Type of bond in products of the interaction between primary amines and the copolymer of divinyl ether and maleic anhydride

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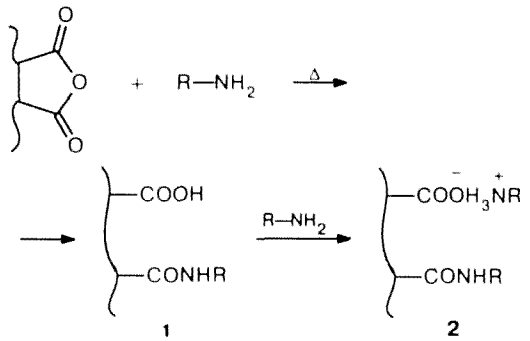
The nature of the bond in the products of the interaction between primary amines and the copolymer of divinyl ether and maleic anhydride has been studied by IR and electron spectroscopy. The reaction in acetone proceeds with the formation of H-bonded ionic charge transfer complexes where p—π-conjugation is possible. It is proposed that the biological activity of macromolecular therapeutic systems based on copolymers of maleic anhydride and drugs containing a primary amino group is due to their ability to reversibly dissociate and the presence of local fragments of p—π-conjugation stabilizing the negative charge.

Key words: copolymers of maleic anhydride, primary amines, H-bonds, charge transfer complexes.

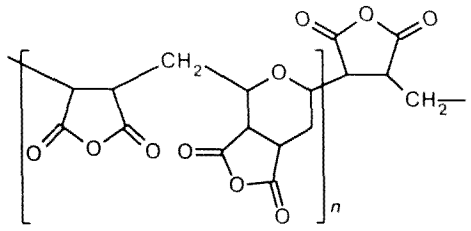
Polymeranalogous transformations of copolymers of maleic anhydride (MA) are usually considered to be reactions of the MA cycles. For example, the interaction between primary amines and MA cycles follows a scheme[1] that includes the formation of an amide (**1**) and a salt with amine (**2**):



1 **2**

Therefore, several investigators traditionally assumed,[2] and persist in holding the viewpoint,[3,4] that the interaction between MA copolymers and drugs containing a primary amino group results in the formation of an amide bond whose presence has been proved by a band in the range of 1645—1650 cm^{-1} in the IR spectra of the reaction products.

However, anhydride cycles are hydrolyzed with relative ease, and one fails to obtain absolutely dry polymer containing merely non-hydrolyzed anhydride cycles.[5] Previously,[6] we carried out a detailed study of the hydrolysis of a copolymer of divinyl ether and MA (DIVEMA):



and showed that even in specially dried acetone the polymer managed to hydrolyze by nearly 30 % in the time characteristic of polymeranalogous transformations.[6]

Thus, carboxyl groups, whose reactivity is essentially higher than that of amino groups[1,7] and whose spectral manifestations of the products formed are similar[8—10] (Table 1) are present in the polymer along with anhydride cycles. Therefore, the presence of a band in the 1645—1650 cm^{-1} region (which is referred to in Refs. 3 and 4) in the IR spectrum of the reaction product does not allow one to draw an unambiguous conclusion on its structure or on the nature of the bond formed.

In this connection, the question on the nature of the bonding of primary amines to DIVEMA has an ambiguous answer and is the subject of this spectral (IR and UV) study.

Decylamine, $CH_3(CH_2)_9NH_2$ (DA), and rubomycin (Rbm), one of the antitumor antibiotics of the anthracycline series widely used in clinics, were the objects of the investigation:

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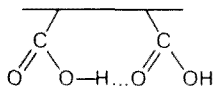
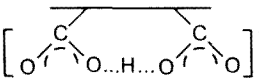
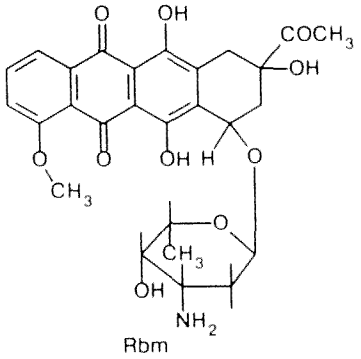
Table 1. Frequencies of the main vibrational bands (ν) characteristic of the feasible products of the interaction between Rbm and DIVEMA (in the solid phase)

