MODEL ANALOGS OF NUCLEIC ACIDS (REVIEW)

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Literature data on the synthesis and investigation of nucleic acid analogs modified with respect to the sugar-phosphate skeleton are examined.

At the current stage of the development of biochemistry, model analogs of nucleic acids (NA) modified with respect to the sugar–phosphate skeleton may be of interest as "instruments" for the investigation of replication, transcription, and translation phenomena. Their effect on these processes probably may be realized as follows: first, at the level of interaction with the matrixes, due to complexing of the macromolecules of the analogs with certain portions of the NA; second, at the level of interaction with the enzymes participating in nucleic metabolism. This sort of interaction may be expressed as inhibition or stimulation of the functional activity of the enzymes. Interaction of the NA analogs with diverse protein-regulators of gene activity, which may lead to a change in the functioning of the individual sections of DNA, is also conceivable.

The research in the field of NA analogs modified with respect to the sugar-phosphate skeleton can be divided into a number of fundamental groups devoted to model analogs of NA in which the natural monosaccharides are replaced by their derivatives or other monosaccharides; model analogs of NA modified with respect to the phosphate diester bonds or the phosphate group; model analogs of NA obtained by modification of high-molecular-weight substances by derivatives of heterocyclic bases; model analogs of NA obtained by polymerization of derivatives of heterocyclic bases containing active unsaturated groups capable of the formation of a macromolecular chain; model analogs of NA in which the monosaccharide portion is replaced by dihydroxyalkyl chains substituted by heterocyclic bases; and model analogs of NA obtained by polycondensation of amino acids substituted by heterocyclic bases.

SYNTHESIS OF MODEL ANALOGS OF NUCLEIC ACIDS

Model Analogs of NA in Which the Natural Monosaccharides Are Replaced by Their Derivatives or by Other Monosaccharides

The synthesis of analogs of NA containing different sugars or their derivatives is undertaken primarily to ascertain the preservation of the biological functions of the biopolymers modified in this way.

An analog of the valine GpUpaU codon containing an arabinoside was synthesized by the action of T^1-ribonuclease on a mixture consisting of uridine 3',5'-uracilarabinoside and guanosine 2',3'-cyclophosphate [1]. An analog of the valine codon ($GpUpaC^1$) containing the arabinoside of cytosine was obtained in the same way. Attempts to synthesize polyarabinonucleotides by an enzymatic method were unsuccessful [2].

Somewhat later it was shown that when polyuridylic acid is used as the starting polymer, under certain conditions one can achieve epimerization at $C_{(2')}$ through a step involving the formation of 2',3',5'-cyclic triesters [3, 4]. Nagyvary also succeeded in obtaining poly-

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arabinouridylic acids [5] by polymerization of O_2, 5'-cyclouridine 2',3'-cyclophosphate by the method in [6].

The corresponding NA analogs were obtained by the action of polynucleotide phosphorylase on nucleoside 5'-diphosphates containing 2'-O-methyl- [7-9], 2'-O-ethyl- [9], 2'-fluoro- [10], 2'-chloro- [11], 2'-amino- [12, 13], and 2'-azido-2'-desoxyribose [12, 14].

Thus one should note that the enzymatic method of synthesis, although it is one of the possible methods for the preparation of NA analogs, nevertheless has limited application, inasmuch as enzyme systems present extremely high requirements for the structural peculiarities of the monosaccharide portion of the polymeric chain. Thus replacement of the D-ribose in the starting 5'-diphosphate by L-ribose is already sufficient to deprive the corresponding enzymes of the possibility of bringing about polymerization [15].

Model NA Analogs Modified with Respect to the Phosphate Diester Bonds or the Phosphate Group

The polymerization of 2',3'-cyclophosphates is widely used to synthesize model NA analogs containing, in contrast to the natural prototypes, 2',5'-phosphate diester bonds [6]. The average degree of polymerization of the oligomers synthesized by this method is 10-12. The resulting oligomers are characterized by a random distribution of the 2',5'- and 3',5'-phosphate diester bonds. A number of oligoadenylic acids containing only 2',5'-phosphate diester bonds were synthesized in 1961 [16] by enzymatic hydrolysis of oligoadenylic acid obtained by the method in [6].

Analogs with a modified (thiophosphate) or completely altered phosphate group (with a carboxymethyl group in place of the latter) seem of interest for the establishment of the degree of the effect of changes in the NA structure on their functions.

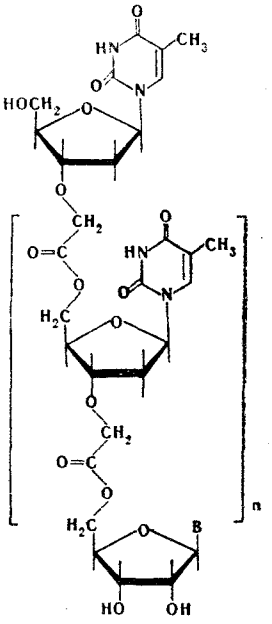
A number of analogs of trinucleotides, for example, GpUPU, an analog of the valine codon in which the phosphate group is replaced by a thiophosphate group [17], were obtained by the action of ribonuclease T^1 [17]. Diuridine 3',5'-phosphorothioate [18] and guanosine 2',3'-cyclo-phosphate were used as the substrates. A GpUpU analog in which one of the P—O bonds (between UU) is replaced by a P—C bond [19] was obtained by utilization of 5'-desoxyuridine 5'-phosphonine-3'-uridine [19] and guanosine 2',3'-cyclophosphate as the substrates.

Thiophosphate O,O-esters of dinucleosides were obtained by condensation of nucleoside phosphorothioates with nucleosides containing a free hydroxyl group [18, 20]. A disadvantage of this method is the formation of oligomeric sequences of a mixture of O,O- and O,S-diesters in each step of the synthesis. The stepwise synthesis of thiophosphate analogs of NA through a step involving the formation of O,O,S-triesters was accomplished in 1973 in Czechoslovakia [21, 22].

A number of polyribonucleotide analogs of NA in which the phosphate diester bond is replaced by an O,O-thiophosphate bond — polyr($_S$A$_S$U) [23], polyr(U$_S$) [23], polyr(A$_S$U) [24], and polyr($_S$U$_S$C) [24] — have been obtained by enzymatic methods. Thus polyr($_S$A$_S$U) was synthesized by means of DNA-dependent RNA-polymerase, poly(AT), and analogs of the substrate — ^{35}S-uridine 5-triphosphorothioate [25].

Research on the synthesis of NA analogs in which the phosphate diester bond is replaced by an oxoethylene bridge [carboxymethyl analogs, abbreviated poly(**cbm** N), where N is any nucleoside] was begun in 1968 [26]. Carboxymethyl derivatives of nucleosides were obtained by reaction of protected nucleosides with sodium chloroacetate [26-28]. Pyrimidine dinucleoside carbonate was synthesized by direct reaction of phosgene with appropriately protected nucleosides [29]. Good results in the synthesis of dinucleoside carbonates were obtained by means of transesterification [28, 30]. Oligomers of the general formula were obtained by stepwise synthesis [26, 27, 31-33].

Polymers with a maximum molecular weight ($4.7 \cdot 10^4$) were obtained by polycondensation of 3'-O-carboxymethylthymidine with 0.1 equivalent of 2',3'-isopropylideneuridine in the presence of dicyclohexylcarbodiimide [32].

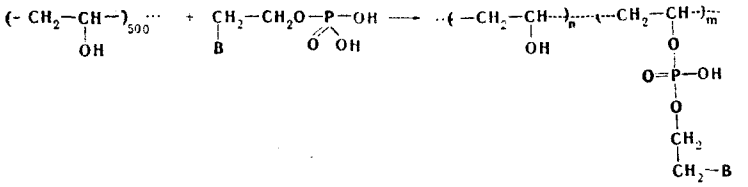


n = 1, X - uracil, cytosine, adenine, guanine, hypoxanthine, n > 1, B - uracil or cytosine.

