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Kinetic Studies of Acylation of Polyethylene Glycol Hydroxyl Groups

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ABSTRACT

The reactivity of polyethylene glycol (PEG) hydroxyl groups was studied by acylation with benzoyl bromide in the presence of a catalyst (tributylamine). The reaction rate constants were calculated for all forms of H-complexes in PEG solutions in CCl_4 and dioxane.

INTRODUCTION

Polyethylene glycol (PEG) macromolecules can form several types of intra- and intermolecular hydrogen bonds due to the interaction of terminal hydroxyl groups with polymer chain oxygen atoms. The various forms of hydrogen-bonded hydroxyls vary considerably in reactivity. This makes it difficult to obtain a number of PEG derivatives of practical importance. The optimization of synthesis conditions requires a preliminary study of the effect of hydrogen bonding of the PEG terminal hydroxyl groups. For a complete description of kinetic behavior of reactions of associated OH-groups, it is necessary: 1) to distinguish all forms of H-complexes in PEG solutions, to determine their relative fractions depending on the polymer molecular weight (MW) and con-

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centration; and 2) to find the reaction rate constants of each of the above-mentioned forms.

Studies of hydrogen bonds in PEG solutions permitted isolation of all forms of H-complexes and to calculate their fractions depending on the polymer chain length [1, 2]. For a complete description of the reactivity of PEG hydroxyl groups, the reactivity of each form of H-complexes had to be determined.

EXPERIMENTAL

Materials

PEG of MW lower than 1 000 was dried over phosphoric anhydride in a vacuum at 353 K. PEG of higher MW was used without preliminary purification. For all PEG samples the breadth of the molecular weight distribution (MWD), $\overline{M}_w/\overline{M}_n$, determined by GPC did not exceed 1.1.

1-Propanol and 1-butanol were dried as described in Ref. 3. Cetyl alcohol was used without preliminary purification. Methoxyethanol (MOE) and ethoxyethanol were dried over calcium sulfate and distilled at 397 and 408 K, respectively [3]. Triethylene glycol monobutyl ether was distilled at 393 K (3 Pa) [4]. Tetraethylene glycol was distilled at 450 K (13 Pa) [5], then dried over phosphoric anhydride in a vacuum desiccator for 2 days.

Benzoyl bromide was synthesized from benzoic acid and phosphorus tribromide [6]. Acetic anhydride was distilled at 413 K [3]. Pyridine was dried over KOH for 5 days and distilled over barium oxide at 388 K [3]. Tributylamine (TBA) was purified as follows [7]: 2 mL of benzoyl chloride was added to 100 mL of TBa, the mixture was stirred for 20 min, the precipitate was filtered off, and the TBA was distilled twice over sodium at 493 K. Dioxane was dried as described in Ref. 3. Diethyl ether (DE) was distilled over calcium hydride at 307.5 K. Carbon tetrachloride was distilled twice over phosphoric anhydride at 349 K [3].

Reaction Between Hydroxyl-Containing Compounds and Benzoyl Bromide

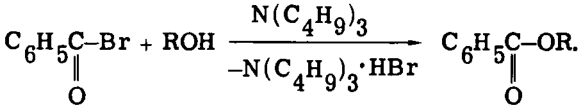
The reaction of compounds containing hydroxyl groups with benzoyl bromide in the presence of TBA was carried out in a thermostatically controlled cell with a reflux condenser with stirring and nitrogen flow. The temperature was 303 K. IR spectroscopy was used to study the reaction kinetics. Samples (1 mL) were taken from the reaction mixture at regular time intervals and the reaction was stopped by reacting unreacted benzoyl bromide with a 1.5-fold excess of diethylamine:

$$C_6H_5\underset{\underset{O}{\|}}{C}{-}Br + (C_2H_5)_2NH \longrightarrow C_6H_5\underset{\underset{O}{\|}}{C}{-}N(C_2H_5)_2 + HBr.$$

This permitted us to follow the reaction course both by the decrease in the initial reagent concentration, i.e., in benzoyl bromide concentration (by the absorption band corresponding to stretching vibrations of the carbonyl group of N,N-diethylbenzamide, at 1 640 cm^{-1}) and by the increase in the product concentration (by the absorption band of stretching vibrations of the ester carbonyl group, at 1 730 cm^{-1}).

