for the study of processes leading to the distribution of nitro derivatives of polycyclic aromatic hydrocarbons in the environment. These are formed in combustion processes, including smoking, and constitute a significant part of the carcinogenic compounds of airborne particulate matter.[58]

Conclusions

We do not claim that we have once and for all solved the problem of ET mediated nitration reactions, but we believe that two conclusions are presently possible to draw:

(i) If a radical cation is formed from an ArH/NO_2^+ reaction and the nitrous acid catalyzed pathway has been properly suppressed by addition of a nitrous acid scavenger, it is formed via an inner-sphere ET mechanism (eq 10).

(ii) If the nitrous acid catalyzed pathway has not been excluded by addition of a scavenger, the radical cation in all probability is formed via an outer-sphere ET mechanism with NO^+ as the oxidant.

Financial support from the Swedish Natural Science Research Council and the Knut and Alice Wallenberg Foundation is gratefully acknowledged.

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Polysaccharide Conformations and Kinetics

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Of the three classes of biopolymers—proteins, nucleic acids, and polysaccharides—the polysaccharides have been the Cinderella of the group. This is not to imply that proteins and nucleic acids are the Ugly Sisters, but simply that when biopolymers like insulin and DNA are compared with, for example, starch, most people would feel that polysaccharides are unworthy of close attention. This Account aims to show that polysaccharides are worthy of detailed study by chemists interested in structure and dynamics and that kinetics are useful in helping to establish the conformational states of these macromolecules in solutions.

We have been particularly interested in thermally reversible conformational transitions shown by a number of polysaccharides used as food hydrocolloids.[1]

(a) Xanthan (Figure 1) is an extracellular bacterial polysaccharide used widely as a thickener and a stabilizer to control the rheology of aqueous phases for a number of industrial applications. This is often referred to as giving "body" to fluids or emulsions. A 1% aqueous solution of xanthan has a viscosity 10 times that of water, and the pseudoplastic shear thinning behavior of xanthan solutions makes them particularly useful in food products such as sauces and salad dressings. Xanthan is used in the petroleum industry as a viscosifier for drilling fluids.[2] Its use may result in enhanced oil recovery since an increase in the viscosity of the aqueous solution used as a driver fluid to extract oil from a reservoir will delay the onset of water breakthrough into the oil being pumped out. A pilot plant has recently been commissioned in the U.K. to culture xanthan strains as biotechnological products.

(b) Carrageenans and agar (Figure 2) are a group of polysaccharides that are structural components of red seaweeds and are used in the food industry as gelling agents, particularly in cold-setting desserts. In food gels this type of polysaccharide, typically present at the 1% level, creates a three-dimensional network which gives the product the desired texture and shape. These gels are strongly dependent on the salt type and ionic strength, and clear gels are obtained by mixing polysaccharides such as agarose sulfate and ι- and κ-carrageenan with salts.

A principal aim of our work has been to determine the primary processes in salt-induced conformational changes and gelation. We first discuss polysaccharide conformations in the solid state and in solution, and then we describe the detailed information obtained from kinetic studies.

Polysaccharide Structures

A consequence of regularly repeating units in the backbone of polysaccharides is that they generally adopt geometrically regular spatial arrangements in the solid state. These have been categorized by Rees,[3] with

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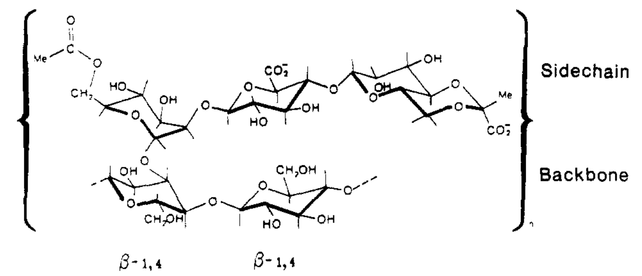


Figure 1. Primary structure of xanthan. Approximately one-third of the side chains have no pyruvate.

