MODELS OF MATRIX REACTIONS

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INTRODUCTION

Much living matter is made up of macromolecules: there are the polysaccharides, the proteins, the nucleic acids. It is not this fact in itself that is exciting, but the ability of the organisms to produce macromolecules of the most complex structure over and over again and with the greatest precision: these molecules are not only always of the same size and structure but also of identical configuration; even their conformations are identical. Biological macromolecules arise and disappear; but since their biological function is frequently dependent on their exact structure, life depends on the possibility of the continually repeated production of identical complex macromolecules of the most different types. Much is already known about the method by which this magnificent achievement in synthesis is effected in the organisms; usually extraordinarily subtile reactions on matrices are involved. It is also known, however, that these reactions are not carried out by those methods which are used to synthesize macromolecules in the laboratory; that, in fact, they cannot be carried out by these methods.

First the most important polymerization reactions of the synthetic chemistry by which macromolecules can be prepared will be considered briefly; I wish in particular to point out the limits which are set for these methods at the present time. We shall thus consider the degree of precision with which these synthetic methods can be used today and with what degree of precision a desired structure can be obtained.

MACROMOLECULES OBTAINED BY VINYL POLYMERIZATION

The usual free radical and ionic polymerizations of unsaturated compounds (e.g. vinyl and acrylic derivatives) yield macromolecules of essentially linear structure which are composed of repeat units of largely uniform arrangement. Apart from the irregularities which stem especially from anomalous propagation or transfer steps, the linear chains exhibit two non-uniform structural features: the steric arrangement of the substituents is usually irregular, i.e. atactic, and the length of the molecular chains is not uniform but can be characterized only by a distribution function.

By means of stereo-regulating initiators and under suitable conditions, namely at low temperatures and in apolar solvents, polymers with tactic chain configurations *can* be obtained. It is even possible to prepare molecules far more homogeneous in size and of a very narrow molecular weight distribution by means of a special experimental technique with exact time programming[1] and under the conditions of "living polymer"[2] synthesis, particularly in the case of anionic initiation, where there are almost no side

reactions. This is certainly a great advance. But it is by no means justifiable to speak of the chains prepared according to the above procedures as configuratively and molecularly uniform.

MACROMOLECULES OBTAINED BY POLYCONDENSATION

Polycondensation reactions, if carried out in the usual way, also produce only polymer mixtures which even have a relatively broad distribution of molecular sizes. For fundamental reasons, i.e. because the remaining end groups usually have equal reactivity regardless of the molecular size of the intermediates, the preparation of molecularly uniform substances cannot be expected to succeed in polycondensation reactions of this kind.

In order to accomplish this two principles can be used, namely step by step synthesis and duplication. In neither case can equilibrium reactions be used, because in such reactions bonds already formed are again split. This would mean that what has been achieved would again be destroyed.

Step reaction synthesis

It takes place in successive reaction steps in each of which one structural unit is added. The number of the reaction steps x determines the degree of polymerization $(x + 1)$. Frequently it is even necessary to remove a protective group after each reaction step before the next step can take place. This clearly shows that this procedure is rather laborious. Moreover, it follows that this method is promising only if side reactions can be largely excluded.

Step by step syntheses of this kind have been carried out in various ways during the past 20 years. They yielded numerous series of oligomers and led to important discoveries about the corresponding polymers, for example polyamides[3], polyurethanes[4], and phenol-formaldehyde resins[5] (*Figure 1*).

The greatest importance is attached to this method of step reaction synthesis in the case of oligopeptides. For here the task is to add the desired amino acid residue at each reaction step so that the sequence of the structural units, i.e. of the amino acid residues, can be chosen at will. The history of these synthetic methods begins with protective groups, especially for the *N*-terminal amino group of the amino acids; it continues with the activation of the carboxyl group that is to be linked to the free amino group of the subsequent amino acid. It also includes the removal of the protective groups, which must take place before the next reaction step and without entailing the cleavage of previously formed peptide bonds. It culminates in the use by Merrifield[6] of gels which are capable of swelling as protective groups and in the very substantial simplification of the experimental manipulation which resulted.