Structural element	ν/cm^{-1}	Assignment	Reference
—C(=O)—NH	1680—1630	ν(C=O), Amide I	9, 10
	1570—1515	δ(NH), Amide II	9, 10
	1305—1200	ν(C—N), Amide III	9, 10
	1732—1726	ν(C=O), free	6
	1712	ν(C=O), free	11, 12*
	1670—1650	ν(C=O), bound	9
	1669	ν(C=O), bound	11, 12*
	1648—1642	ν(C=O), bound	6
	1300—1200	ν(C—O)	9
	1630—1575	$\nu_{as}(CO_2)$	13
	1420—1400	$\nu_s(CO_2)$	13
	1585, 1560	$\nu(CO_2)$, bound	14
	1598, 1572	$\nu(CO_2)$, bound	11, 12*
$-NH_3^+$	1620—1575	$\delta_{as}(NH_3)$	9, 10
	1500—1450	$\delta_s(NH_3)$	9, 10

* A solution in D_2O.



Experimental

The DIVEMA copolymer with an alternating 2:1 structure was obtained from the corresponding monomers following the reaction of radical cyclocopolymerization,[15] purified from low-molecular impurities by extraction in ether, and dried to constant weight *in vacuo*. According to ebullioscopic data, the specimens of DIVEMA were characterized by M_n = 15500.

Decylamine of "chemically pure" grade was distilled in an inert medium.

A commercial hydrochloric salt of Rbm was used in the experiments.

Acetone was purified using the standard procedure;[16] the water content in dried acetone was 0.044 mol L^{-1}.

The reaction of DIVEMA with DA was carried out in acetone at room temperature. The concentration of polymer in the solution was 0.02 g cm^{-3}, which satisfies the condition $C<1/[\eta]$ at $[\eta]$ = 0.47 in acetone, *i.e.*, dilute solutions of the copolymer were used (see Ref. 17). The molar ratio of reagents, DA : DIVEMA, was varied from 0.1 : 1 to 10 : 1. In this case, the concentration of the reaction mixture was varied from 0.08 to 0.22 mol L^{-1}.

DIVEMA—Rbm conjugates were obtained in acetone at ~20 °C following the procedure given in Ref. 18, isolated by precipitation from ether, washed with excess chloroform, and dried to constant weight *in vacuo*. The content of Rbm in the conjugate was determined by electron spectroscopy (λ 480 nm) in an aqueous solution (C = 0.003—0.001 g cm^{-3}).

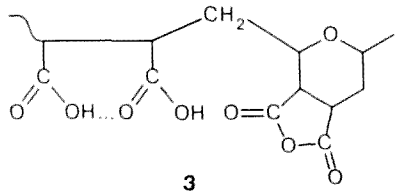
FT-IR spectra were recorded on a Bruker IFS-113v spectrometer (Germany). Samples were prepared as a layer left on a Si plate after evaporation of the solvent from its solution, or as pellets with KBr.

Electronic spectra were recorded on a Specord M40 instrument (Carl Zeiss Jena, Germany).

The stability of conjugates was estimated by HPLC on a Novapak C-18 column with a mobile phase of acetonitrile (32 %)/phosphate buffer (pH 3.16) (68 %), a flow rate of 1 mL min^{-1}, a sample volume of 20 μL, concentration 0.1 wt. %, UV-detector (254 nm).

Results and Discussion

Along with the anhydride cycles, the DIVEMA copolymer contains a substantial number of carboxyl groups, which form either intramolecular dimeric H-bonded associates (**3**) or intramolecular H-bonded linear polyassociates (**4**) containing, as we showed on the molecular models, no more than four carboxyl groups.