Model NA Analogs Obtained by Modification of High-Molecular-Weight Substances by Means of Derivatives of Heterocyclic Bases

To synthesize model NA analogs with high molecular weights a number of investigators have attempted to use incorporation of natural heterocyclic bases or their derivatives in the existing macromolecular chain.

Macromolecular analogs of the corresponding homopolynucleotides were obtained by reaction of polyvinyl alcohol (degree of polymerization 500) with N-(2-dihydrophosphato)ethyl derivatives of adenine, hypoxanthine, thymine [34, 35], uracil, and cytosine [36] under the influence of dicyclohexylcarbodiimide:



The maximum degree of substitution of the hydroxyl groups of polyvinyl alcohol was achieved for thymine derivatives (68%), whereas the minimum degree of substitution was obtained for adenine derivatives (12%). Similar macromolecular products were also obtained in the case of 5-chloro-, 5-bromo-, 5-ethylamino-, and 5-diethylamino-substituted N-(2-dihydrophosphato) ethyl derivatives of uracil [37]. Macromolecular water-soluble derivatives of adenine, guanine, cytosine, and uracil were obtained [38, 39] by reaction of polyacrylic acid hydrazide with dialdehydes of the corresponding ribonucleosides [40]. The degree of substitution for the purine-containing polymers is 10%, whereas it is half this value for the pyrimidine-containing analogs. The structures of the resulting polymers have not been established definitely, although it has been shown that the dialdehydes of ribonucleosides react with only one molecule of the hydrazide [41].

Several synthetic pathways are realized during the modification of natural polypeptides. One of them consists in the fact that the amino group is used for the construction of the pyrimidine ring [42]. In other cases the latter reacts with dialdehydes of nucleosides [43]. Carboxy [44-46] and 5'-carboxymethyl [47] derivatives of nucleosides have also been used as the nucleoside component. Carboxymethyl derivatives of heterocyclic bases have served as

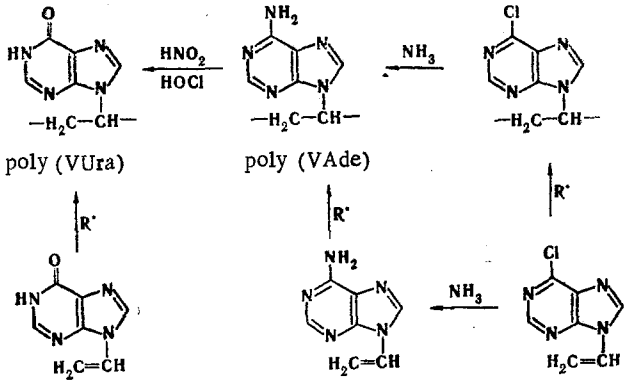
agents for the modification of bacterial dextran and protamine [48]. Good results were obtained with bacterial dextran by utilization of trifluoroacetic anhydride as the catalyst. Maximum substitution (33%) was achieved in the case of the thymine derivative, whereas minimum substitution (3.7%) was attained in the case of the hypoxanthine derivative. In the modification of protamine the reaction was carried out by the method of mixed anhydrides [49]. The maximum degree of substitution was achieved for thymine derivatives (25%).

A general disadvantage of the introduction of heterocyclic bases in the polymeric chain is the impossibility of substitution of all of the functional groups in the polymer. This leads to a statistical distribution of the bases along the polymer chain and may limit the possibility of associative interaction of analogs of this type with polynucleotides.

Model NA Analogs Obtained by Polymerization of Derivatives of Heterocyclic Bases Containing Active Unsaturated Groups Capable of Forming a Macromolecular Chain

The broad front of research has been directed to the synthesis and study of polyvinyl NA analogs obtained by radical polymerization of N-vinyl derivatives of purine and pyrimidine bases [50-55].

Poly(1-vinyluracil) [poly(VUra)] was obtained both by polymerization of(1-vinyluracil [52, 56, 57] and by radical polymerization of(1-vinyl-4-ethoxy-2-pyrimidone and subsequent hydrolysis [57]. Poly(1-vinylcytosine) [poly(VCyt)] was obtained by amination of poly(1-vinyl-4-ethoxy-2-pyrimidone) [58]. Poly(1-vinylthymine) [poly(VThy)] was obtained by radical polymerization of(1-vinylthymine [56, 59]. A considerable number of studies have been devoted to the development of methods for the synthesis of poly(9-vinylpurines) [52, 53, 56, 59-61]. The following scheme for the synthesis of poly(9-vinylhypoxanthine) [poly(VHyp)] and poly(9-vinyladenine) [poly(VAde)] has been proposed [61]:



High-molecular-weight products [56, 62] based on N-(β-methacryloylhydroxyethyl) derivatives of thymine, adenine, theophylline, and 2-chloro-6-methylpurine [62] were obtained by radical polymerization. Poly(MThy) and poly(MTheo), in addition to poly(VUra), have been used as carriers for the chromatographic separation of nucleic acid bases [63].

In the case of the thymine derivative, Kondo and co-workers [56] also synthesized copolymers with acrylamide – poly(MThy AA), maleic anhydride – poly(MThy MA), and N-vinylpyrrolidone. The copolymers contain equimolecular amounts of each polymer.

In 1966 it was proposed that vinyl derivatives of nucleosides be used as monomers [64-67]. The monomers were obtained by reaction of protected nucleosides with acryloyl chloride and 3-vinylacryloyl chloride [64-66]. Polymerization of the acryloyl and vinylacryloyl derivatives leads to the formation of water-insoluble polymers. Water-soluble polymers with low percentages of heterocyclic bases were obtained by copolymerization of the latter with acrylamide (Table 1). Attempts to raise the percentage of the heterocyclic bases in the polymer chain led to a decrease in the solubility and molecular weights of the polymers [66].

A series of studies of the synthesis of polymers on the basis of methacryloyl derivatives of nucleosides and their use as carriers for the chromatography of mono-, di-, and trinucleotides [68-71] are of interest.

TABLE 1. Nucleic Acid Analogs Based on Unsaturated Derivatives of Nucleosides

Name	Code	Sedimentation constant	Heterocycle content, %	Lit. citation
Poly[5'-O-(3-acryloyl)thymidine]	Poly (AT)	—	100	64
5'-O-(3-Acryloyl)thymidine–acrylamide copolymer	Poly (AT·AA)	—	3,3—13,9	64
5'-O-(3-Acryloyl)uridine–acrylamide copolymer	Poly (AU·AA)	10^5 *	5,7	64
		4,9	7,7	66
Poly[5'-O-(3-acryloyl)cytidine]	Poly (AC)	—	100	67
5'-O-(3-Acryloyl)cytidine–acrylamide copolymer	Poly (AC·AA)	2,72	5,5	67
5'-O-(3-Acryloyl)guanosine-acrylamide copolymer	Poly (AG·AA)	1,31; 1,61	5,5	67
Poly[5'-O-(3-vinylacryloyl)uridine]	Poly (VAU)	$2{,}4 \cdot 10^3$ *	100	65
5-O-(3-Vinylacryloyl)uridine–acrylamide copolymer	Poly (VAU·AA)	$2{,}4 \cdot 10^3$ *	7	65

*Molecular weights.

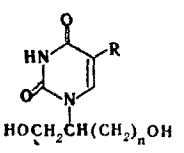
Rather unusual NA analogs in which the sugar residue is replaced by 2-pyrrolidone derivatives were synthesized in 1973 [72, 73]. This system was selected for two reasons: first, because of the similarity between 2-pyrrolidone and the five-membered ring of ribose or desoxyribose and, second, because of the widely known ability of N-vinylpyrrolidone to to form water-soluble polymers. Polyvinylpyrrolidone analogs of poly(U) [72] and poly(A) [73] were obtained by radical polymerization under the influence of 2,2'-azobisisobutyronitrile.

adenine and uracil

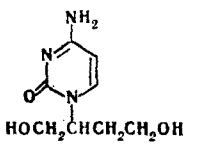
Model NA Analogs in Which the Monosaccharide Portion is Replaced by Dihydroxyalkyl Chains Substituted by Heterocyclic Bases

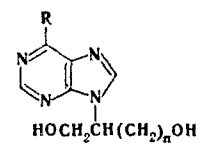
In conformity with the idea expressed in 1962 [74], the synthesis of model NA analogs with retention of the natural heterocyclic bases and the polyelectrolyte character of the polymer chain containing polymethylenediol fragments in place of the sugar residue [75-78] seemed of definite interest.