Duplication[7]

This procedure is based upon the use of bifunctional compounds, e.g. diols and diisocyanates. One of the components is used in very great excess, so that the other bifunctional component reacts predominantly at both ends with the bifunctional component which is in excess; thus only a small fraction of the products is of higher molecular weight, and they can readily be removed after the first step. The main product of the reaction is again a

bifunctional substance, which can in turn be subjected to the same kind of duplicating procedure as the component in excess. The limitations of this procedure are to be found in the purification process, which is doubtless simpler here than in the case of a mixture consisting of an uninterrupted

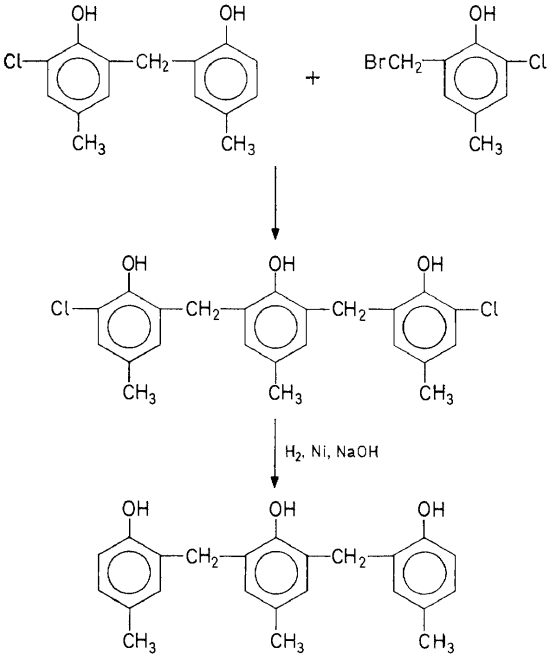

Figure 1. An example of step reaction synthesis for obtaining polymers

series of adjacent polymer homologues, such as is formed in the usual polycondensation reactions. Fordyce and Hibbert[8] attempted to prepare molecularly homogeneous polyethylene oxide diols by duplication. They were apparently successful in the first two steps up to a degree of polymerization of 42 (mol. wt 1866). But the products of yet higher molecular weight which were prepared by the same scientists in two additional steps were surely no longer molecularly homogeneous.

The results obtained by attempts made in Mainz to prepare polyurethanes of uniform molecular weight from diisocyanates and diols were hardly better. The use of partition chromatography and thin layer chromatography for purification did lead somewhat further: molecularly uniform polymers up to a molecular weight of about 4000 were obtained. Presumably, however, even gel chromatography, which is yet more efficient, cannot overcome certain limitations.

Another example of a doubling synthesis is the preparation of oligomers consisting of *p*-cresol nuclei with interconnecting methylene bridges (*Figure 2*). These oligomers are further discussed later on in this paper.