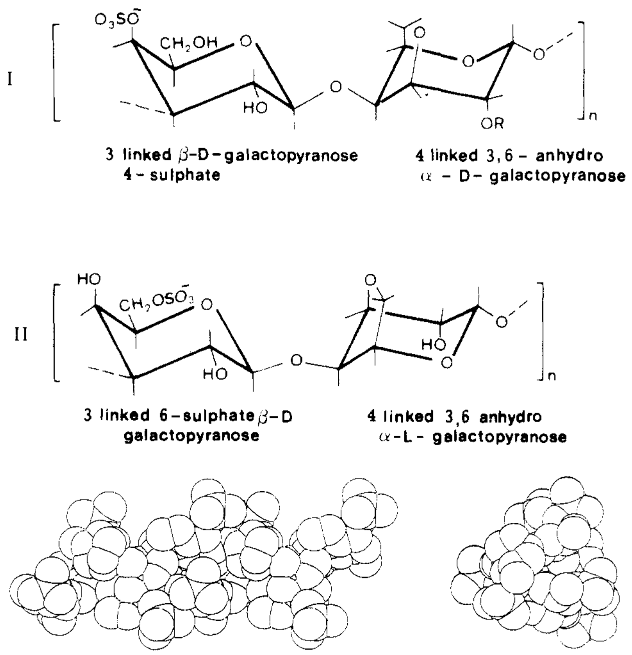
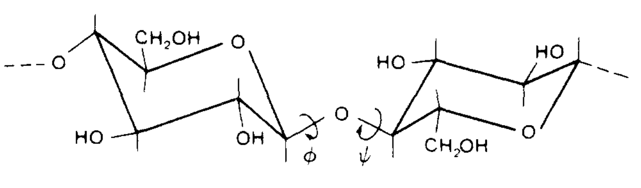


Figure 2. (top) Idealized disaccharide repeating unit of (I) ι-carrageenan (R = SO_3^-), κ-carrageenan (R = H) and (II) agarose sulfate. (bottom) Double-helix conformation of ι-carrageenan characterized by fiber diffraction studies,[5a] viewed along and down the helix axis.

key influences on structure being the geometrical relationship within each sugar unit and the ring positions involved in the glycosidic bonds.

A comparison of cellulose (A) and amylose (B) provides an excellent illustration of the importance of the form of sugar unit, since both are polymers of glucose differing only in the mutarotation at the Cl position, yet they have quite different structural and biological characteristics. As can be seen from the diagram, cellulose consists of regular repeating β-1,4-linked glucopyranose units which give the polymer an extended structure. This results in cellulose existing as extended helical ribbons in the solid state and in plant walls, with the structure being stabilized by side-by-side packing involving interchain hydrogen bonding. In amylose the α-linkage leads to the production of helices in the solid state, for which three crystalline forms have been identified—the polymorphic double-helical forms, A and B, and the single-helix "V" form.



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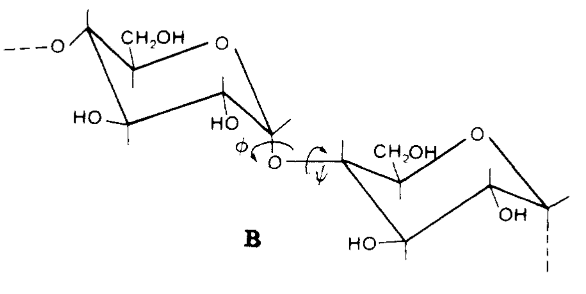

B

Biopolymers such as the polysaccharides xanthan and carrageenan have long chain lengths (>500) and are analogous to synthetic polymers in their chain length polydispersity. Because of this it is not possible to produce single crystals for X-ray measurements. In order to obtain information in the solid state, fibers are drawn to cause alignment of the chains, and these are used for X-ray diffraction studies. This approach in combination with model-building calculations has been the source of most information about polysaccharide conformations in the solid state.[3] The interpretation of fiber diffraction patterns is often ambiguous even when high-quality diffraction data are available. This has been the case with xanthan, with the diffraction evidence consistent with either a fivefold single helix or a fivefold double helix.[4] With the solid-state data currently available the controversy regarding the structure cannot be resolved unless independent data from studies of the molecule in solution are also considered.

In the carrageenans (Figure 2) the 1,3-glycosidic linkage results in the molecules making a turn from one residue to the next. For ι-carrageenan the X-ray fiber diffraction[5a] studies have provided very high quality data which strongly support the double-helix structure shown in Figure 2. Double helices have also been proposed for κ-carrageenan[6] and agarose sulfate,[5b] although in these cases interpretation of the diffraction data is more ambiguous. An important feature of these structures is the disposition of the sulfate ester groups on the outside of the double helices, which allows the charges of the polyanions to be balanced by incorporation of cations into the structure in the solid state.