S. A. Giller and co-workers synthesized a number of phosphate esters [79-81] based on dihydroxyalkyl derivatives of purine [82, 83] and pyrimidine [84-86] bases:

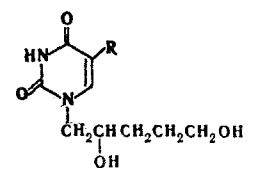


n = 1, R = H;
n = 2, R = H, CH_3



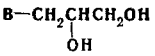


n = 1, 2, 3, R = OH, NH_2



R = H, CH_3

Oligothymidylic acid analogs containing phosphate diester bonds with a degree of polymerization of five to eight were obtained by polycondensation of N_1-(1',4'-dihydroxy-2'-butyl)thymine monophosphate esters under the influence of dicyclohexylcarbodiimide or aromatic sulfonyl chlorides. The polycondensation of N_1-(1',4'-dihydroxy-2'-butyl)thymine with the corresponding 1',4'-diphosphate under the influence of arenesulfonyl chlorides made it possible to synthesize oligomers with an average degree of polymerization of 27 containing primarily phosphate diester bonds [77, 78]. A communication regarding the synthesis of NA analogs based on heterocyclic base-substituted 1,2-propanediols [88-90] was published in 1971 [87].



B = uracil, cytosine, theophylline, hypoxanthine, thymine, and 5-halo-substituted uracils.

Nucleic acid analogs were obtained by polycondensation of 3-(3-hypoxanthinyl)- and 3-(9-hypoxanthinyl)-1,2-propanediols with phenylphosphoryl chloride to give oligomers with low molecular weights (1000-1200) containing three hypoxanthine residues. The same synthetic method was used to obtain oligomers based on cytosine, theophylline, and uracil derivatives [91]. Poly(A) analogs were obtained by reaction of i-adenyl-2,3-propylene carbonate with phosphoric acid. The polycondensation of analogs of nucleotides based on 1,2-propanediol derivatives in the presence of dicyclohexylcarbodiimide [92, 93], imidazole, or triethylamine hydrochloride [94] has also been studied. The molecular weights of the oligomers obtained were somewhat higher than 1000.

Model NA Analogs Obtained by Polycondensation of Amino Acids Substituted by Heterocyclic Bases

The last section of the present review of the literature on the synthesis of NA analogs pertains to the preparation of peptide chains having natural heterocyclic bases in the side groupings of the amino acid residues. The studies in this area are extremely limited and were made primarily in the Institute of Organic Synthesis of the Academy of Sciences of the Latvian SSR by M. Yu. Lidak and co-workers.

The synthesis of a number of N_1-pyrimidyl- and N_9-purinylamino acids has been developed [95-103]. It should be noted that the racemates have been separated into their optically pure forms only in the case of α(N_1-uracilyl)alanine [96, 103].

In 1971, Koning and Panditt [104] obtained oligo- and polypeptides based on substituted α-aminocapronic acid. M. Yu. Lidak simultaneously synthesized a number of oligomers by copolymerization of α-(N_1-uracilyl)alanine with glycine or tyrosine [105]; the usual methods of peptide synthesis by means of activated esters and dicyclohexylcarbodiimide were used. Some di- and tripeptides containing purine- or pyrimidine-substituted α-alanine and serine fragments were similarly obtained in 1974 [106]. Pyrimidylpoly-α-amino acids were synthesized by polycondensation of p-nitrophenyl esters.

PHYSICOCHEMICAL PROPERTIES OF MODEL ANALOGS OF NUCLEIC ACIDS

One of the chief indexes of the three-dimensional structure of models of oligo- and polynucleotides is deviation of the optical properties of solutions of them from additivity and dependence of the UV spectra on the temperature and added urea or propylene glycol.

Certain information regarding the secondary structure of analogs of polynucleotides is obtained by studying their interaction with polynucleotides.

The dinucleoside analog 3'-O-(uridine-5'-O-ylacetyl)thymidine, in which the phosphate diester bond is replaced by a carboxymethyl bond, displays a hypochromic effect of 8% [27]. The dinucleotide analog 2'-desoxyadenosyl-3',5'-thymidine-3'-ylacetic acid has a hyperchromic effect of 5% at 248 nm and 6.7% at 260 nm [33]. The hypochromism of the dithymidine monophosphate analog based on N_1(1',4'-dihydroxy-2'-butyl)thymine is 4.1%. Phenomena of this sort can be explained by the increased "flexibility" of the molecules of the analogs as compared with the natural prototypes. This is confirmed by Stuart–Briegleb models, which show that in analogs of this overlapping of the bases may be greater than in the natural

dinucleoside monophosphate. 1-Carboxymethylthyminedextran displays a hypochromic effect of 30% at 268 nm in a citrate buffer, but this effect is not observed in 7 M urea solution [48]. Polyvinyl NA analogs, specifically, poly(VCyt) and poly(VAde), also display rather large hypochromic effects [58, 59] comparable to the corresponding effects in polynucleotides. However, phenomena of this sort are generally characteristic for vinyl polymers [107, 110]. The reason for the hypochromism of the vinyl polymers is parallel packing of the bases in the isotactic portions of the chains, which have a helical structure [110]. This effect is not associated with the formation of a secondary structure similar to the structure of homopolynucleotides; this is confirmed by the lack of a dependence of the UV spectra of solutions of the polyvinyl analogs mentioned above on the temperature and added urea or propylene glycol, which, as is well known, disrupt the secondary structure of polynucleotides [111-113]. In this connection it should be noted that in poly(VAde) and poly(VCyt) the stabilization of the protonated form [58, 59] that is observed for the corresponding homopolynucleotides [112, 114] is absent.

Poly[3-(N_1-uracilyl)-N-vinyl-2-pyrrolidone] has a hypochromic effect on the order of 25% [72], and Koomen and Panditt attribute this to the presence of a secondary structure similar to the structure of homopolynucleotides.

The ability of the synthesized polymers to form associates with polynucleotides is of importance in connection with the fact that this to a considerable degree determines the behavior of NA analogs in biochemical systems.

It has been shown that chemically synthesized polyuridylic and polyadenylic acids containing both 2',5'- and 3',5'-phosphate diester bonds do not react with one another, whereas oligocytidylic and oligoguanylic acids (n = 10) of similar structure form an associative complex [6]. It was found that oligoadenylic acids with 2',5'-phosphate diester bonds form complexes with polyuridylic acid [15, 16].

Polyarabinofuranoside analogs of NA do not react with polynucleotides [3]. An analysis of the structures of such polymers by means of Stuart–Briegleb models made it possible to conclude that the location of the bases in the analogs of this type does not make it possible for them to form hydrogen bonds with the complementary bases of homopolynucleotides [3].

The interaction of natural matrices with NA analogs obtained by incorporation of purine and pyrimidine derivatives in the polymeric chain has been studied in a number of papers. Their structural peculiarities impose restrictions on the formation of complexes with polynucleotides (Table 2, complexes 1-23). Thus, the largest hypochromic effect is noted in the case of the complex of DNA with the poly(A) analog based on polyacrylic acid hydrazide previously fractionated on DNA-agar (complex 16) [38, 39]. In a series of analogs based on polyvinyl alcohols the largest hypochromic effect (16%) was noted for the pva(Thy)·DNA complex (complex 3) [34]; this is associated with the relatively large percentage of thymine (68%) in the polymer chain; pva(Ade), which contains only 12% adenine, does not react with RNA, whereas it does react with DNA to give complex 2, the hypochromic effect of which is 6.5% [34].