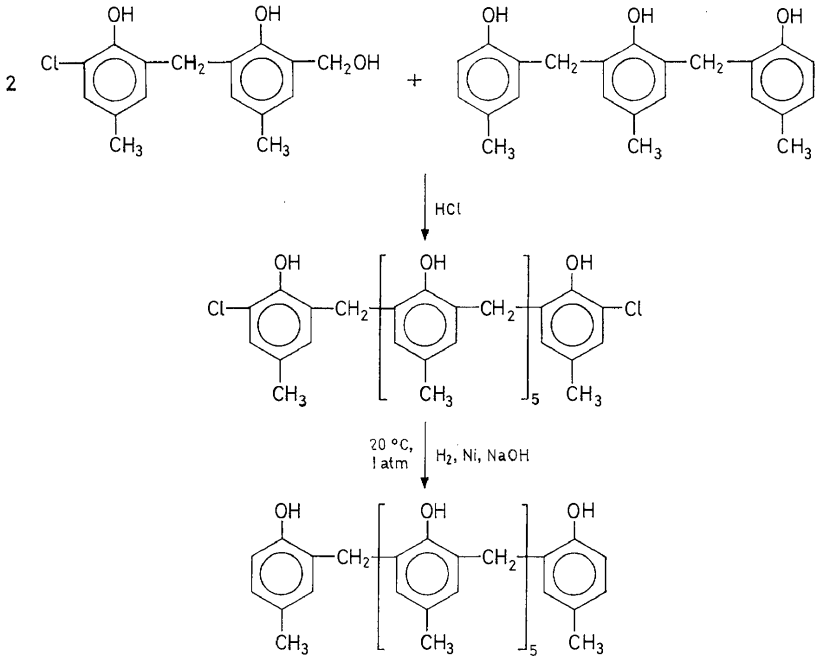

Figure 2. An example of doubling synthesis for obtaining oligomers

General remarks

The basic principle of both step by step synthesis and duplication is a series of successive reaction steps which are independent of one another and between which purification operations must be carried out. The purpose is realized only if the reactions proceed with the greatest possible yield on the one hand and if, on the other hand, all side products can be largely removed. Therefore, Merrifield's idea[6] was brilliant when he thought of using a gel capable of swelling within limits as a protective group, so to speak, and at the same time as a point of attachment in peptide synthesis. In this manner the successive reaction steps can be carried out simply, without isolating the desired reaction product. By clean reaction conditions and a sufficiently great excess of the reaction component of low molecular weight the quantitative progress and completion of each reaction step are assured; the gel is then freed of all substances of low molecular weight by washing and thus prepared for the next reaction step. This involves technical manipulations which are to be carried out in a precisely fixed order and with exact timing. The support gel which is capable of swelling to a limited extent is no matrix: it does not determine the structure or the configuration of the peptide formed; it merely supports the reactions, functioning as a solid swollen reaction phase which allows all necessary operations to take place between itself and a liquid phase, and which makes it possible to remove excess reagents and side products merely by rinsing with solvents. Automation of the process is possible, as it involves two phases that can easily be separated.

REACTIONS ON MOLECULAR MATRICES

By reactions on matrices we here mean such reactions for the preparation of molecules or macromolecules in which at least *one* structural or configurative feature of the molecules or macromolecules formed is due to the influence of the matrix. This influence of the matrix must not be restricted to the initiation of the preparative reaction but must persist throughout the entire process, for instance throughout the propagation reaction of a polymerization.

The present discussion is chiefly concerned with molecular matrices. We shall not consider here the formation of polymers at active centres of crystal surfaces (isotactic polystyrene, on amylsodium or $TiCl_3/Al(C_2H_5)_2Cl$, for instance), in clathrates (e.g. of butadiene in urea), or in the interior of layer lattices (Montmorillonite), nor shall we consider the polymerization of monomers in the crystalline state (i.e. solid state polymerization of trioxane), although it can be stated that in each of these cases as well the environment of the monomer during polymerization has an effect on the structure, or at least on the conformation of the resulting macromolecules.

The restriction to molecular matrices means that the matrix must be a molecule or macromolecule and must influence the formation of the new molecules or macromolecules in solution in such a way that the latter exhibit at least one constitutional feature which they would not have if prepared under the same reaction conditions but without a matrix. The effect of the matrix molecules upon the reaction of the starting materials can in principle be induced through (i) van der Waals forces, (ii) hydrogen bonds, (iii) electrostatic forces, and (iv) covalent bonds. These forces are to cause the monomers from which the new molecule or macromolecule is to be prepared to become oriented at the surface of the molecular matrix and to be brought into positions that are favourable for the intended reaction. What follows is a discussion of the cases listed above.

Matrices which function through van der Waals forces

Mention should here be made of certain observations of Melville and Watson[9]. These workers found that thoroughly purified poly(methyl methacrylate) (PMMA) initiates the polymerization of monomeric methyl methacrylate (MMA). This polymerization was found to be independent of the molecular weight of the polymers added and therefore could not have been caused by the end groups. Other monomers, such as styrene or vinyl acetate, are not polymerized by PMMA. Similarly, polystyrene does not initiate the polymerization of styrene, nor does poly(vinyl acetate) initiate that of vinyl acetate.