Solution Conformations. With the techniques of sedimentation, light scattering, and viscometry, polysaccharides have been characterized in solution as having the conformations of random coils, rods, or wormlike chains. The dramatic viscosifying effect of xanthan is related to the extended, stiff secondary structure shaped by the cellulose type backbone as described above. A number of workers have shown that native xanthan (M_w = 10^6–10^7) resembles DNA in the rheological behavior of a wormlike chain, with persistence lengths in excess of 40 nm.[7a,8] This suggests that

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fractions obtained from xanthan by hydrolytic chain cleavage which have $M_w \leq 10^5$ behave as rigid rods in solution.

There has been a lively debate about the number of chains involved in the ordered structure of xanthan, although much of the information used to fuel this argument is circumstantial. For instance, it has been observed[7b] that in cadoxan, a strongly basic denaturing solvent, xanthan samples have M_w values half those observed in aqueous solution. This suggests that the light-scattering measurements in aqueous solution have been carried out under conditions where the native material exists as dimers. A highly pyruvated xanthan has recently been shown to give monomers in aqueous solution,[8] and it was suggested that a xanthan sample may be either a single or a double strand depending on how it has been treated after the fermentation step. Cation activity measurements,[9] conductivity,[10] and increased ion association on ordering[11] as analyzed by Manning theory[12] are consistent with monomers. Both the equilibrium solution measurement and X-ray fiber diffraction evidence leave these questions unanswered, and we shall show later how kinetic evidence has helped to interpret conversion between the various forms of xanthan possible in solution.

For ι-carrageenan, which has been cleaved at anomalous non-anhydro rings[3] to give segments with improved structural regularity, there is strong evidence that the double helix, shown to exist in the solid state, is the ordered tertiary form in solution. This evidence has been obtained from light-scattering and osmometry measurements of the changes in polysaccharide during the transition from disorder to order on decreasing the temperature, which is accompanied by a doubling of both number-average and weight-average molecular weights.[13,14]

A feature of helix-forming polysaccharides is that the order–disorder transitions on increasing the temperature are often accompanied by changes which may be monitored by optical rotation, circular dichroism, or nuclear magnetic resonance. The midpoint temperature, T_m, defined as the temperature at which the mole fractions of disordered and ordered residues of the polymer are equal, increases with salt concentration. This can be understood in terms of increased counterion condensation and charge screening by the ionic atmosphere. This screening is more effective in the ordered state since it has the higher charge density.[12a] The nature of the added salt also affects the order–disorder transition in many polysaccharides. This salt effect comes either from changing the quality of the solvent by different amounts for the two states or from the cations binding at specific sites as distinct from the general counterion condensation predicted by polyelectrolyte theory. For ι- and κ-carrageenan the binding of potassium ions at the sulfate ester group has been demonstrated by infrared spectroscopy.[9] Cation-specific effects have been shown to correlate with ion size; for monovalent ions Rb^+ ions provide optimum stabilization of the ordered forms.[15]

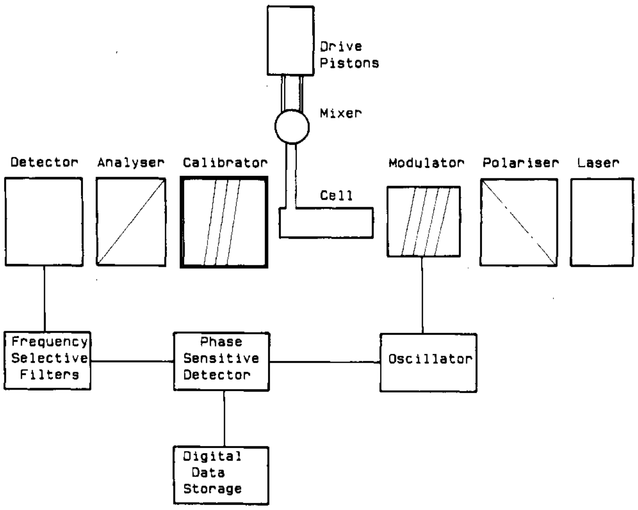

Figure 3. Block diagram of the laser optical rotation stopped-flow apparatus.