An extremely slight hypochromic effect is observed in the complexing of NA analogs obtained by polymerization of unsaturated derivatives of nucleosides (complexes 26-28). This value is 10% in the case of the 5'-O-(3-acryloyl)uridine–acrylamide copolymer previously fractionated on DNA-agar [64].

The polyvinyl analogs of NA are capable of undergoing reaction with complementary homopolynucleotides and RNA (Table 2, complexes 29-35) [56-59, 61, 116]. However, in contrast to the complexes of homopolynucleotides, the complexes obtained in this case are characterized by a broad and incompletely reversible melting range [57-59]. The melting range of the associates indicates the weakly cooperative character of the interaction of the components of the chain. The complexes of the vinyl analogs with homopolynucleotides are quite stable. Thus the melting points of the poly(VCyt)·poly(G) [58] and poly(C)·poly(G) [117-118] associates differ only very slightly. The magnitudes of the hypochromic effects, the irreversibility of the melting ranges, and the optical rotatory dispersion spectra [61] indicate the irregular character of the investigated complexes of polyvinyl analogs of NA with polynucleotides.

TABLE 2. Complexes of Nucleic Acid Analogs with Polynucleotides and with One Another

No.	Interaction between[a]	Solvent	λ, nm	Hypochromic effect, %
1	2	3	4	5
1	pva(Ade)·RNA	0,1 *M* Na_2HPO_4	260	0
2	pva(Ade)·DNA		260	6,5
3	pva(Thy)·DNA		266	16
4	pva(Thy)·RNA		266	12
5	pva(Hyp)·RNA		259	0
6	pva(Hyp)·DNA	H_2O	259	0
7	pva(Theo)DNA		268	0
8	pva(Cyt)·DNA		267	0
9	pva(Cyt)·DNA	0,1 *M* Na_2HPO_4	267	0
10	pva(Cyt)·RNA		267	0
11	pva(Ura)·DNA		261	3
12	pva(Ura)·DNA		261	3
13	pva(Ura)[b]·RNA		261	0
14	pah(A)[c]·DNA	0,3 *M* NaCl—0,03 *M* Na citrate	260	0
15	pah(A)[c]·Poly U		260	0
16	pah(A)[d]·DNA		260	35
17	pah(A)[d]·Poly U		260	19
18	pah(G)[d]·DNA		250	9
19	pah(G)[d]·Poly C		250, 260, 280	0
20	pah(G)[d]·DNA		280	0
21	pah(G)[d]·DNA		250	24
22	pah(G)[d]·Poly C		260	−10
23	pah(G)[d]·Poly G		250, 260, 280	0
24	Poly(cbmThy-Dextran)·DNA			13[f]
25	Poly(cbmThy-dextran)·DNA			9[g]
26	Poly(AU·AA)·DNA	0,15 *M* NaCl—0,015 *M* Na citrate	260	10
27	Poly(VAU) DNA		260	5
28	Poly(VAU)Poly (A)		260	5
29	Poly(VAde)Poly (U)	0,01 *M* tri(hydroxymethyl) aminomethane, 0.01 M NaCl	255	23[h]
30	Poly(VAde)·Poly(U)	0,001 *M* sodium cacodylate	255	15[i]
31	Poly(VAde)·Poly(U)	$5\cdot10^{-3}$ *M* sodium cacodylate, $5\cdot10^{-4}$ $MgCl_2$, $5\cdot10^{-2}$ *M* NaCl	260	26[j]
32	Poly(VAde)RNA	H_2O (1 *M* NaCl)	258	13
33	(Vthy·AA)·RNA copolymer	H_2O	260	0
34	Poly(VCyt)Poly (I)	25% propylene glycol, 10^{-2} *M* NaCl, $5\cdot10^{-3}$ *M* Na-acetate	260	15
35	Poly(VUra)Poly (A)	10^{-3} *M* sodium cacodylate, $5\cdot10^{-3}$ *M* NaCl, 10^{-3} *M* $MgCl_2$	265	8
36	Poly(MUra)·RNA	H_2O (0,1 *M* Na_2HPO_4)	260	3
37	Poly(cbmT) Poly (A)	0,1 *M* — 1 *M* NaCl	266	8
38	Poly(cbmT·U)Poly (A)	0,3 *M* NaCl, 10% DMF, 0,03 *M* Na-citrate	260	5[k]
39	$(cbmT)_3$·Poly(A)	0,3 *M* NaCl, 0,01 *M* glycylglycine	260	31
40	$(cbmT)_4$·Poly(A)		260	31
41	Oligo(9Adep)m·DNA	0,1 *M* Na_2HPO_4	260	3
42	Oligo(9Adep)m·RNA		260	3
43	Oligo(3Adep)m·DNA	0,1 *M* Na_2HPO_4	260	0
44	Oligo(3Adep)m·RNA		265	0
45	Poly(VAde)Poly (VUra)	H_2O — trimethyl phosphate	258	5
46	Poly(MAde)Poly (MUra)	Trimethyl phosphate	260	3
47	(Vade·AA)copolymer (VThy·AA)copolymer	H_2O	260	0
48	Poly(VAde)·(VUra·MA) copolymer	H_2O	257	0
49	pva(Ade)pva (Thy)	0,1 *M* NaH_2PO_4	265	3
50	pah(A)[e] Poly(AU·AA)	0,03 *M* Na citrate, 0,3 *M* NaCl	260	8
51	pah(A)[d] Poly(AU·AA)		260	21

[a]Analogs based on polyvinyl alcohol are indicated by pva, and analogs based on polyacrylic acid hydrazide are indicated by pah. [b]n = 18. [c]This is the analog that is not adsorbed on DNA-agar. [e]The unfractionated analog. [f]4 deg. [g]14 deg. [h]72 h, 25 deg, 50% poly(U). [i]24 h, 4 deg, 37% poly(U). [j]50% poly(U). [k]18 h, 4 deg, measurement at 20 deg, 2T:1A. [l]1T:1A. [m]Oligomers based on 3-(9-adenyl)- and 3-(3-adenyl)-2-dihydroxypropyl phosphate.

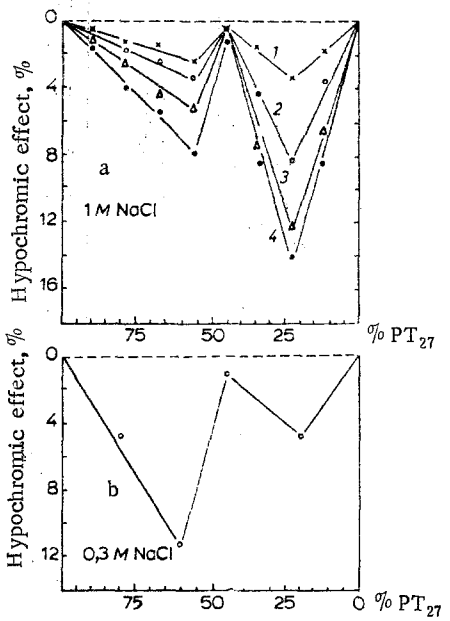


Fig. 1. Results of experiments on the hybridization of poly(A) and PT_{27} at pH 7 in a 0.015 M sodium citrate buffer: a) 10 deg (1); 2 (2); −3 deg (3); −8 deg (4); b) 3 deg.

A. S. Jones and co-workers studied the reaction of analogs containing carboxymethyl bonds with polynucleotides (Table 2, complexes 37-40). They showed that poly(cbmT·U) reacts with poly(A) to give a number of complexes. A 1A:1T complex is formed in the reaction of oligomers with chains three and four links long with poly(A); a 2T:1A complex is formed in the case of a polymer with a chain length on the order of 160 links [32], i.e., the composition of the associates, as in the case of the natural prototypes, depends on the chain length of the interacting polymers. In contrast to polynucleotides that form complexes only in salt solutions [119, 120], poly(cbmT) reacts with poly(A) in both aqueous and salt solutions; this is due to the neutral charge of the analogs with carboxymethyl bonds [32, 27].