On the basis of these observations M. Szwarc[10] has proposed the following mechanism (which is somewhat simplified here):

(i) The monomeric MMA molecules come into contact with the MMA repeat units of the PMMA and become oriented in the process.

(ii) The polymerization of the oriented MMA molecules begins with the formation of biradicals that are attached to the matrix chains. The propagation reaction is a kind of zipping reaction with a free radical mechanism.

(iii) In this reaction an image of the PMMA molecule is formed. The reaction is therefore termed replica-polymerization.

The question whether this is really a polymerization at a macromolcular matrix has not yet been settled. In order to do so it would have to be determined whether the tacticity or the size of the newly formed macromolecules is determined by the matrix.

It is even questionable whether a contact between matrix and monomer molecules that is sufficiently tight and permanent to induce a replica-polymerization in M. Szwarc's sense can really be established by van der Waals forces alone.

In this connection we must mention an important paper by Farina, Natta, and Bressan[11]. They polymerized benzofuran with aluminium trichloride and (+)β-phenylalanine in toluene at − 75°; initially the polymers obtained had only weak optical activity. As the polymerization progressed this optical activity increased to a maximum, then slowly decreased. In the presence of the optically active catalyst system added polymer displayed an autocatalytic effect. This effect occurred regardless of whether the added polymer was itself optically active or inactive. Thus polybenzofuran can be considered as a matrix for the formation of optically active polybenzofuran with an optically active initiator.

It is, however, certain that in the more favourable cases in which polymerization can take place at surfaces a participation of these surfaces must be assumed. The following polymerizations are presumably of this kind:

(i) Polymerization on glass surfaces[12] of gaseous formaldehyde to polyoxymethylene films at − 80° under vacuum.

(ii) Acid-initiated polymerization of acetaldehyde[13] during crystallization of the monomer; in the supercooled state the liquid monomer does not polymerize at the same temperature.

(iii) Polymerization of *p*-quinone methides to polymeric films at 0° and at − 80° on glass surfaces[14].

(iv) Polymerization of liquid acetaldehyde on alumina[15]. Spectral evidence shows that electron pairs of the oxygen are introduced into vacant orbitals of the aluminium atoms; the polymerization is thus cationic.

(v) Polymerization of various monomers in Montmorillonite.

It has since been recognized that in several of the above cases the polymerization of the monomers is not spontaneous but catalytic. The participation of the surfaces then consists solely in an orientation of the monomer molecules, and it is not certain that this orientation is a necessary condition for the propagation reaction or that it influences the structure of the resulting polymers.

Matrices which bind the monomers by means of hydrogen bonds

The interactions of matrices and monomers through hydrogen bonds are understandably of great interest, for hydrogen bonds are very important in both nucleic acids and proteins; they might also contribute to the orientation of the building blocks before the latter are linked to one another in biosynthesis.

In analogy to the experiments of Melville and Watson[9] it might be attempted to polymerize monomeric acrylic acid in the presence of poly(acrylic

acid), or monomeric methacrylic acid in the presence of poly(methacrylic acid). By means of hydrogen bonds the monomeric unsaturated carboxylic acid molecules could be attached to the macromolecules of the polyfunctional acid more firmly than would be the case with van der Waals forces. But, aside from the problem of finding a suitable solvent, it would be very difficult to prove after the polymerization that the only macromolecules that had been formed were those whose structure was influenced by the original attachment of the monomers to the carboxyl groups of the polyvalent acid molecules by means of hydrogen bonds. I am indebted to M. Szwarc and R. T. LaLonde[16] for the information that the photochemical dimerization of methacrylic acid in the presence of *cis*-cyclobutane-1,3-dimethyldicarboxylic acid is being investigated in Syracuse (cf. *Figure 3*);