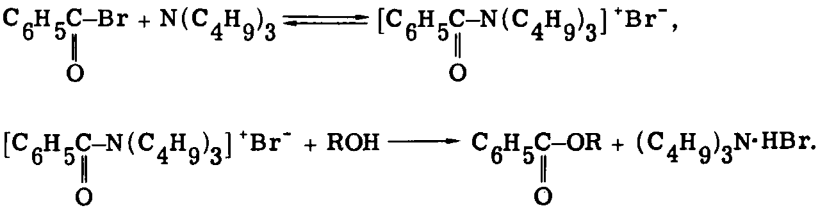
RESULTS AND DISCUSSION

The reactivity of hydroxyl groups toward the benzoylation reaction was studied in the presence of tributylamine (TBA) as a catalyst:



$$C_6H_5\underset{\underset{O}{\|}}{C}{-}Br + ROH \xrightarrow[-N(C_4H_9)_3\cdot HBr]{N(C_4H_9)_3} C_6H_5\underset{\underset{O}{\|}}{C}{-}OR. \qquad (1)$$

Reaction (1) is practically irreversible, and its mechanism has been well studied for low-molecular weight alcohols [8]. These reactions can proceed either by a nucleophilic mechanism or by a general base mechanism, depending on the nature of the reagents and solvent. Taking the regularities found for low-molecular weight alcohols as the basis, we assume that with slightly acidic hydroxyl-containing compounds (cellosolves, PEG) and TBA, general base catalysis proceeding via the formation of hydrogen-bonded ROH . . . $N(C_4H_9)_3$ is highly improbable. This assumption is confirmed by the absence of the absorption band of H-complexes with TBA, which would be at 3 300 cm^{-1} [9] in the IR spectra of reaction mixtures. Thus, Reaction (1) most probably proceeds by a nucleophilic mechanism via the formation of an acylammonium complex (AAC):

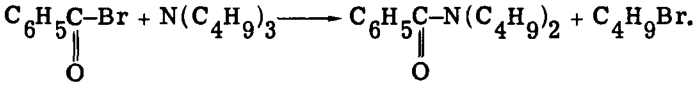


$$C_6H_5\underset{\underset{O}{\|}}{C}{-}Br + N(C_4H_9)_3 \rightleftharpoons [C_6H_5\underset{\underset{O}{\|}}{C}{-}N(C_4H_9)_3]^+Br^-,$$

$$[C_6H_5\underset{\underset{O}{\|}}{C}{-}N(C_4H_9)_3]^+Br^- + ROH \longrightarrow C_6H_5\underset{\underset{O}{\|}}{C}{-}OR + (C_4H_9)_3N\cdot HBr.$$

The reagents for PEG benzoylation were chosen for the following reasons. A sufficiently active acid halide, viz., benzoyl bromide, was used as an acylating agent. It provided a fast rate under mild conditions. TBA was taken as a catalyst because of the good solubility of its complex in the reaction mixture, and this results in a homogeneous medium for the reaction. The latter makes TBA preferable to other amines, in particular, triethylamine and pyridine.

Since benzoyl bromide is readily hydrolyzed, the concentration used was 1.1-2.0 times that of the hydroxyl groups. Since TBA functions both as an acceptor of hydrogen halide and as a catalyst, it is used in two- or fivefold excess. A greater excess of benzoyl bromide and TBA is not desirable due to a possible side reaction between them to form N,N-dibutylbenzamide [10]:



$$C_6H_5\underset{\underset{O}{\|}}{C}{-}Br + N(C_4H_9)_3 \longrightarrow C_6H_5\underset{\underset{O}{\|}}{C}{-}N(C_4H_9)_2 + C_4H_9Br. \qquad (2)$$

The kinetics of benzoylation was studied by IR spectroscopy. Reaction (1) was followed both by a decrease in the concentration of benzoyl bromide, and by an increase in that of the ester. With a twofold excess of TBA the reaction rate constants are calculated by a third-order equation, and with a fivefold excess by a second-order equation. Typical plots of the kinetic data are given in Figs. 1 and 2.

If different forms of associated hydroxyls have different activities in dilute solutions of PEG in CCl_4 (Fig. 3), the observed reaction rate constant, k_{obs}, is determined by the equation [11]

$$k_{obs} = k_{fr}\alpha + k_1\beta + k_2\gamma + k_3\Delta, \qquad (3)$$

where α, β, γ, and Δ are relative fractions of free OH groups and H complexes 3a, 3b, and 3c, respectively; while k_{fr}, k_1, k_2, and k_3 are their respective rate constants.