In a study of the complexing of NA analogs based on N_1-(1',4'-dihydroxy-2'-butyl)thymine S. A. Giller and co-workers showed [77] that analogs with a degree of polymerization of five to eight do not react with poly(A) at −3 to 20 deg; a hypochromic effect also was not noted for oligomers characterized by high molecular weights but containing a considerable number of pyrophosphate bonds. An analog based on N_1-(1',4'-dihydroxy-2'-butyl)thymine with a degree of polymerization of 27 (abbreviated PT_{27}) containing primarily phosphate diester bonds reacts with poly(A) in a citrate buffer. In this case, one observes an interesting phenomenon — the formation of two complexes with different compositions (Fig. 1): the first contains 60% PT and 40% poly(A) [1.5 PT:1 poly(A)], and the second contains 20% PT and 80% poly(A) [1 PT:4 poly(A)]. A decrease in the temperature and an increase in the ionic strength of the solution promote primary formation of a 1 PT:4 poly(A) complex (Fig. 1a), whereas an increase in the temperature and a decrease in the ionic strength of the solution to a greater degree favor the formation of a 1.5 PT:1 poly(A) complex (Fig. 1b). The complexing of PT_{27} with poly(A) occurs quite slowly. Thus the hypochromic effect of the 1 PT:4 poly(A) complex in 1 M NaCl at −8 deg reaches a maximum value (14.2%) when a mixture of the components is allowed to stand for 72 h. It should be noted that the oligomers based on N_9-(3-adenyl)-2-hydroxypropyl phosphate (mol. wt. 1000) forms complexes with RNA and DNA (Table 2, complexes 41 and 42).

A study of the reaction of complementary NA analogs with one another is of great independent interest. It is precisely here in the case of favorable structural prerequisites that one might expect the formation of complexes having cooperative character. However, one can refer only to the reaction of atactic poly(VAde) and poly(VUra), which form a complex in aqueous trimethyl phosphate solutions [56] (complex 45). The hypochromic effect of the complex between poly(AU·AA) and a polyadenylic acid analog based on polyacrylic acid hydrazide increases sharply when a previously fractionated hydrazide analog is used (complexes 50 and 51). Extremely small hypochromic effects or no hypochromic effect at all [56] are also characteristic for complexes 46-49 formed in the reaction of other complementary analogs with one another.

The regularity of the structure, the chain, length, and the conformational similarity are decisive factors during complexing. Chemical and stereochemical irregularity of the structure, by virtue of which the possibilities of complexing of the analogs with one another and with natural matrixes are markedly limited, are characteristic for most of the analogs. A comparison of the analogs and a purposeful selection of a preferred class of compounds from the point of view of their ability to undergo complexing are extremely difficult because of the fact that the investigated analogs differ markedly with respect to their structures, molecular weights, and other physicochemical properties and also because different matrixes have been used by the various researchers for the investigation of complexing.

Nucleic acid analogs modified with respect to the $C_{(2')}$ position of ribose or desoxyribose have been studied to ascertain the effect of the 2'-OH group on the conformational stabilities of the polyribonucleotides. Despite the fact that the conformational stabilities of polyribonucleotides and polydesoxyribonucleotides are different, there is presently no satisfactory explanation for this phenomenon.

A number of authors have shown that the presence of an intramolecular bond with participation of a 2'-OH group cannot be the reason for the high stability of the secondary structure of polyribonucleotides, inasmuch as poly-2'-O-methyluridylic acid [poly(U_M)] and poly-2'-O-methyladenylic acid [poly(A_M)] are thermally more stable than their natural prototypes [7, 121]. However, a 2'-methoxy group does not affect the stability of the complex of poly(A_M) with poly(U), although in the case of poly(U_M) a certain increase in the stability of the complex is noted. Poly(2'-azido-2'-desoxyuridylic)acid [poly(U_A)] has a highly ordered structure [14] in the single-helix and double-helix forms, whereas replacement of the 2'-OH group by Cl [122], F [10], or H [123] destabilizes the structure of the homopolynucleotides. At the same time, poly(U_{Cl}) [122] and poly(U_F) [10], like poly(U_A) [14], form rather stable complexes with poly(A), and this makes it possible to conclude that there are different stabilizing effects in the single-helix and double-helix conformations of the polynucleotides.

BIOCHEMICAL PROPERTIES OF MODEL ANALOGS OF NUCLEIC ACIDS

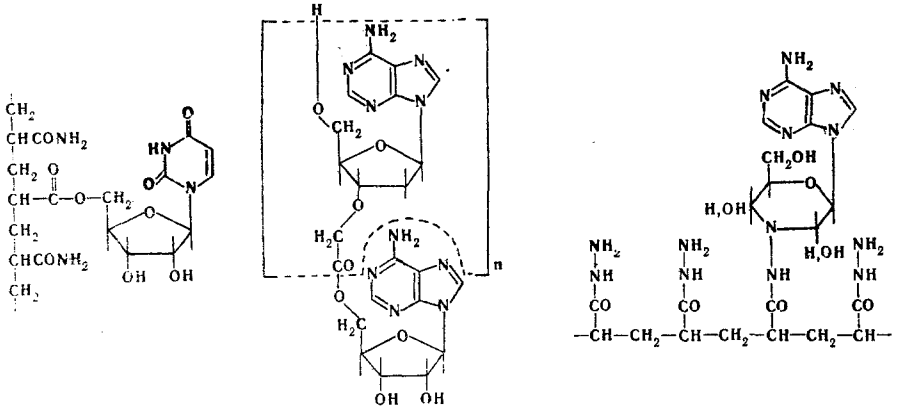
The greatest number of investigations of NA analogs in biological systems have been devoted to an analysis of their effect on the matrix functions of NA in DNA- and RNA-polymerase systems and also in protein-synthesizing systems. The effect of the analogs on the protein-synthesizing systems has been investigated in two directions: on the one hand, the possibilities of the use of NA analogs as **matrices** for the synthesis of polypeptides have been studied, and, on the other hand, their effect on the matrix activity of natural or synthetic polynucleotides has been investigated. It has been established that most analogs of polynucleotides cannot perform matrix functions in protein-synthesizing systems [1, 19, 124, 125]. Thus the ability of the GpUpU triplet, in which the P—O bond between UU is replaced by a P—C bond, to stimulate the bonding of C_{14}-valyl-tRNA with ribosomes has been studied. In contrast to the normal GpUpU triplet, this compound is incapable of insuring the addition of RNA to the ribosome, and, inasmuch as this bonding is a necessary step in the biosynthesis of protein, it is evident that this sort of triplet cannot serve as a matrix in a protein-synthesizing system. The same group of researchers has shown that trinucleotides in which ribose is replaced by arabinose are also incapable of forming complexes with ribosome with C_{14}-valyl-tRNA [1]. In complete conformity with this research it has been shown that poly(AU) does not bind phenylalanine—tRNA in ribosomes and does not support the synthesis of polyphenylalanine in a protein-synthesizing system [5]. Although it does stimulate the addition of valyl-tRNA to ribosome, GpU$\overset{S}{\overset{\|}{P}}$U does so to a much lesser extent than in the case of the normal triplet [17].

The polyvinyl analogs of poly(VAde) and poly(VUra) are also incapable of acting as matrixes in the synthesis of protein [124].