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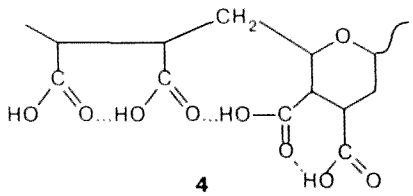

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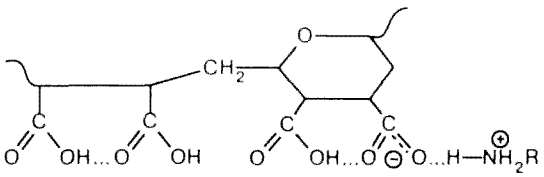
In these associates there is delocalization of electrons, which must be reflected in the electronic spectra. Therefore, we studied the electronic spectra of a solution of DIVEMA in acetone with additives of water

(from 0.1 to 5 wt. %). Two bands at 213 and 333 nm were observed in the UV spectrum at a low content of water in acetone (0.1 wt. %), when the H_2O : the DIVEMA repeating unit ratio was equal to 0.56. The intensity of the latter band increased while that of the former band decreased until it almost completely disappeared at the H_2O : the DIVEMA repeating unit ratio of 28 : 1 (5 wt. %) with increasing water content. Simultaneously, a new band at 323 nm appeared in the UV spectrum at the ratio 1 : 1. Its intensity first increased, reached its maximum at the H_2O : the DIVEMA repeating unit ratio of 5 : 1, and then decreased until it completely disappeared at the ratio 10 : 1.

An analysis of the IR and electronic spectra obtained in the course of hydrolysis of the DIVEMA copolymer allows one to assign the band at 333 nm to the tetramer (structure **4**), and the band at 323 nm to the dimer (structure **3**).



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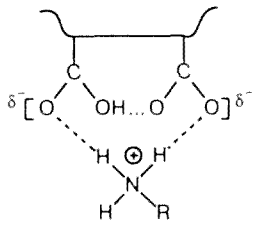

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It is the stabilization of the linear tetramer, in which the electron delocalization is higher than in the dimer, that the peculiar character of the DIVEMA macromolecule, whose conformation becomes more compact due to a similar association, occurs.[19] Increasing the degree of association in a linear H-bonded polyassociate is known to increase its proton-donor properties. Hence, the acidity of the tetramer should be significantly higher than that of the H-bonded dimer in DIVEMA or in analogous low-molecular dicarboxylic acids.

Thus, the formation of H-bonded associates of acid groups and their participation in reactions must be taken into account when polymeranalogous transformations are performed.

To solve the formulated problem, the DIVEMA—DA system was studied in detail. Two samples of the copolymer were used: a specially obtained non-hydrolyzed DIVEMA-1 (Fig. 1, curve *1*) and a DIVEMA-2 pre-hydrolyzed by ~10 % (Fig. 1, curve *2*). The molar ratio of the DA : DIVEMA components was varied from 0.1 : 1 to 10 : 1.

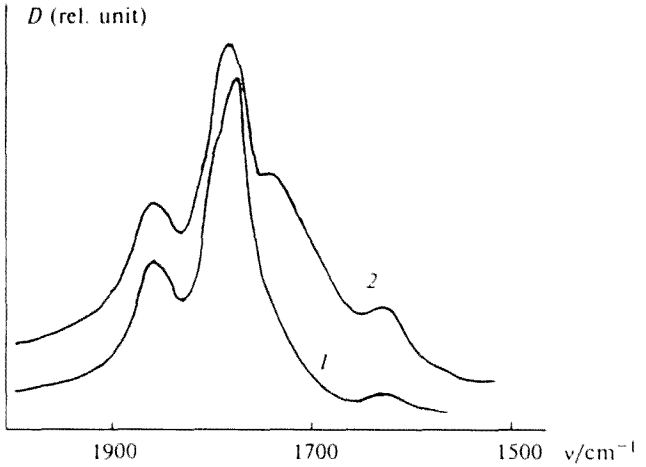


Fig. 1. FT-IR spectra of the copolymer DIVEMA: *1*, non-hydrolyzed specimen, *2*, specimen hydrolyzed ~10 %.