The determination of constants from Eq. (3) is based on a set of model systems with a set of more and more complicated hydrogen bonds. The simplest systems are dilute solutions of aliphatic alcohols (1-propanol and 1-butanol), containing only unbonded hydroxyl groups. The value of k_{fr} determined for these systems is 0.048 $L^2/(mol^2 \cdot s)$ (Table 1). It seems that aliphatic alcohols are not sufficiently good models of the unbonded OH groups of PEG, since they do not take account of the inductive effect of oxygen atoms observed in polymers which causes a decrease in the reactivity of hydroxyl groups compared to those of alcohols. It is impossible, however, to find a suitable model that takes account of this effect, because hydroxyl-containing compounds with oxygen atoms in the γ-position can form intra-

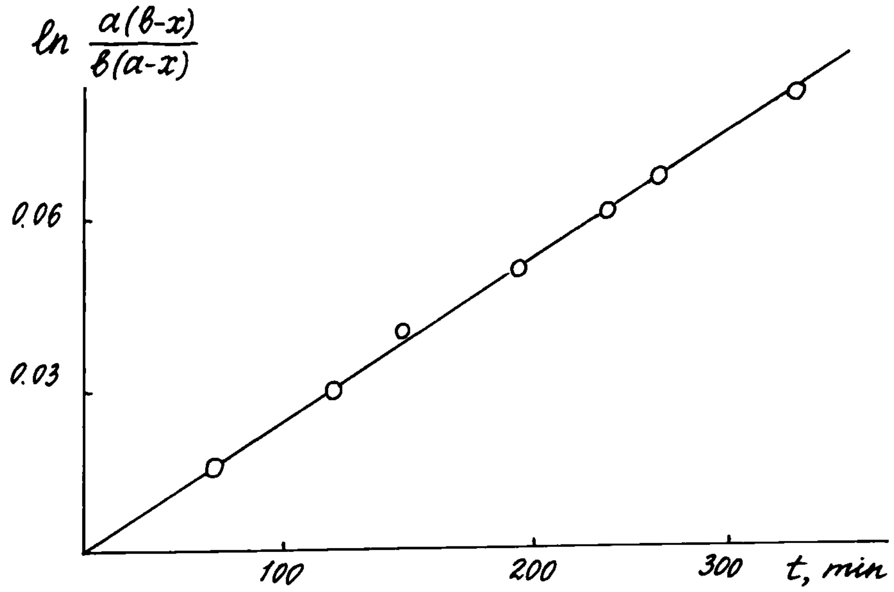


FIG. 1. Kinetic plots for triethylene glycol monobutyl ether benzoylation in CCl_4 ($a = C^{\circ}_{OH} = 0.011$ mol/L, $b = C^{\circ}_{bbr} = 0.0125$ mol/L, $c = C^{\circ}_{TBA} = 0.05$ mol/L, "x" is the current concentration of the reaction product).

molecular hydrogen bonds in five-membered rings. As shown below, it is not necessary to know the precise value of the constant k_{fr} for description of the PEG kinetics, since the fraction of unbonded hydroxyl groups in polymer solutions is small (Table 1).

Dilute solutions of ethylene glycol ethers (methoxyethanol (MOE) and ethoxyethanol) in which two forms of OH groups (free and intramolecularly bound in five-membered rings (3a)) are present can be used as model systems for determining the rate constant k_1 of 3a H-complexes. The value of k_1 is calculated from Eq. (3) on the basis of the known quantities α, β, and k_{fr}. It is 0.065 $L^2/(mol^2 \cdot s)$. Comparison of k_{fr} and k_1 (Table 2) indicates that hydroxyl groups bound in five-membered rings have higher reactivity than free ones.