The only positive result within this plan was obtained in [23], in which it was established that the triphosphate analog of polyuridylic acids insures the inclusion of phenylalanine in a polypeptide at a 45% level as compared with poly(U) [23]. In analyzing the reasons for the inability of most of the NA analogs to stimulate the addition of aminoacyl-tRNA to ribosomes and support the synthesis of protein, various authors present similar explanations [1, 19, 124, 125]. Inasmuch as the specific bonding with the matrix is determined by codon—anticodon interactions, the change in the three-dimensional structure and the acidity of the

analog matrixes as compared with natural prototypes is of substantial significance [17]. The same factors may play a substantial role also in disruption of the interaction of the components in the system (ribosome, matrix, and aminoacyl t-RNA). In connection with these results, data obtained by S. A. Giller and co-workers, who have shown that analogs of oligothymidylic acid based on N_1-(1',4'-dihydroxy-2'-butyl)thymine stimulate inclusion of phenylalanine in the poly(U) matrix in a protein-synthesizing system [126], are of interest. The effect reaches a maximum value of 160%. The reason for stimulation by the analog of the biosynthesis of polyphenylalanine in the poly(U) matrix in a cell-less system is not clear. This sort of phenomenon is not observed during translation of the natural matrix — RNA bacteriophage MS_2.

The principal results in the investigation of the ability of the analogs to inhibit the matrix properties of polynucleotides in a protein-synthesizing system reduced to the fact that NA analogs with a modified polyribosophosphate skeleton are capable of inhibiting the synthesis of polypeptides in a cell-less system that is ordinarily stimulated by synthetic homopolynucleotides of complementary composition. In this case, this effect occurs even when the interaction of the analog and the polynucleotides is not very great. Thus it has been shown that electrically neutral analogs of three types inhibit the bonding of aminoacyl-tRNA with ribose [125] that is stimulated by **matrices** of complementary composition.



The highest degree of inhibition is achieved in the case of analogs with carboxymethyl bonds. In this system the effectiveness of the carboxymethyl polymer is equal to that of poly(A). It has been shown that poly(VAde) inhibits poly(U)-stimulated bonding of aminoacyl-tRNA with riboses and inclusion of phenylalanine in polypeptides. In precisely the same way, poly-(VUra) inhibits the poly(A)-stimulated synthesis of polylysine [124]. The (VAde·VUra) copolymer is a less effective inhibitor. Thus most of the presently synthesized NA analogs cannot be used as **matrices** in view of the high requirements presented to the matrix in a cell-less system.

Yet another difficulty is the fact that the data accumulated in molecular biology are insufficient to formulate the requirements presented to such matrixes during their directed synthesis. The fact that polyr($_S$U) displays a matrix activity that is only half that of polyr(U) constitutes evidence that the synthesis of **matrices** of this sort is fundamentally possible. The use of analogs as inhibitors of protein synthesis is evidently possible even at the present time.

A second trend in the investigation of the behavior of analogs in biological systems is an attempt to use them as interferonogens. It is well known that the synthesis of an interferon is stimulated by complexes of homopolynucleotides, and the poly(C)·poly(I) complex [127] is one of the most powerful interferonogens. It may be assumed that an increase in the interferonogenic activity may be achieved through an increase in the stability of the interferonogens with respect to the nucleases and an associated increase in the residence time of the polymers in the cell. On the other hand, an increase in the effectiveness of the action of the polymer may be associated with an increase in its ability to penetrate the cell. It has been shown that polyr($_S$U) is resistant to the action of a number of nucleases [23], and similar data have been obtained by the same group of researchers during a study of polyr($_S$C) [128]. It is no less interesting that poly(AU) inhibits pancreatic ribonuclease with respect to the natural substrate, and the inhibition is realized competitively [5]. In

a number of cases, for example, for polyvinyl analogs, substantial factors are a decrease in the charge to mass ratio and an increase in the capacity for aggregation of the poly(VCyt)·poly(I) complex as compared with the poly(I)·poly(C) complex [129]. It has been established that the poly(I)·poly(VCyt) complex has high activity in in vitro experiments on the generation of antivirus resistance in a tissue culture of human fibroblasts. Replacement of the polycytidyl components in the poly(I)·poly(C) complex by a polythiocytidylic component increases the ability of the associate to induce resistance to virus infection and activate the synthesis of an interferon both in vivo and in vitro [128]. The fact that, in addition to more active induction of the resistance to virus infection, the action of poly(I)·poly(sC) is prolonged [128], is essential. Complexes with partial substitution of the phosphate diester bond by a thiophosphate bond have activity intermediate between that of natural and polythiophosphate associates [128].

Analogs of oligothymidylic acid based on N_1-(1',4'-dihydroxy-2'-butyl)thymine inhibit the biosynthesis of RNA catalyzed by DNA-dependent RNA-polymerase. Giller and co-workers have shown that the step that suppresses the analog is mainly initiation of new RNA chains [126].

Another attempt to use analogs in biological systems involved a study of the effect of polyvinyl analogs on the replication of RNA-containing viruses in animal cells [130]. Pitha and co-workers compared the effect of poly(A), poly(U), poly(VAde), and poly(VUra) on replication of the Maloney leukemia virus. All of the polymers suppress replication of the virus in a culture of mice fibroblasts. The fact that, while inhibition by means of poly(A) and poly(U) was a maximum when they were added to the initial stages of virus infections, poly(VAde) and poly(VUra) were effective in later periods was of interest. In an investigation of the possible reasons for the antivirus activity of polyvinyl analogs and polynucleotides, the authors studied their effect on the activity of polymerase. It was found that poly(U) and poly(VUra) are effective inhibitors of this enzyme. The effect is apparently associated with competition of these polymers with inoculation for bonding of poly(A). The fact that poly(VAde) activates RNA-dependent DNA-polymerase in these systems was unexpected and inexplicable.

It is apparent from this review that definite approaches to the study of the biological activity of NA analogs have presently been formulated. In addition, it is clear that the data thus far obtained are inadequate for definite conclusions relative to the possibility of the purposeful utilization of NA analogs in one or another system. Further detailing and, on the one hand, a more comprehensive study of the synthesized polymers, and, on the other, the preparation of new model systems are required.

LITERATURE CITED

1. J. Smrt and F. Sorm, Biochim. Biophys. Acta, 138, 210 (1967).
2. A. M. Michelson, J. Dondon, and M. Grunberg-Managro, Biochim. Biophys. Acta, 55, 529 (1962).
3. J. Nagyvary, Fed. Proc., 26, 292 (1967).
4. J. Nagyvary, 21st Congress of IUPAC, Abstract N-48, Prague (1967).
5. J. Nagyvary, P. Provenzale, and I. Clark, Biochem. Biophys. Res. Commun., 31, 508 (1968).
6. A. M. Michelson, J. Chem. Soc., 3655 (1959).
7. A. M. Bobst, F. Rottman, and P. A. Cerutti, J. Mol. Biol., 46, 221 (1969).
8. B. Zmudzka and D. Shugar, Febs Lett., 8, 52 (1970).
9. J. Tazawa, S. Tazawa, I. L. Alderfer, and P. O. P. Ts'o, Biochemistry, 11, 4931 (1972).
10. B. Janik, M. P. Kotick, T. H. Kreiser, L. V. Reverman, R. G. Sommer, and D. R. Wilson, Biochem. Biophys. Res. Commun., 46, 1153 (1972).
11. J. Hobbs, H. Sternbach, M. Sprinzi, and F. Ecstein, Biochemistry, 11, 4336 (1972).
12. J. Hobbs, H. Sternbach, M. Sprinzi, and F. Ecstein, Biochemistry, 12, 5138 (1973).
13. J. Hobbs, H. Sternbach, and F. Ecstein, Biochem. Biophys. Res. Commun., 46, 1153 (1972).
14. P. F. Torrence, J. Water, and B. Witkop, J. Am. Chem. Soc., 94, 3638 (1972).
15. J. Frič, W. Guschlbauer, and A. Holy, Febs Lett., 9, 261 (1970).
16. M. N. Lipsett, L. A. Heppel, and D. F. Bradley, J. Biol. Chem., 236, 857 (1961).
17. V. Lisy, F. Ecstein, and J. Skoda, Coll. Czech. Chem. Commun., 33, 2734 (1968).
18. F. Ecstein, Tetrahedron Lett., 3495 (1967).
19. A. Holy, D. Grünberger, J. Smrt, and F. Sorm, Biochim. Biophys. Acta, 138, 207 (1967).
20. F. Ecstein, Tetrahedron Lett., 1157 (1967).