Pouring together colorless starting solutions of DA and DIVEMA-2 at a ratio of 2 : 1 leads to the appearance of a light-yellow color, and gelatinization proceeds in the reaction mixture after ~2 h with decoloration. The intensity of coloring increases as the concentration of amine in the mixture increases, and the time preceding the onset of gelatinization simultaneously decreases. For example, the DA—DIVEMA reaction mixture of composition 10 : 1 is intense brown when the starting solutions are mixed, and both gelatinization and decoloration proceed immediately.

These effects are sluggish for the systems with DIVEMA-1. For instance, one can detect yellow coloring at the ratio 2 : 1 only after ~2 h. The time preceding the onset of gelatinization also increases accordingly (4 h).

Coloring is usually associated with the occurence of a system of polyconjugation[20] as well as with the displacement of the electron density due to the formation of charge transfer complexes (CTC).[21,22]

The FT-IR spectra of the products of the interaction between decylamine and DIVEMA when the DA : DIVEMA ratio is 0.1 : 1 already have a band at 1550 cm^{-1} whose intensity increases as the amine content in the system increases. A band at 1640 cm^{-1} appears simultaneously whose intensity also increases as the amine content increases. However, its intensity remains less than the intensity of the band at 1550 cm^{-1} (Fig. 2).

In secondary amides, the band in the 1640 cm^{-1} region (Amide I) is usually more intense than that in the 1550 cm^{-1} region (Amide II).[9] This is inconsistent with the results observed and indicates the absence of an amide bond in the system. This is confirmed by the absence of the band in the 1200—1300 cm^{-1} region (Amide III). The intense band at 1221 cm^{-1} in the spectrum of the starting DIVEMA, which may be assigned both to an anhydride cycle[10] and a COOH group, decreases to nearly complete disappearance when the DA : DIVEMA ratio is 4 : 1 (Fig. 2) as the amine concentration increases. At the same time, an absorp-

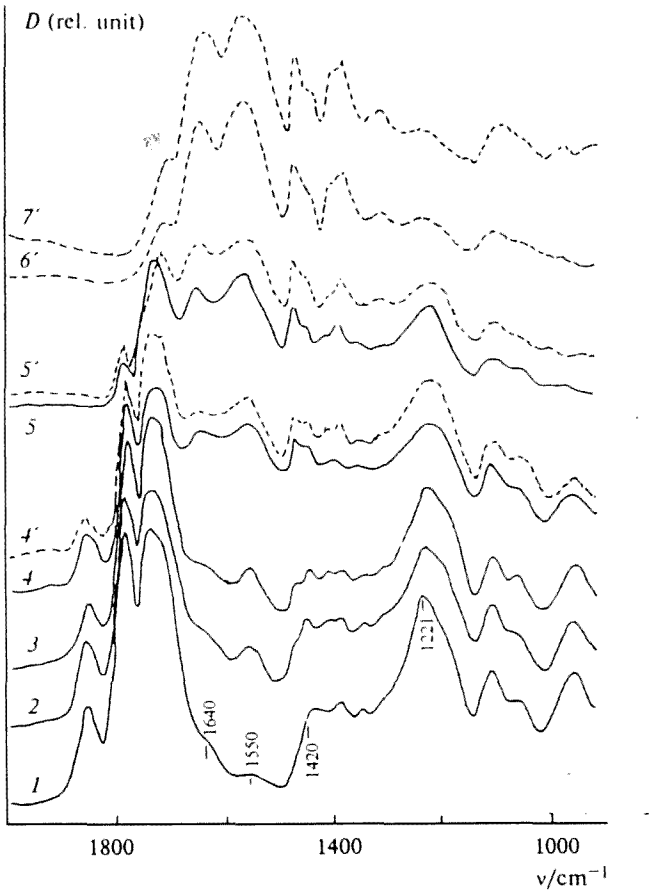
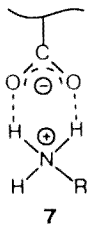