Taking PEG solutions, we determined k_2 and k_3. The observed rate constants, k_{obs}, of Reaction (1) for polymers of various MW are listed in Table 1. It also presents the relative mole fractions of all the

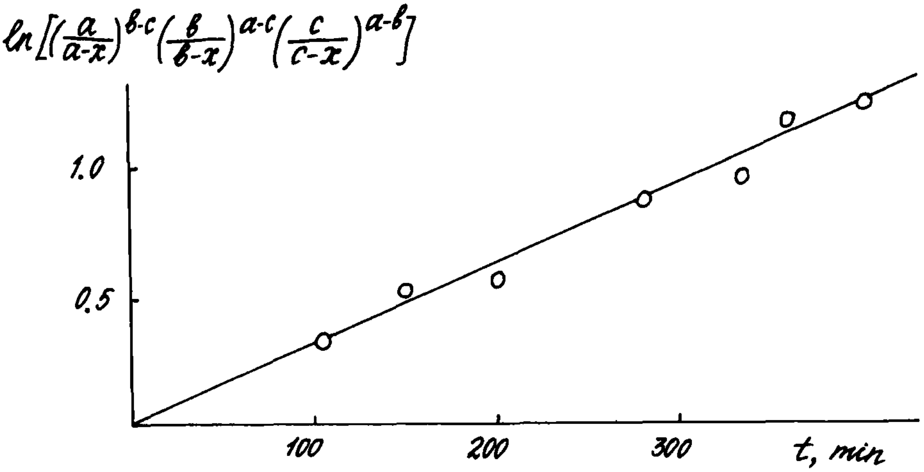


FIG. 2. Kinetic plots for benzoylation of PEG (MW 1 000) in dioxane ($a = C^{\circ}_{OH} = 0.041$ mol/L, $b = C^{\circ}_{bbr} = 0.08$ mol/L, $c = C^{\circ}_{TBA} = 0.1$ mol/L, "x" is the current concentration of the reaction product).

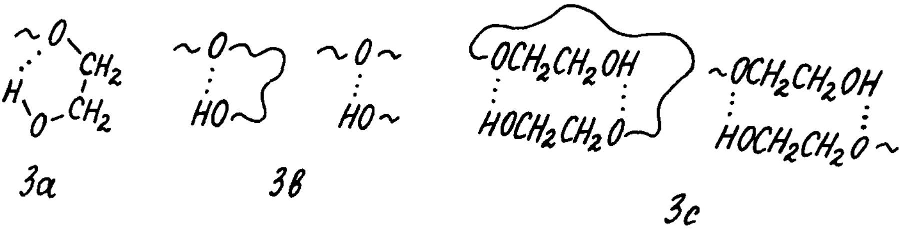


FIG. 3. H complexes in PEG solutions in CCl_4.

forms of H-complexes in PEG solutions in CCl_4 and the value of the second term in Eq. (3) for k_{obs}, calculated from the known value of k_1. It is seen from Table 1 that $k_1\beta$ dominates the value of the observed rate constant. In other words, PEG reactivity is determined by OH-groups participating in the formation of intramolecular hydrogen bonds in five-membered rings (3a). Free hydroxyl groups are of little importance because of their negligible amount in PEG solutions. As to the other hydrogen bond complexes, in spite of their considerable fractions of the total amount of OH-groups, they do not appreciably influence the polymer reactivity. This happens only when k_2 and k_3 are at

TABLE 1. Relative Mole Fractions α, β, γ, and Δ of Free OH Groups of the 3a, 3b, and 3c H Complexes in CCl_4 Solutions and the Observed Rate Constants of the Benzoylation Reaction[a]

Compound	α	β	γ	Δ	$k_1\beta \times 10^2$, $L^2/(mol^2 \cdot s)$	$k_{obs} \times 10^2$, $L^2/(mol^2 \cdot s)$
H-C_3H_7OH	1.00	-	-	-		4.7 ± 0.3
H-C_4H_9OH	1.00	-	-	-		4.9 ± 0.3
H-$C_{16}H_{33}OH$	1.00	-	-	-		6.0 ± 0.5
$CH_3OCH_2CH_2OH$	0.09	0.91	-	-		6.3 ± 0.3
$C_2H_5OCH_2CH_2OH$	0.09	0.91	-	-		6.3 ± 0.3
$C_4H_9(OCH_2CH_2)_3OH$	0.05	0.56	0.27	0.12	3.7	4.7 ± 0.3
PEG MW 300	0.03	0.36	0.20	0.41	2.3	2.7 ± 0.1
PEG MW 600	0.04	0.39	0.31	0.26	2.5	2.9 ± 0.1
PEG MW 1 000	0.04	0.40	0.40	0.16	2.6	2.9 ± 0.1
PEG MW 3 000	0.04	0.40	0.56	-	2.6	2.9 ± 0.1
Butoxy-PEG MW 3 000	0.04	0.41	0.55	-	2.7	2.9 ± 0.1
PEG MW 6 000	0.04	0.40	0.56	-	2.6	2.8 ± 0.1
$CH_3OCH_2CH_2OH$ + $C_2H_5OC_2H_5$	0.04	0.40	0.56	-	2.6	2.8 ± 0.1

[a] C_{OH}, 10^{-2} mol/L; temperature, 303 K.

