150	0.578	2.473	108.81
14	210	0.583	2.494	109.75
15	270	0.574	2.455	108.04
16	330	0.528	2.258	99.36
17	390	0.510	2.181	95.97
18	450	0.495	2.117	93.14
19	840	0.335	1.433	63.04
20	900	0.334	1.429	62.86

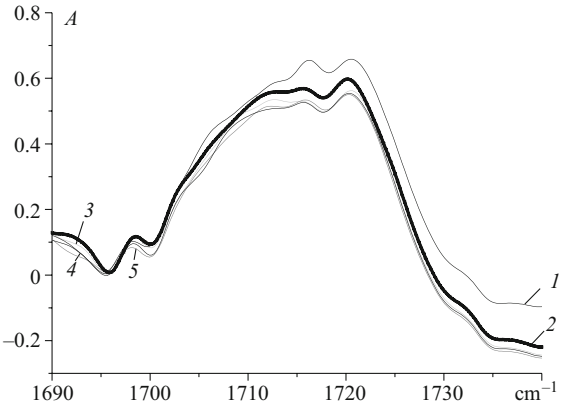

Fig. 5. Change of spectrum of AA-DP-Ut (10:1:10) mixture after reaction for 3 min (*1*), 20 (*2*), 30 (*3*), 40 (*4*), and 60 (*5*).

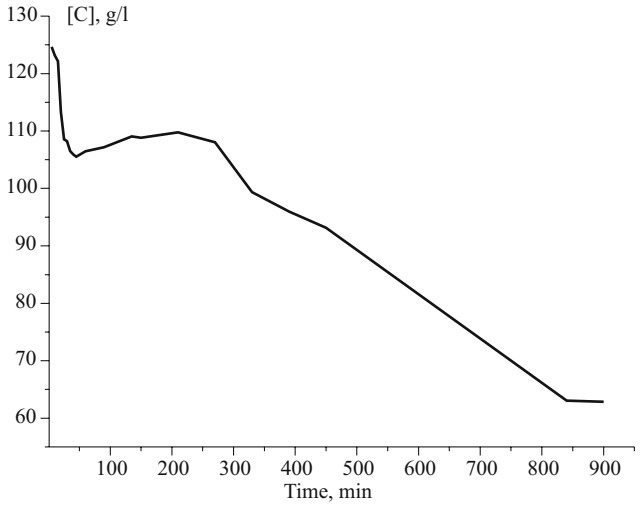

Fig. 7. Change of concentration of carbonyl groups in AA-DP-Ut (10:1:10) as a function of time.

were dissolved in water:alcohol (10:1). The volume of the reaction mixture taking into account the required concentrations of reagents was 6 mL. Spectra of all solutions were recorded on an IFS-66 IR-Fourier spectrometer in CaF_2 cuvettes (0.0067 cm, 4000 – 1400 cm^{-1}). Spectra were processed using the OPUS program set.

The decrease of intensity of the AA ν_{CHO} stretching band during the course of the reaction can be followed very closely using IR spectroscopy. This band, which occurs at 1720 cm^{-1}, is rather strong. Therefore, dilute solutions can be used. IR spectra of DP and the final product MDHTHIQ lack bands in this region. Therefore, this spectral region is suitable for studying the kinetics of the reaction of AA and DP.

Figure 1 shows the spectra of AA and a freshly prepared AA-DP (10:1) mixture. The spectrum of AA in aqueous alcohol shows splitting of the ν_{CHO} band. This is due to the presence in solution of both free AA molecules (1721 cm^{-1}) and those associated through H-bonds to proton-donating hydroxyls of alcohol or water (1715 cm^{-1}). The band from associated carbonyls in the spectrum of AA–DP (curve 2) is broader and has an inflection at 1710 cm^{-1}. This indicates that they may also be associated with amino or hydroxyl groups of DP. The reaction is insignificant during the first hour, as indicated by the almost complete overlap of the absorption spectra (Fig. 2), the optical densities (*D*) and AA concentrations in Table 1, and the short initial portion of the curve in Fig. 3. The AA concentration decreases rather quickly during the next 5 h, as can be seen from Table 1 and Figs. 3 and 4. Then, after 5 h of reaction, the AA concentration changes little and does not change at all after 12 h. An analysis of the spectra (Fig. 3) leads to the conclusion that the band at 1721 cm^{-1} shifts to long wavelengths as the reaction proceeds. One slightly split broad band remains after 5 h and corresponds to a carbonyl associated with a complex of amino or hydroxyl groups of DP. There is practically no free AA under these conditions. After drying the AA-DP (10:1) solution, a dark orange viscous oil formed in the container after 30 d. Its IR spectrum, according to databases in the OMNIC program set, was identified as 1-methyl-6,7-hydroxy-1,2,3,4-tetrahydroisoquinoline.