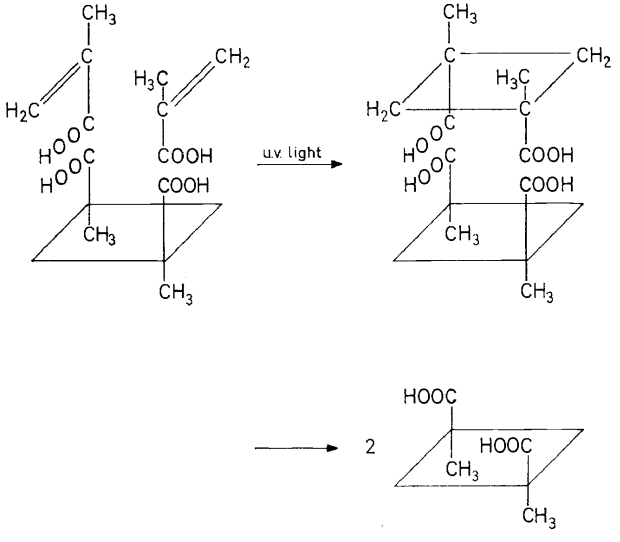

Figure 3. Photochemical dimerization of methacrylic acid in the presence of *cis*-cyclobutane-1,3-dimethyldicarboxylic acid

in the case of a replica-polymerization this should in turn produce *cis*-dicarboxylic acid. Molecular models show that an orientation of two molecules of methacrylic acid to *cis*-cyclobutane-1,3-dimethyldicarboxylic acid by means of hydrogen bonds which is favourable for the reaction is least hindered when the methacrylic acid molecules are oriented in such a way that a 1,3-disubstituted cyclobutane derivative results.

Matrices which function through electrostatic forces: heteropolar binding of the monomers

Mention should here be made of a valuable paper by Kargin, Kabanov[17] and coworkers. They found that 4-vinylpyridine polymerizes in organic solvents upon alkylation of the tertiary nitrogen. Polymerization takes place

only in so far as the alkylation proceeds, and the polymer contains only structural units with quaternary nitrogen; the excess 4-vinylpyridine does not polymerize. The reaction is started by a strong polarization of the vinyl double bond, but it is not formulated as being purely anionic. Apparently this polymerization requires not only an anionic chain end of the growing polymer but also a strongly polarized double bond of the monomer.

If 4-vinylpyridine (in great excess) is added to a methanolic or aqueous solution of polystyrene sulphonic acid (PSS), a precipitate forms consisting of stoichiometric amounts of polystyrene sulphonic acid and of polyvinylpyridine (PVP); the excess 4-vinylpyridine does not polymerize. If a monovalent aromatic sulphonic acid (for example *p*-toluenesulphonic acid) is used in comparable concentration, polymerization does not take place. The authors believe that in the case of polystyrene sulphonic acid the 4-vinylpyridine molecules become quaternized through proton addition, arrange themselves along the PSS macromolecules and are then polymerized (as in the case of alkylation) (cf. *Figure 4*). The PSS constitutes a matrix for this polymerization of the protonized 4-vinylpyridine molecules. The polymeric salt of polystyrene sulphonic acid and polyvinylpyridine is insoluble and precipitates. The authors were not successful in separating the polyvinyl-

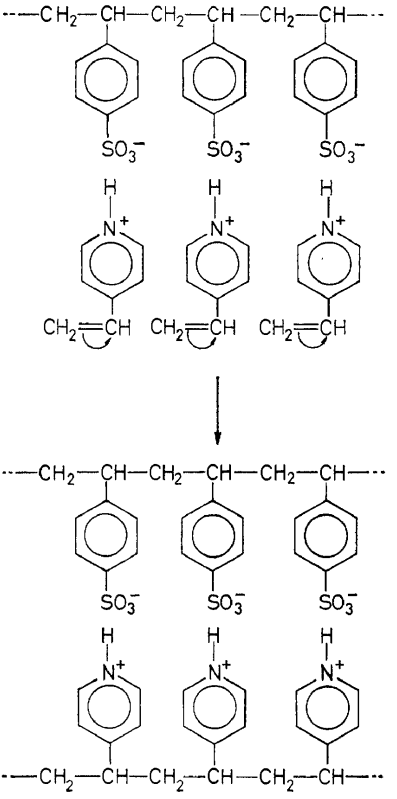

Figure 4. An example of polymerization through electrostatic forces

pyridine which formed from the polymeric sulphonic acid matrix. But if a salt of polystyrene sulphonic acid and of polyvinylpyridine which has been previously obtained by a different process, is prepared, the separation of the polymeric amine from the polymeric sulphonic acid does succeed.