Fig. 2. FT-IR spectra of the products of the interaction between DA and DIVEMA-1 (*1*—*5*) and DIVEMA-2 (*4'*—*7'*) at different amine : polymer ratios: 0.1 : 1 (*1*); 0.25 : 1 (*2*); 0.5 : 1 (*3*); 0.87 : 1 (*4*, *4'*); 2 : 1 (*5*, *5'*); 4 : 1 (*6'*); 10 : 1 (*7'*).

tion band in the IR spectra in the 1420—1390 cm^{-1} region (see Table 1), whose intensity increases as the amine concentration (Fig. 2)increases, confirms the presence of the carboxylate ion in the products.

Thus, the main product of the interaction between the primary amine and the DIVEMA copolymer are H-bonded ionic pairs in which the anion can have different structures (**5**—**8**); the ratio of those structures is dependent on the amine concentration.



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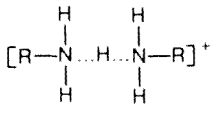

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When the amine/polymer ratio exceeds the equifunctional ratio (2 : 1), complex ammonium cations of type **8**, which are stabilized by a strong H-bond[23] but are less strongly bonded to the anion, can be formed.

In all ionic compounds **5**—**8** partial transfer of the charge is possible; in structures **6** and **7** areas of local p—π-conjugation can arise. It is known[24] that when H-bonds are formed in molecules containing π-electrons and lone electron pairs, quasiaromatic cycles can be formed in which free π- and p-electrons comprise a unified system, and the hydrogen atom participates in the formation of a conjugated cycle leaving a free p-orbital for those electrons. Then p—π-conjugation occurs, which must be visible in the electronic spectra. In fact, the UV spectra of the products of the interaction between decylamine and DIVEMA-1 (DIVEMA-2) in acetone have a number of new bands in the 300 to 500 nm region not found for the starting compounds (Fig. 3). Their appearance is usually associated with the