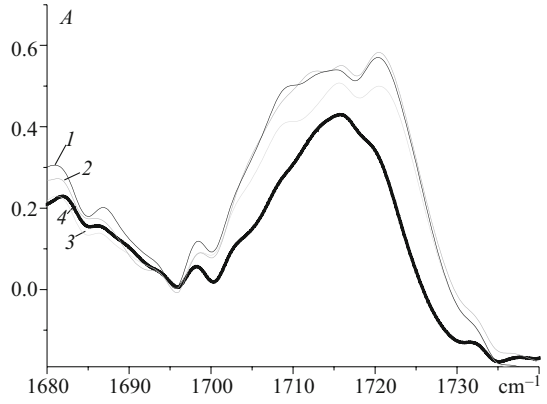

Fig. 6. Change of spectrum of AA-DP-Ut (10:1:10) mixture after reaction for 135 min (*1*), 210 (*2*), 450 (*3*), and 840 (*4*).

Next, the kinetics of the reaction in the ternary system AA-DP-Ut obtained by mixing solutions of the reagents were studied.

Figures 5 and 6 show the change of IR spectra of the ternary mixture AA-DP-Ut (10:1:10) with time. Even the first spectrum of the mixture that was recorded 3 min after mixing the solutions of the reagents looked different than the spectrum of the binary mixture in this region. Bands of free AA (1721 cm^{-1}) and a band at 1716 cm^{-1} have about the same intensity. Then a broad shoulder with several inflection points appears in the long-wavelength region. This indicates that rather strong complexes involving H-bonds between carbonyl, hydroxyl, and thiol groups of the components are formed rapidly in the ternary system. The formation of two of these complexes, for which CHO bands at 1716 and 1698 cm^{-1} are characteristic, is most probably the most energetically favorable because these bands persist in the spec-

trum (Fig. 6) even after the band of free AA has disappeared. The presence of several rather weak and a few strong complexes can explain the rather complicated kinetics of disappearance of free carbonyl groups (Fig. 7).

Free carbonyl groups are consumed quickly by the formation of associates in 40 – 45 min during the first portion of this reaction. Then, an induction period is observed for almost 3 h, during which the concentration of free carbonyls even increases slightly. This may occur due to decomposition of weak associates. The concentration of free AA decreases with simultaneous disappearance of the ν_{CHO} bands of the associates after 210 min. After 600 min, the spectrum exhibits one broad band with ν_{max} 1716 cm^{-1} and a weak band at 1698 cm^{-1}, which are due to strong associates. The spectrum does not change after 900 min of reaction.

If the relative rates of disappearance of carbonyls in the binary and ternary systems at the same molar AA-DP ratio are analyzed, then it becomes obvious that this reaction in the binary system occurs 1.5 times faster. The ability of Ut to inhibit the formation of tetrahydroisoquinolines from DP and AA that was observed in the experiment indicates that further study of this new type of pharmacological activity for this known antidote is needed due to its capability to inhibit the development of alcohol addiction.

Thus, the kinetics of the reaction of AA and DP were studied. The reaction product was 1-methyl-6,7-hydroxy-1,2,3,4-tetrahydroisoquinoline. It was found that carbonyls disappear mainly during the first 5 h of the reaction. The reaction of AA and DP occurs differently in the ternary system AA-DP-Ut. Formation of MDHTHIQ is significantly inhibited and the yield of the reaction product decreases. Formation of MDHTHIQ is inhibited partly due to the formation of thioacetals and partly due to the formation of strong complexes for which bands with ν_{max} 1716 and 1698 cm^{-1} (CHO) were characteristic.

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