It could seem natural to regard the polymerization of 4-vinylpyridine with polystyrene sulphonic acid as a matrix reaction in which the protonized 4-vinylpyridine molecules are linked electrostatically[18] to the polyanions of the polystyrene sulphonic acid and polymerized on this anionic macromolecular matrix. But this reaction cannot be considered as a matrix reaction unless the polyvinylpyridine generated has the same degree of polymerization and the same molecular weight distribution as the polystyrene sulphonic acid matrix[19].

Matrices which bind the monomers with covalent bonds

It is possible to polymerize monomers which are linked by a covalent group to a molecular matrix and which still comprise a functional group capable of taking part in a polymerization reaction. The result of the reaction is largely determined by the steric positions of the monomer units, which cannot abandon their positions at the matrix because of the covalent bonds. Thus the starting position of the monomer units for the intended reaction is far more definitely fixed when the monomers are tied by covalent bonds than when they are bound by van der Walls forces, hydrogen bonds

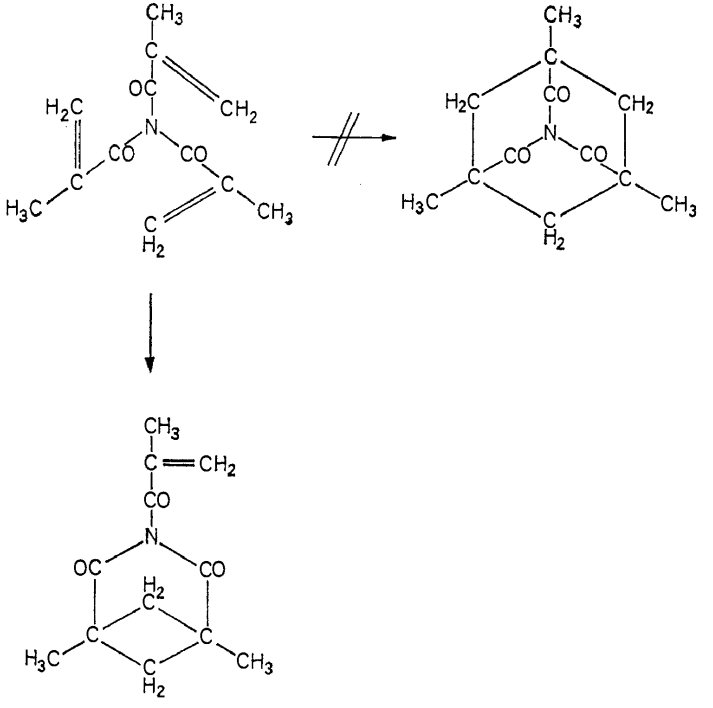

Figure 5. Ultraviolet initiated polymerization of *N,N*-dimethacryloylmethacrylamide

or ionic forces. The other factors which determine the result of the polymerization are above all the concentration and the conformation of the reacting molecules. While the concentration can be chosen, the conformation can be affected through the choice of solvent.

LaLonde and Aksentijevich[16] investigated the u.v. light initiated polymerization of *N,N*-dimethacryloylmethacrylamide in ethereal solution (2 per cent). They expected a cyclohexane derivative to result but obtained a 1,3-cyclobutane derivative (in 60 per cent yield), the formation of which is analogous to that of the four-membered ring of a α-truxillic acid from cinnamic acid.