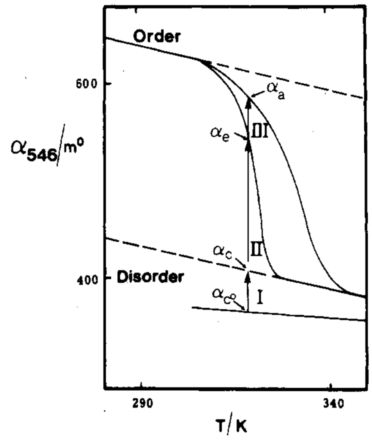

Figure 4. Optical rotation vs. temperature profile for κ-carrageenan in distilled water and for heating and cooling in 0.1 mol dm^{-3} KCl solution. Dashed lines represent extrapolations of all-helix and all-coil rotations.[17b] Three sequential reaction phases are found in the salt-jump kinetic experiments: (I) a conformation change in the disordered form, (II) conformational ordering, and (III) aggregation.

Kinetics of Conformational Ordering

By mixing certain polysaccharides with salt in a stopped-flow apparatus, it is possible to follow the disorder-to-order transition. The rate of reaction is often such that it occurs in the millisecond to minutes time scale and is therefore ideally suited for study by the stopped-flow method. A block diagram of our optical rotation stopped-flow apparatus is given in Figure 3,[16] and the measurements are based on the principle of Faraday modulation polarimetry. Noise levels with a 1-W, 514-nm argon ion laser beam as the light source

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are less than 10 μdeg with a 10-ms time constant.

A typical ordering process which involves the formation of aggregates, κ-carrageenan in KCl, is illustrated in Figure 4. A conformational change in the disordered form $C^\circ \rightarrow C$ (I) occurs in less than 5 ms, which is the stopped-flow dead time. Conformational ordering (II) results in the optical rotation change from α_c to α_e. The final phase (III) is a slower aggregation process on a time scale of minutes to days, at temperatures within the ordering transition. This aggregation changes the quasi-equilibrium rotation α_e to the final equilibrium value α_a.

Order of Reaction. Primary formation of a monomer or a dimer in the salt-induced conformational transition can be distinguished simply by determining the order of reaction with respect to the polysaccharide, both in terms of the kinetics at a single polymer concentration and in terms of the rate dependence on polymer concentration. The results help to determine the number of chains involved in the activated complex for ordering of these polysaccharides in solution and so are useful in resolving the nature of the ordered form and in determining the factors influencing the solution conformations.

For xanthan, first-order kinetics were observed, both from reaction progress curves and from variation of rate with polymer concentration. Data were in accordance with a reversible first-order reaction for the primary conformational ordering, consistent with single-helix formation.[11]

$$C \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H \qquad (1)$$

For ι-carrageenan,[17a,18a] κ-carrageenan,[17b,18b,c] and agarose sulfate,[19] the kinetics were found to be second order in the forward direction and first order in the reverse, consistent with chain dimerization and double-helix formation.

$$2C \underset{k_{-1}}{\overset{k_2}{\rightleftharpoons}} H_2 \qquad (2)$$

The effect of variation of chain length was studied for κ-carrageenan by using three samples with $\bar{n}_w$, the average number of residues per polymer, ranging from 20 to 350.[18c] Again, the evidence favors intermolecular double-helix formation, since the kinetic behavior was the same for short- and long-chain samples; intramolecular double-helix formation via reverse folding of single chains can only occur in long chains.

Nucleation and Growth. Helix formation in many biopolymers occurs by a cooperative process in which a primary nucleation event is followed by a sequence of faster growth steps leading to the stable ordered conformation. This type of process is represented in eq 3 in which the symbols H and C represent individual

$$\begin{array}{ccccccc} & \text{nucleation} & & & \text{growth} & & \\ \text{CCCCC--} & & \text{HHCCC--} & & \text{HHHCC--} & & \text{HHHHH--} \\ & \overset{k_{\text{nuc}}}{\rightleftharpoons} & |\,| & \rightleftharpoons & |\,|\,| & \rightleftharpoons & |\,|\,|\,|\,| \\ \text{CCCCC--} & & \text{HHCCC--} & & \text{HHHCC--} & & \text{HHHHH--} \end{array} \qquad (3)$$