21. A. Malkievicz and J. Smrt, Coll. Czech. Chem. Commun., 38, 2953 (1973).
22. A. Malkievicz and J. Smrt, Coll. Czech. Chem. Commun., 38, 2962 (1973).
23. F. Ecstein and H. Gindl, Febs Lett., 2, 262 (1969).
24. F. Ecstein and H. Gindl, Eur. J. Biochem., 13, 558 (1970).
25. F. Ecstein and H. Gindl, Biochim. Biophys. Acta, 35, 149 (1967).
26. M. H. Halford and A. S. Jones, Nature, 217, 638 (1968).
27. M. H. Halford and A. S. Jones, J. Chem. Soc., C, 2667 (1968).
28. J. R. Tittensor, J. Chem. Soc., C, 2656 (1971).
29. M. P. Mertes and E. A. Coats, J. Med. Chem., 12, 154 (1969).
30. A. S. Jones and J. R. Tittensor, Chem. Commun., 1240 (1969).
31. M. D. Edge and A. S. Jones, J. Chem. Soc., C, 1933 (1971).
32. M. D. Edge, A. Hodgson, A. S. Jones, and R. T. Walker, J. Chem. Soc., C, 1991 (1972).
33. M. D. Edge, A. Hodgson, A. S. Jones, M. MacCoss, and R. T. Walker, J. Chem. Soc., Perkin I, 290 (1973).
34. T. Seita, K. Yamauchi, M. Kinoshita, and M. Imoto. Makromol. Chem., 154, 263 (1972).
35. T. Seita, M. Kinoshita, and M. Imoto, Makromol. Chem., 164, 345 (1973).
36. T. Seita, K. Yamauchi, M. Kinoshita, and M. Imoto, Makromol. Chem., 164, 15 (1973).
37. T. Seita, M. Kinoshita, and M. Imoto, Bull. Chem. Soc. Japan, 46, 1762 (1973).
38. A. S. Jones and N. Taylor, Nature, 215, 505 (1967).
39. M. G. Boulton, A. S. Jones, and R. T. Walker, Biochim. Biophys. Acta, 246, 197 (1971).
40. I. Khim, and W. Kohn, J. Am. Chem. Soc., 82, 6380 (1960).
41. J. E. M. Midgley, Biochim. Biophys. Acta, 108, 340 (1965).
42. S. Tanenbaum and S. Beiser, Proc. Nat. Acad. Sci. of the US 49, 662 (1963).
43. B. F. Erlanger and S. M. Beiser, Proc. Nat. Acad. Sci., of the US, 52, 68 (1964).
44. M. Sela, H. Unger-Waron, and Y. Schester, Proc. Nat. Acad. Sci. of the US, 52, 285 (1964).
45. M. H. Karol, S. W. Tanenbaum, Proc. Nat. Acad. Sci. of the US, 57, 713 (1967).
46. H. Unger-Waron, E. Hurwitz, J. C. Jaton, and M. Sela, Biochim. Biophys. Acta, 138, 513 (1967).
47. J. P. Coat and S. David, Carbohydrate Res., 12, 335 (1970).
48. A. S. Jones, P. Lewis, and S. F. Witkers, Tetrahedron, 29, 2293 (1973).
49. N. F. Albertson, Organic Reactions, Vol. 12 (1962), p. 157.
50. J. Pitha and P. O. P. Ts'o, J. Org. Chem. 33, 1341 (1968).
51. N. Ueda, K. Kondo, M. Kono, K. Takemoto, and M. Imoto, Makromol. Chem., 120, 13 (1968).
52. H. Kaye, Polym. Lett., 7, 1 (1969).
53. K. Kondo, H. Iwasaki, N. Ueda, K. Takemoto, and M. Imoto, Makromol. Chem., 125, 289 (1969).
54. K. Takemoto, F. Kawakubo, and K. Kondo, Bull. Chem. Soc. Japan, 44, 1718 (1971).
55. M. Imoto and K. Takemoto, Synthesis, 173 (1970).
56. K. Kondo, H. Iwasaki, K. Nakatani, N. Ueda, K. Takemoto, and M. Imoto, Makromol. Chem., 125, 42 (1969).
57. J. Pitha, P. M. Pitha, and P. O. P. Ts'o, Biochim. Biophys. Acta, 204, 39 (1970).
58. P. M. Pitha and A. M. Michelson, Biochim. Biophys. Acta, 204, 381 (1970).
59. P. M. Pitha and J. Pitha, Biopolymers, 9, 965 (1970).
60. K. Takemoto, F. Kawakubo, and K. Kondo, Makromol. Chem., 148, 131 (1971).
61. J. Pitha, P. M. Pitha, and E. Stuart, Biochemistry, 10, 4595 (1971).
62. K. Kondo, H. Iwasaki, N. Ueda, K. Takemoto, and M. Imoto, Makromol. Chem., 120, 21 (1968).
63. N. Ueda, K. Nakatani, K. Kondo, K. Takemoto, and M. Imoto, Makromol. Chem., 134, 305 (1970).
64. F. Cassidy and A. S. Jones, Eur. Polym. J., 2, 319 (1966).
65. A. S. Jones, M. K. A. Khan, and R. T. J. Walker, J. Chem. Soc, C, 1454 (1968).
66. M. G. Boulton, A. S. Jones, and R. T. Walker, J. Chem. Soc., C, 1216 (1968).
67. M. I. Cooper, R. S. Goody, A. S. Jones, J. R. Tittensor, and R. T. Walker, J. Chem. Soc., C, 3183 (1971).
68. H. Schott, G. Greber, and L. Bucsis, Makromol. Chem., 136, 303 (1970).
69. H. Schott, G. Greber, and L. Bucsis, Makromol. Chem., 136, 307 (1970).
70. H. Schott and G. Greber, Makromol. Chem., 149, 253 (1971).
71. H. Schott and G. Greber, Makromol. Chem., 149, 261 (1971).
72. G. Koomen, and U. Panditt, J. Chem. Soc., Perkin I, 1929 (1973).
73. G. Koomen, A. Kroon, F. MacCable, A. Goores, R. Peerebom, and U. Panditt, J. Chem. Soc., Perkin I, 1934 (1973).