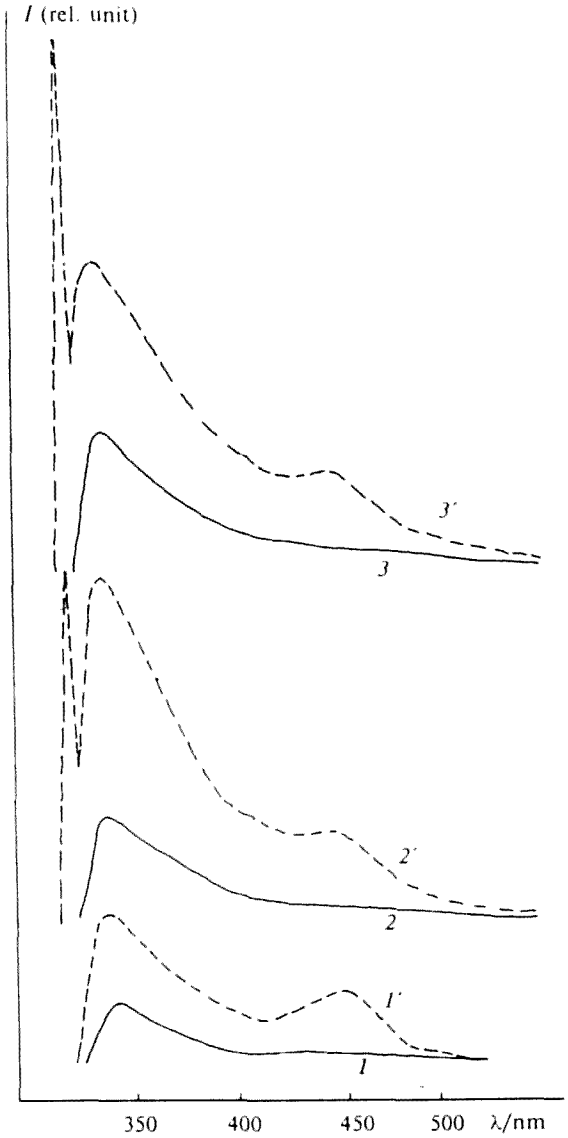

Fig. 3. Differential electronic spectra of products of the interaction between decylamine and DIVEMA-1 (*1*—*3*) and DIVEMA-2 (*1'*—*3'*) at amine : polymer ratios equal to 0.87 : 1 (*1*, *1'*); 1.5 : 1 (*2*, *2'*), and 2 : 1 (*3*, *3'*).

Table 2. The main bands in the differential spectra of complexes of DIVEMA-1 with decylamine

Molar ratio DIVEMA : DA	λ/nm (*I*/a.u.)		
1 : 0.25	361 (0.05)	—	—
1 : 0.5	356 (0.06)	448 (0.01)	—
1 : 0.87	344 (0.17) 341 (0.46)*	448 (0.02) 448 (0.21)*	— 514 (0.01)*
1 : 1.5	341 (0.30) 327 (1.07)* 338 (1.05)*	448 (0.03) 448 (0.27)*	— 514 (0.07)*
1 : 2	341 (0.42) 327 (1.65)* 338 (0.94)*	448 (0.07) 448 (0.28)*	514 (0.04) 514 (0.11)*
1 : 10	327—338 (>4)*	448 (1.40)*	514 (0.68)*

* Data refer to complexes of DIVEMA-2 with DA.

formation of donor-acceptor CTC.[20] The intensity of the charge transfer bands (CTB) increases as the amine portion of the reaction mixture increases. However, at equal amine/polymer ratios, the intensity of CTB is higher for the products containing the partially hydrolyzed polymer (DIVEMA-2).

Computer processing of the spectra obtained using the Peak Fit program allowed us to separate three main bands (Table 2). The appearance of the longest-wave band (514 nm) in the electronic spectrum at the amine : polymer ratio of 2 : 1 is in good correlation with the coloring of solution and the subsequent gelatinization. This band should probably be assigned to complexes with structures **7** and **8**, where the energy of hydrogen bonding is somewhat higher than in structure **6** and much higher than in structure **5** and, hence, the extent of the charge transfer is also higher. One can assign the positionally stable band at 448 nm, which appears when the amine : polymer ratio is 0.25 : 1, to structure **6**, and the positionally unstable bands in the 320 to 380 nm region to structure **5** and to a linear polyassociate of COOH-groups (structure **4**), since it is known[20] that bands in the ~350 nm region appear, usually, in the spectra of compounds containing a carbonyl group involved in a conjugation system and correspond to $n\rightarrow\pi^*$-transitions.

Thus, the results of the studies of the vibrational and electronic spectra of the model systems showed that the interaction between the DIVEMA copolymer and a primary amine in acetone results in the formation of H-bonded ionic complexes in which local $p-\pi$-conjugation is possible. Such complexes are very sensitive to the slightest changes in the medium and can disintegrate with ease because of the shift of the protolytic equilibrium in the system. We attempted to achieve this by washing the products obtained in the interaction between decylamine and DIVEMA in chloroform (which is a good solvent for amine) for 20 h at room temperature. Comparison of the FT-IR spectra of several systems before and after their contact with chloroform showed that the products obtained at the ratio DA : DIVEMA = 0.87 :1 are fairly stable. At the same time, when the products contain excess amine (ratio of components in the complex 4 : 1), the amine is readily washed off although (according to IR spectroscopy data) it is bound amine. Free carboxyl groups appear as a result (the intensity of the ν(C=O) band in the 1740 cm^{-1} region increases noticeably while the $\delta(NH_3^+)$ and $\nu(COO)^-$ bands in the 1630 and 1580 cm^{-1} regions, respectively, decrease). After being washed, the products of the interaction between DA and DIVEMA of composition 4 : 1 and 0.87 : 1 and their IR spectra essentially coincide, *i.e.*, complexes with different stability in chloroform are among the reaction products.