TABLE 2. Benzoylation Rate Constants of Different Forms of H Complexes in PEG Solutions at 303 K[a]

$k_{fr} \times 10^2$	$k_1 \times 10^2$	k' $(k_2) \times 10^2$	k'' $(k_3) \times 10^2$
4.8	6.5	0.2	0.2

[a] In $L^2/(mol^2 \cdot s)$.

least an order of magnitude smaller than k_{fr} and k_1. Thus, the constant k_1 and the mole fraction of H-complex 3a suffice for the description of the kinetic behavior of PEG. The values of k_{fr}, k_2, and k_3 are of less importance because of their negligible contributions to the reaction rate constant.

Since we are comparing reactivities of low molecular weight compounds with those of high molecular weight compounds, it is necessary to estimate the possible effect of polymer chain steric hindrances on OH-groups activity. Cetyl alcohol, $C_{16}H_{33}OH$, is a suitable object for a model experiment. Comparison of benzoylation rate constants of 1-propanol, 1-butanol, and cetyl alcohol shows that the length of the aliphatic substituent, inert with respect to the hydroxyl group, does not affect its reactivity appreciably (Table 1). It is also interesting to test if the reactivity of the second hydroxyl group in PEG molecule is changed after the first one has reacted. For this purpose we studied the formation of hydrogen bonds and the reactivity of OH-groups in solutions of butoxy-PEG (MW 3 000) in CCl_4. Comparison of the data for PEG (MW 3 000) and butoxy-PEG (MW 3 000) (Table 1) shows that the rate constant is similar for polymers with one or two terminal hydroxyl groups, if the fraction of 3a complexes remains unchanged.

The results in Table 1 show that PEG reactivity is determined by hydroxyl groups intramolecularly bound in five-membered rings (3a) and that the other H-complexes are much less active. This can be confirmed by studies of benzoylation kinetics in the system $CH_3OCH_2CH_2OH$ (MOE)-$C_2H_5OC_2H_5$ (DE) in CCl_4. Dilute solutions of MOE, which can be regarded as a model of the end of the PEG polymer chain, contain two forms of hydroxyl groups, viz., free OH-groups and those bound intramolecularly in five-membered rings (3a). DE, being a model of an internal fragment of the PEG chain, forms intermolecular hydrogen bonds with MOE OH-groups, and these have characteristics ($\Delta \nu$, ΔH) similar to 3b type hydrogen bonds in PEG solutions.

Addition of DE to the MOE solution in CCl_4 models the distribution of 3a and 3b H-complexes in polymer solutions. The observed rate constants k_{obs}, of Reaction (1) in the MOE-DE system and in PEG solutions are similar (Table 1). Simultaneously, comparison of rate constants of MOE benzoylation in the presence of DE and in its absence (Table 1) shows that either causes a decrease in MOE OH-groups activity. This shows again the considerably smaller reactivity of 3b complexes compared to 3a complexes and free hydroxyl groups. However, neither in PEG solutions nor in a model system can we determine k_2 and k_3 with sufficient accuracy because of their small magnitudes compared to k_{fr} and k_1.

Reaction (1) in a donor solvent, in the absence of highly reactive hydroxyl groups, both free and intramolecularly bound in five-membered rings, should permit estimation of the reactivity of H-complexes with low activity. Since DE precipitates PEG, another ether, viz., dioxane, having a dielectric constant similar to that of CCl_4 [3], was used. A cyclic compound was selected as a model for internal fragments of the PEG chain because the six-membered ring is unstrained in dioxane, as confirmed by its high enthalpy formation, ΔH°_{298} = -75.30 kcal/mol [13]. (The corresponding value for DE is -60.28 kcal/mol [13].) Dioxane can form complexes with hydroxyl groups 4a and 4b (Fig. 4) which, to judge by their spectral and thermodynamic characteristics, are close to the corresponding 3b and 3c complexes in polymer solutions in CCl_4.