residues in the helix and coil conformations, respectively, and helix growth occurs from a nucleus which involves several helix–residue pairs. For oligonucleotides and the carrageenans this is manifested in the observed second-order rate constant k_2 of eq 2 going through a maximum as temperature increases and then decreasing to zero at the melting temperature, T_m. In order to calculate the nucleation rate constant, k_{nuc}, from the observed second-order rate constant, the equilibrium constant for the growth step of a single helix–residue pair, K^{-1}, has to be taken into account as in eq 4.[20]

$$k_2 = k_{nuc}(1 - K) \qquad (4)$$

Differential scanning calorimetry measurements give the enthalpy change for the growth step and allow K to be calculated independently at any temperature and hence allow k_{nuc} to be obtained. At T_m helix growth and decay are equally probable, and so the rate of helix formation is almost zero. Above this temperature the junction between helix and coil blocks cannot propagate to stabilize the initially formed double-helix nucleus.

We have found that there is a striking correlation between the nucleation rate constant and the structure in the double-helix-forming polysaccharides. For agarose sulfate k_{nuc} is 2–3 orders of magnitude greater than for the carrageenans.[19] The double helix suggested from X-ray measurements for the carrageenans[5a,6] is more compact, and therefore probably has more steric constraints, than the hollow-helical structure suggested by X-ray analysis of agar and its esters.[5b]

For single-helix-forming biopolymers, a mathematical model employing statistical thermodynamics predicts the change or rate-limiting step from nucleation to growth in moving through the transition.[21] This theory had not been tested because the rates of ordering of polyamino acids[22] are too rapid to observe on the time scale of the stopped-flow method which is particularly appropriate for generating the large perturbations suitable for observing nucleation. We have shown that for xanthan it is experimentally feasible to determine the change in rate-limiting step. Consequently, we have been able to carry out the first test of the model and have shown that it is valid at least with respect to the ordering of this polysaccharide.[11]

Detailed studies of the kinetics of primary conformational ordering in xanthan have led to the distinction between (1) a "two-state all-or-none" process, in which an individual chain is driven from an all-coil to an all-helix conformation, and (2) a statistical process in which blocks of helix residues grow within a single chain. Figure 5 shows how the choice between the models is made by comparing kinetics first starting with xanthan in the fully disordered form at temperatures greater than the end of the transition for the salt-free solution and then starting at temperatures within the transition and thus with partially ordered xanthan. It was found[11] that the rate constant increased sharply when T was decreased to the melting temperature (T_m°) for the salt-free xanthan, demonstrating the changeover from nucleation to growth control in accordance with the statistical process. Kinetic data were shown to be

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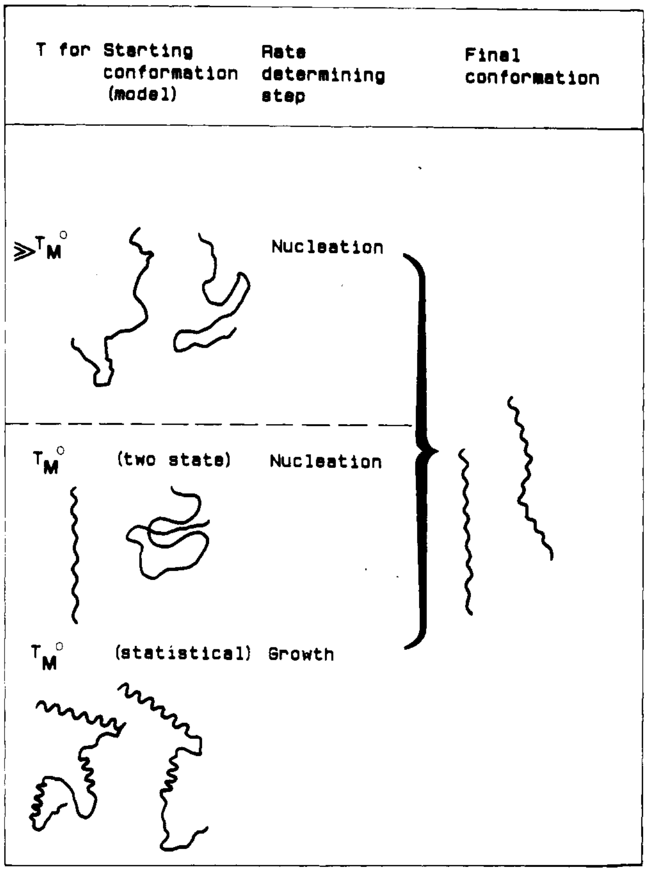