Based on the results of the studies of the model complexes of DA with DIVEMA, one can draw the conclusion that the nature of binding of the antibiotic with the polymer in the Rbm—DIVEMA conjugates also is ionic in character.

An analysis of the FT-IR spectra of the specimens of Rbm, of its salt form $RbmH^+Cl^-$, and of Rbm—DIVEMA conjugates with varied amounts of the antibiotic (Fig. 4) showed that the latter is not identified if its content in the conjugate is 1 mol. % Rbm, whereas the bands of the inner vibrations of rubomycin are clearly seen at 10 mol. % Rbm content. However, a broad band of 1560 cm^{-1} whose intensity increases as the content of antibiotic increase appears in the spectra of conjugates (Fig. 4, curves *3—5*) independently of the amount of rubomycin in the conjugate.

The band at 1640 cm^{-1}, on which is based the conclusion in the literature,[3,4] that amide bond formation occurs, appears as a shoulder of much lower intensity than the 1560 cm^{-1} band. At the same time, the intensities of the 1855 and 1780 cm^{-1} bands, characteristic of the ν(C=O) vibrations of anhydride cycles, decrease, while the intensity of the 1725 cm^{-1} band, assigned to the carboxyl group, increases.[11]

It should be noted that the formation of the amide bond resulting from the interaction of the amino group with the anhydride cycle is also followed by the formation of a carboxyl group (structure **1**). However, in this case, the concentration of acidic groups must not exceed the concentration of bound amine. In our experiment the introduction of only 1 mol. % rubomycin (one NH_2 group per 100 repeating units of DIVEMA, *i.e.*, per 200 anhydride cycles) cut the concentration of the anhydride cycles to less than half (Fig. 4, curve *3*). In this case the concentration of carboxyl groups increases correspondingly and appreciably exceeds the amount of acid formed in the process of natural (background) hydrolysis of DIVEMA in acetone in the blank experiment (Fig. 4, curve *2*).

It is to be noted that the hydroxyl groups in the Rbm molecule do not react with copolymers under the reac-

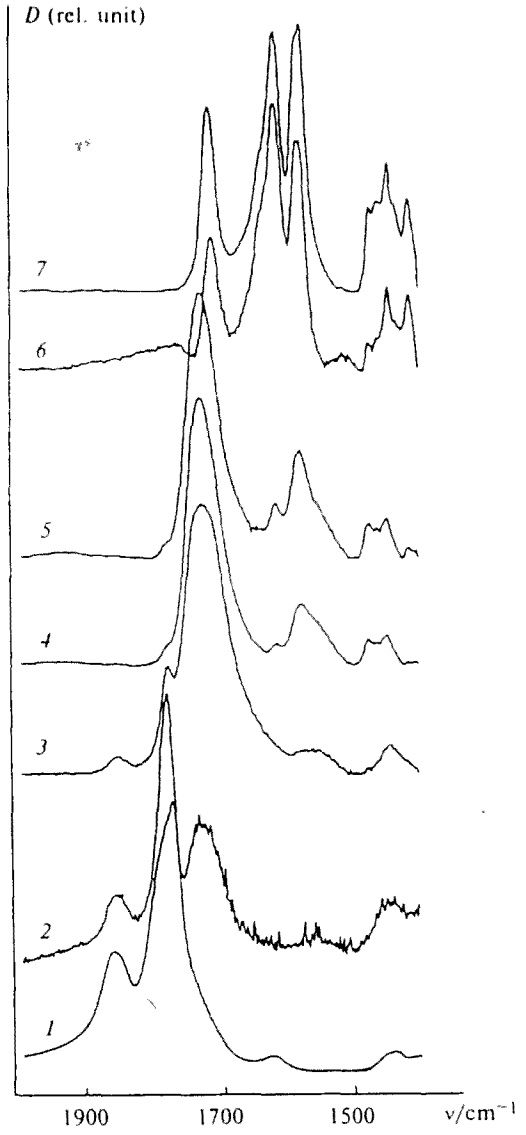

Fig. 4. FT-IR spectra of solid specimens of the starting copolymer DIVEMA (*1*); DIVEMA after blank experiment (*2*); conjugates of DIVEMA—Rbm containing 1 (*3*); 4.5 (*4*), and 10.4 (*5*) mol. % of Rbm, respectively; Rbm hydrochloride (*6*) and basic form of Rbm (*7*).