74. S. A. Giller, All-Union Conference on Physiologically Active Polymeric Substances [in Russian, Riga (1962), p. 10.
75. S. A. Giller, R. A. Zhuk, M. Yu. Lidak, A. É. Berzinya, Ya. Ya. Shluke, I. N. Goncharova, and I. N. Getsova, Summaries of Papers Presented at the Seventh International Symposium on the Chemistry of Natural Compounds [in Russian], Zinatne, Riga (1970), p. 235.
76. S. A. Giller, Z. A. Shomshtein, and T. A. Popova, Khim. Geterotsikl. Soedin., 409 (1975).
77. S. A. Giller, Z. A. Shomshtein, and T. A. Popova, Khim. Geterotsikl. Soedin., 416 (1975).
78. S. A. Giller, Z. A. Shomshtein, and T. A. Popova, Khim. Geterotsikl. Soedin., 540 (1975).
79. S. A. Giller, L. A. Sherin', R. A. Zhuk, and A. É. Berzinya, Khim. Geterotsikl. Soedin., 1971 (1974).
80. S. A. Giller, I. N. Goncharova, I. N. Getsova, L. I. Mironova, É. I. Bruk, G. F. Nazarova, and L. N. Petrulyanis, Khim. Geterotsikl. Soedin., 1674 (1974).
81. S. A. Giller, T. A. Popova, and Z. A. Shomshtein, Khim. Geterotsikl, Soedin., 401 (1975).
82. M. Yu. Lidak, Ya. Ya. Shluke, B. V. Zarinya, and S. E. Porite, Khim. Geterotsikl. Soedin., 262 (1971).
83. S. A. Giller, I. N. Getsova, I. N. Goncharova, L. N. Petrulyanis, L. I. Mironova, G. F. Nazarova, and É. I. Bruk, Khim. Geterotsikl. Soedin., 1680 (1974).
84. S. A. Giller, R. A. Zhuk, A. É. Berzinya, L. T. Kaulinya, and L. A. Sherin', Khim. Geterotsikl. Soedin., 1662 (1974).
85. R. A. Zhuk, L. A. Sherin', E. É. Liepin'sh, and S. A. Giller, Khim. Geterotsikl. Soedin., 1666 (1974).
86. S. A. Giller, R. A. Zhuk, A. É. Berzinya, and L. T. Kaulinya, Khim. Geterotsikl. Soedin., 694 (1975).
87. T. Seita, K. Yamauchi, M. Kinoshita, and M. Imoto, Makromol. Chem., 148, 321 (1971).
88. N. Ueda, T. Kawabata, and K. Takemoto, J. Heterocyclic Chem., 8, 827 (1971).
89. K. Kondo, M. Miyata, and K. Takemoto, Bull. Chem. Soc. Japan, 44, 2554 (1971).
90. T. Seita, M. Kinoshita, and M. Imoto, Bull, Chem. Soc. Japan, 46, 1572 (1973).
91. T. Kawabata, N. Ueda, and K. Takemoto, Chem. Lett., 1, 55 (1973).
92. T. Seita, K. Yamauchi, M. Kinoshita, and M. Imoto, Makromol. Chem. 154, 255 (1972).
93. T. Seita, K. Yamauchi, M. Kinoshita, and M. Imoto, Makromol. Chem., 164, 7 (1973).
94. T. Seita, M. Kinoshita, and M. Imoto, Makromol. Chem., 166, 15 (1973).
95. M. T. Doel, A. S. Jones, and N. Taylor, Tetrahedron Lett., 2285 (1969).
96. N. T. Azorer and Yu. P. Shvachkin, Zh. Obshch. Khim., 34, 411 (1964).
97. S. A. Giller, Yu. P. Shvachkin, M. Yu. Lidak, and Ya. Ya. Shluke, Khim. Geterotsikl. Soedin., 124 (1968).
98. M. Yu. Lidak, M. K. Plate, I. Zh. Lulle, and Yu. P. Shvachkin, Khim. Geterotsikl. Soedin., 570 (1971).
99. M. Yu. Lidak, Ya. Ya. Shluke, and Yu. P. Shvachkin, Khim. Geterotsikl. Soedin., 955 (1968).
100. M. Yu. Lidak, R. A. Paégle, K. Ya. Petts, M. K. Plate, and Yu. P. Shvachkin, Khim. Geterotsikl. Soedin., 193 (1968).
101. H. Koning and U. Panditt, Rec. Trav. Chim. 90, 874 (1971).
102. A. Nollet and U. Panditt, Tetrahedron, 25, 5989 (1969).
103. E. Schnabel, Ann., 702, 188 (1967).
104. H. Koning and U. Panditt, Rec. Trav. Chim., 91, 1069 (1971).
105. M. Yu. Lidak, R. A. Paégle, V. É. Straume, A. É. Shnore, and Yu. G. Shvachkin, Khim. Geterotsikl. Soedin., 404 (1971).
106. M. Doel, A. S. Jones, and R. T. Walker, Tetrahedron, 30, 2575 (1974).
107. R. B. Homer and M. Shintizky, Macromolecules, 1, 469 (1968).
108. V. M. Story, D. McIntrye, and J. O'Mara, J. Res. Nat. Bur. Stand., 71, 169 (1967).
109. C. Loucheux and M. Rinfret, J. Chim. Phys., 65, 235 (1968).
110. C. David, W. Demarteau, and G. Geuskens, Polymer, 10, 21 (1969).
111. J. Brahms, A. M. Michelson, and K. E. Van Holde, J. Mol. Biol., 15, 467 (1966).
112. A. M. Michelson, I. Massoulie, and W. Guschlbauer, Progr. in Nucl. Acid Res., 6, 83 (1967).
113. P. O. P. Ts'o, Ann. New York Acad. Sci., 153, 785 (1969).
114. A. M. Michelson and C. Monny, Biochim. Biophys. Acta, 149, 107 (1967).
115. W. Szer and D. Shugar, Acta Biochim. Polon., 8, 235 (1961).
116. H. Kaye, J. Amer. Chem. Soc., 92, 5777 (1970).

117. A. M. Michelson and F. Pochon, Biochim. Biophys. Acta, 174, 604 (1969).
118. F. Pochon and A. M. Michelson, Proc. Nat. Acad. Sci. US, 53, 1425 (1965).
119. G. Felsenfeld and A. Rich, Biochim. Biophys. Acta, 26, 457 (1957).
120. R. C. Warner, J. Biol. Chem., 229, 711 (1957).
121. B. Zmudzka and P. Shugar, Febs Lett., 8, 52 (1970).
122. J. Hobbs, J. Sternbach, and F. Ecstein, Febs Lett., 15, 345 (1971).
123. J. Hobbs, H. Sternbach, and F. Ecstein, Biochem. Biophys. Res. Commun., 46, 1509 (1972).
124. F. Reinolds, D. Grunberger, J. Pitha, and P. M. Pitha, Biochemistry, 11, 3261 (1972).
125. G. J. Cowling, A. S. Jones, and R. T. Walker, Biochim. Biophys. Acta, 254, 452 (1971).
126. S. A. Giller, É. Ya. Gren, Z. A. Shomshtein, R. A. Zhuk, V. M. Berzin', P. P. Pumpen, and G. F. Rozental', Dokl. Akad. Nauk SSSR, 221, 473 (1975).
127. T. C. Merigan, Nature, 228, 219 (1970).
128. E. de Clerg, F. Ecstein, H. Sternbach, and T. Merigan, Virology, 42, 421 (1970).
129. J. Pitha and P. M. Pitha, Science, 172, 1146 (1971).
130. P. M. Pitha, N. M. Teich, D. R. Lowy, and J. Pitha, J. Proc. Nat. Acad. Sci. of the US, 70, 1204 (1973).

CATALYTIC HYDROGENOLYSIS OF ALKYLFURANS

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The vapor-phase conversion of α-methylfuran and α-methyltetrahydrofuran on a sodium- and potassium-activated palladium catalyst in a stream of hydrogen at atmospheric pressure at 200-450°C was investigated. Hydrogenolysis of α-methylfuran and isomerization of α-methyltetrahydrofuran to give 2-pentanone in both cases occur at 300° with identical selectivities. It is assumed that aliphatic ketones are formed from the alkylfurans on this catalyst via a parallel-consecutive scheme through direct hydrogenolysis of the alkylfurans and isomerization of their tetrahydro derivatives, which are formed as intermediates.

A considerable number of studies have been devoted to the problem of the vapor-phase hydrogenolysis of alkylfurans (for example, see [1, 2]). Metals on carbon, Raney nickel catalysts, nickel on metal oxides, etc. have been tested as catalysts. All of them, except for palladium, are typical catalysts for the hydrogenolysis of the furan ring. Palladium is distinguished by a clearly expressed capacity for hydrogenation of the double bonds of the furan ring over a broad range of temperatures, and its tendency to bring about hydrogenolysis is manifested to only a slight degree.

We have shown that, depending on the conditions used to carry out the catalytic process, activated palladium changes its selectivity and acts as a catalyst for hydrogenation of hydrogenolysis of the furan ring. The vapor-phase conversion of α-methylfuran in a stream of hydrogen at atmospheric pressure on sodium- and potassium-activated palladium catalysts at 200-450° was investigated. The selectivity of this catalyst depends on the temperature at which the catalytic reaction is carried out (Fig. 1).

*Deceased.

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