More promising results were obtained by H. Kämmerer[20] and his coworkers in Mainz. They employed molecularly uniform oligomers as matrices. In such oligomers each structural unit must further contain a reactive group to which the monomer to be polymerized can be attached. There are only a few series of oligomers which fulfill this condition. A very suitable one is that consisting of molecularly and structurally homogeneous condensation products of *p*-cresol and formaldehyde, i.e. *p*-cresol nuclei with connecting methylene bridges, which are relatively easy to obtain with 2–10 cresol units (cf. *Figure 6*). The structure is assured and accurately proved

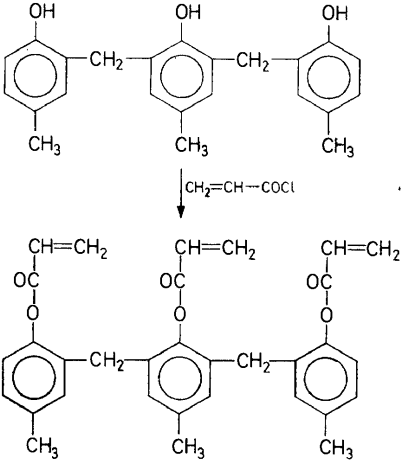

Figure 6. Condensation products of *p*-cresol and formaldehyde

by the synthesis. The reactivity of the phenolic OH groups has been studied in detail. They are used to bind acryloyl or methacryloyl groups; in these reactions quantitative conversion can be effected. The groups to be polymerized are thus bound to the molecular matrix. The purity of the acylated oligomers, like that of the oligomeric matrices, is checked by chromatography.

Stuart models show that the desired polymerization of adjacent acryloyl groups is favoured; it is a kind of cyclopolymerization. In order to make the (intramolecular) cyclization the predominant reaction, i.e. in order to

repress the intermolecular polymerization between acryloyl groups on different molecules, the reaction is effected in high dilution (according to Ruggli–Ziegler). So far the free radical cyclo-oligomerization with azo-bis(isobutyronitrile) (AIBN) for matrices with 2 to 5 cresol nuclei has been studied (cf. *Figure 7*). A relatively high concentration of the azo compound, i.e. a high

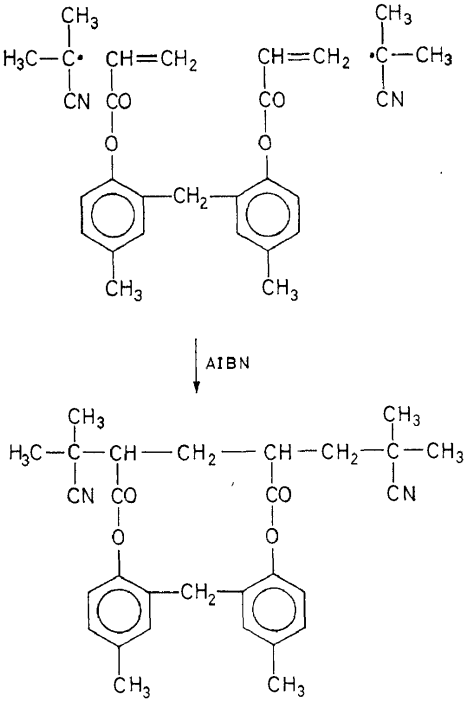

Figure 7. Free radical cyclo-oligomerization with AIBN

radical concentration, is used, so that both initiation and termination occur through isobutyronitrile radicals. The expected cyclo-oligomers could in fact be isolated and obtained in pure form. Alkaline hydrolysis yields the original matrix molecules and oligomeric acrylic acids (or methacrylic acids) of the expected degree of polymerization. (cf. *Figure 8*). For matrices with 2 cresol units a tetravalent carboxylic acid is obtained, which does contain 3 acrylic repeat units in head-to-tail arrangement; the two structural units in the middle derive from acryloyl residues that were linked to the matrix and owe their position to this connection with the oligomeric matrix. The acrylic unit at one end stems from an initiator radical. The carboxyl group at the other end also originates in an isobutyronitrile radical; but this structural unit is bound "incorrectly", namely in head-to-head arrangement.