tion conditions, as has been shown in special experiments.[25]

Hence, the hydrolysis process in the synthesis of Rbm—DIVEMA conjugates is significantly accelerated, apparently due to water trapped in the reaction mixture together with the antibiotic, and it is practically impossible to dry the antibiotic without destroying it.

On the basis of the obtained results one can draw the conclusion that the bond between the antibiotic and the polymer is ionic in nature, and is not the amide bons established in the literature.

Additional confirmation of this conclusion can be found in the behavior of the conjugate in aqueous solution. It has been established by HPLC (~20 °C) that the antibiotic splits off from the polymer in aqueous solution at a pronounced rate, which increases as the amount of rubomycin in the conjugate increases. However, in accordance with IR spectroscopy data, the conjugate is stable in water; in fact, after it was kept in water for 20 days, the content of antibiotic (the 1620 cm^{-1} band) was not changed. But, at the same time, the intensity of the 1108 cm^{-1} band assigned to the ν(C—O—C) vibrations in rubomycin had increased, which can be related to the ordering of the antibiotic molecules in the conjugate, since Rbm, like many planar molecules, is known to have a tendency toward stacking.[26]

At first glance, these results contradict each other. However, when taken together the IR spectroscopy and HPLC data confirm the donor-acceptor nature of the interaction between rubomycin and DIVEMA. In fact, ion pairs dissociate[28] in water, a strongly polar solvent ($\varepsilon = 78.3$),[27] *i.e.*, and the free antibiotic appears after the conjugate is exposed to water as the $RbmH^+$ cation. On the chromatograms of the conjugate specimens (after 120 h incubation in water) the retention times and the shapes of the rubomycin peak coincide with those for its salt form $RbmH^+Cl^-$. Apparently, the self-association of the free rubomycin in solution is more pronounced than that of rubomycin bound to DIVEMA. The transition to the solid phase (evaporation of the solvent during preparation of the specimens for IR analysis) is accompanied by the reduction of the contact ionic pairs in which rubomycin is more associated, which is observed in the experiment.

It should be noted that the appearance of the $RbmH^+$ cation in solution could also be expected in the hydrolysis of the amide bond. However, the amide bond can not be reduced by evaporation of the solvent; therefore the intensity of the bands in the FT-IR spectrum characteristic of COOH groups would increase, but this is not the case. In such a case, if the nature of the bond between rubomycin and DIVEMA under the studied conditions was ionic, the regularities of the isolation of rubomycin from the conjugate with DIVEMA at 37 °C and neutral pH discussed in the literature,[2] and, in particular, flattening of the release curves, could be explained by the establishment of a dissociation equilibrium.

In this connection, it can be assumed that the ability of the macromolecular therapeutic DIVEMA—Rbm system to reversibly dissociate and the presence of fragments of local p—π-conjugation stabilizing the negative charge are responsible for the system's biological activity. Hence it follows that physical mixtures of reagents in solutions, in which exchange reactions are possible, must possess biological activity comparable with that of the conjugate. In order to prove this statement we prepared an aqueous solution of a physical mixture of DIVEMA with hydrochloric rubomycin salt (4.5 mol. %) and found that the exchange reaction occured (the IR spectrum of the product obtained was the same as the

spectrum of the corresponding conjugate). In this case, as was shown by biological tests in experiments *in vivo*, the product obtained has antitumorigenic activity comparable with that of corresponding conjugates.[29] However, the problem of the mechanism of the biological effect of these systems still remains open.

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