A valid comparison of the benzoylation rate constants in CCl_4 and dioxane can be made only if identical reaction mechanisms pertain in both solvents. This is demonstrated by absence of the absorption band of H-complexes with TBA in the IR spectra of the reaction mixtures, which shows that nucleophilic catalysis occurs both in CCl_4 and in dioxane. In the latter case, OH-groups form hydrogen bonds mainly with the donor solvent [14], but not with the more basic TBA since the concentration of the tertiary amine (0.1 mol/L) is lower by two orders of magnitude.

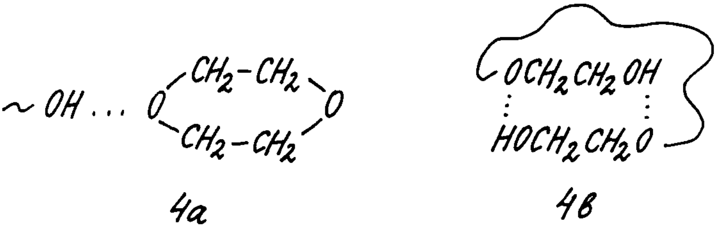


FIG. 4. H complexes in PEG solutions in dioxane.

TABLE 3. Relative Mole Fractions ϵ and δ of the 4a and 4b H complexes in Dioxane Solutions and the Observed Rate Constants of the Benzoylation Reaction[a]

Compound	ϵ	δ	$k_{obs} \times 10^3$, $L^2/(mol^2 \cdot s)$
$CH_3CH_2CH_2OH$	1.00	-	5.0 ± 0.6
$C_2H_5OCH_2CH_2OH$	1.00	-	2.0 ± 0.5
PEG MW 300	0.75	0.25	2.0 ± 0.5
PEG MW 600	0.77	0.23	2.2 ± 0.5
PEG MW 1 000	0.80	0.20	2.0 ± 0.5
PEG MW 3 000	1.00	-	2.0 ± 0.5

[a] $C_{OH} = 5 \times 10^{-2}$ mol/L, dioxane, 303 K.

The rate constants, k_{obs}, of Reaction (1) in dioxane are listed in Table 3. Studies of the kinetics of Reaction (1) with the model compounds 1-propanol and ethoxyethanol, in which all hydroxyl groups participate in the formation of intermolecular hydrogen bonds with ether solvent, have shown that 1-propanol is more reactive, apparently because its oxygen atom is more nucleophilic, in good agreement with the acidity of these compounds [15].

Let us consider k_{obs} of the benzoylation reaction in the PEG homologous series. When several forms of associated OH-groups are found in PEG solutions in dioxane (Fig. 4), the k_{obs} is given by

$$k_{obs} = k'\epsilon + k''\delta,$$

where ϵ and δ are the relative mole fractions of the 4a and 4b H-complexes, respectively, and k' and k" are their reaction rate constants.

The 4a H-complexes in dioxane can be considered as models of the analogous 3b H-complexes in CCl_4. Therefore, the constant k' and k_2 must be close. The value of k" must be identical to k_3, since they characterize the activity of OH groups in the similar forms of hydrogen bonding.

In solutions of ethoxyethanol and PEG (MW 3 000) in dioxane, containing only one form of H complex (4a) $k' = 2 \times 10^{-3}$ $L^2/(mol^2 \cdot s)$. The constancy of k_{obs} (within experimental error) with PEG molecular weight from 300 to 3 000 at various magnitudes of ε and δ (Table 3) shows the close reactivities of the 4a and 4b H-complexes. As expected, k' and k_2' were found to be much smaller than k_1 and k_{fr} (Table 2).

In summary, all the results of the quantitative studies of hydrogen bonds and the activity of PEG OH-groups permit determination of the rate constants for each form of H-complex and description of the kinetic behavior of PEG in solutions. It is shown that, in an inert solvent, PEG reactivity is dominated by hydroxyl groups intramolecularly bound in five-membered rings. The lower PEG reactivity compared to that of its low molecular weight analogs (alcohols, cellosolves, etc.) is the result of a considerable fraction (up to 0.56) of H complexes of low activity in the polymer solutions, formed because of the interaction of end OH groups with the main chain oxygen atoms. As a result, the reaction rates of PEG benzoylation are approximately half those of the model compounds (Table 1). Thus, the results show that hydrogen bonds affect the reactivity of PEG OH-groups.

The suggested approach can be used for studies of functional group reactivities of different heterochain polymers in solutions. Depending on the chemical nature of a macromolecule and terminal functional group, various types of hydrogen bonds with different reactivity may exist. The chain effect may lead to a decrease [16] in the functional group activity or to its increase [17].

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