The steric structure of the oligomers obtained is not yet known. It may be supposed, however, that a configurative influence arises from the cyclopolymerization. The conformation of the cyclic oligomers in the reaction medium is a difficult problem, which is still being studied. It no doubt

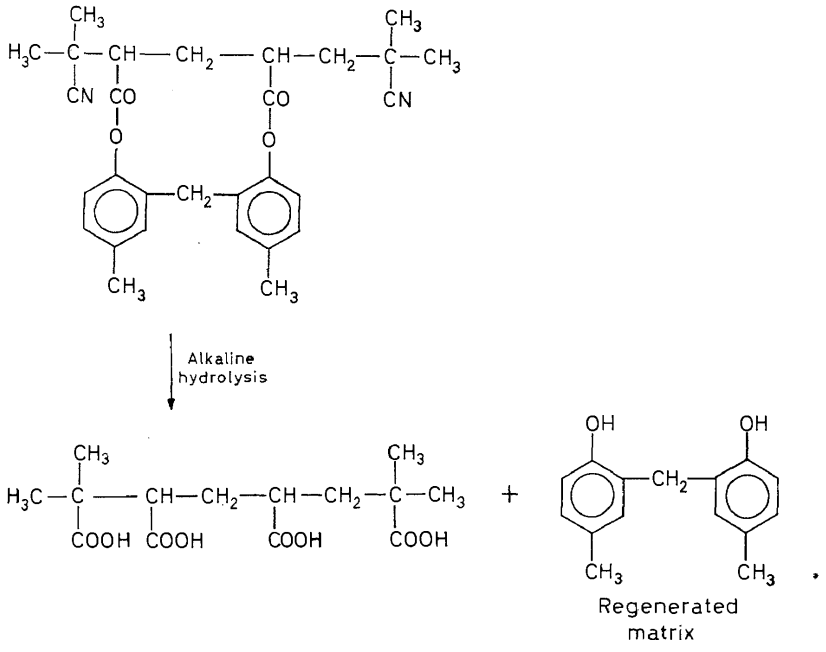

Figure 8. Alkaline hydrolysis of cyclo-oligomers

determines the result of the cyclopolymerization and the reliability of the matrix reaction; this problem must be thoroughly investigated.

General remarks

A consideration of the situation described above for the preparation of structurally and molecularly homogeneous oligomers and polymers suggests a comparison with the synthesis of optically active compounds. By far the most important method for this synthesis involves the preparation of diastereoisomers from synthetic racemic mixtures and with the aid of optically active substances. With a single optically active compound which is capable of forming a separable diastereoisomeric pair with a racemic mixture further optically active compounds can be prepared in this manner. Eventually, this procedure leads to more and more new optically active compounds.

This last method for the synthesis of structurally and molecularly homogeneous oligomers with the aid of an oligomeric matrix has a striking resemblance to the procedure for the preparation of optically active compounds via diastereoisomers. Diastereoisomers are prepared with the aid of optically active substances and racemic mixture; after the separation of the mixture of diastereoisomers the pure diastereoisomers are decomposed in order to regain the original optically active substance and to obtain a new pair of optically active compounds (antipodes).

In the case of the preparation of new structurally and molecularly homogeneous oligomers a structurally and molecularly homogeneous matrix is employed in place of the configuratively homogeneous optically active

compound. Its availability is a prerequisite for the procedure, just as the existence of an optically active compound is a prerequisite for the preparation of new optically active compounds. The molecular matrix now serves in a reaction sequence in which its reactive groups are used for constructing a new daughter molecule, which is bound to the matrix and whose structure and size are determined by the matrix. Finally, the daughter molecule is separated from the matrix. The matrix is then available for new reaction sequences in which either similar or different daughter molecules can again be prepared. These daughter molecules have reactive groups, and, theoretically, they can in turn be employed as matrices. Thus, here too it is possible to use a structurally and molecularly homogeneous matrix in order to prepare, by means of suitable reaction sequences, new structurally and molecularly homogeneous matrices.

At this point I wish particularly to emphasize the fact that, although such synthetic matrix reactions can be looked upon as models of biological reactions, one would not be justified in drawing conclusions regarding biological mechanisms. This would be just as wrong as to assume, on the basis of the separation of diastereoisomers, that nature also prepares optically active compounds in this manner.

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