Figure 5. Two-state all-or-none vs. statistical model for the conformational ordering of xanthan.

consistent with equilibrium parameters determined from the helix melting curve by using the statistical linear Ising model as developed by Zimm and Bragg[23] for helix–coil transitions. Both conformational equilibria and kinetics show that ordering is intramolecular and that helix and coil regions can be present in equilibrium within a single chain. For a salt-free solution of xanthan at T_m°, blocks containing an average of 30 helix residues alternate with blocks of the same average length of coil residues. Each chain of length $\bar{n}_w = 10^3$ therefore contains on average ∼16 ordered and ∼17 disordered regions, the extra disordered region resulting from the extra entropy at the end of the chains.

Activation Parameters and Salt Effects. The activation enthalpy for helix nucleation is found to be close to zero, for both single- and double-helix-forming polysaccharides, when the salt concentration is high. Low activation enthalpies have also been reported for ribonuclease renaturation[24] and for double-helix formation between poly(A) and poly(U).[20] The limiting factor in determining the rate of reaction for ordering in each of these systems is therefore the activation entropy. This implies that there is a low statistical weight for the geometry which must be accessed by fluctuation from the coil conformation before ordering can occur.[24] The largest negative activation entropy per mole of residues within the polysaccharides studied has been observed for xanthan,[11] which has the most complex residue structure (cf. Figures 1 and 2).

It has been argued for polynucleotides that an activation enthalpy close to zero implies that only one or two residue pairs are involved in the rate-determining step for helix nucleation. The reasoning is that preequilibrium formation of the precursor to a nucleus returns the enthalpy per residue involved, and thus a nucleus with more residue pairs would result in a negative value for the activation enthalpy.[20] The same arguments can be applied to the polysaccharides, suggesting that in the nucleation step it is not necessary to form a complete turn of the helix: three disaccharide residues in each chain in the carrageenans[5,6] and five in xanthan.[4]

Salt effects on conformational equilibria, discussed earlier, are paralleled by those on nucleation kinetics. Both the rate of the nucleation step and the equilibrium constant for the growth step are affected in the same way; stabilization of the ordered form reflected in the growth equilibrium constant is accompanied by an increase in rate of the nucleation step.

Studies of salt effects on ι- and κ-carrageenan have shown that the most striking changes are present in the activation parameters for helix nucleation, ΔH^* and ΔS^*. As the salt concentration increases, ΔS^* becomes more negative, reaching a limiting value at high salt concentration, while ΔH^* drops from a large positive value to near zero. There is an effective cancellation of enthalpy and entropy terms in the activation free energy, ΔG^*, which decreases only slightly with increasing salt concentration. When comparing different salts, it is found that the salt with the strongest stabilizing effect on the carrageenan ordered form shows the changeover in activation parameters at the lowest salt concentration. For ι-carrageenan the effect is cation specific and stabilization increases in the order $\mathrm{Me_4N^+} < \mathrm{Na^+} < \mathrm{K^+}$.[17a] For κ-carrageenan both anion- and cation-specific effects are observed, with anion stabilization increasing through the lyotropic series $\mathrm{F^-} < \mathrm{Cl^-} < \mathrm{NO_3^-} < \mathrm{Br^-} < \mathrm{I^-}$.[18b]

It is most likely that the predominant influence of the salt is on the disordered form of the carrageenan chain and that general anion lyotropic effects arise through modification of the solvent quality. The polyanionic nature of the ι- and κ-carrageenan accounts for the observation that an extended rodlike conformation present in solution without added salt changes to a coil with increasing ionic strength as repulsions between sulfated ester groups along the chain become screened.[14,25] This is process I shown in Figure 4 which occurs within the dead time of the stopped-flow apparatus. For κ-carrageenan in NaCl solution, there is a decrease in hydrodynamic radius by a factor of 5 as the NaCl concentration is increased.[25] At low salt concentration the conformational ordering (process II of Figure 4) can thus be pictured as bringing two rodlike single chains into a double-helix transition state, whereas at high salt concentration two coils are brought into the transition state. This also accounts for the observation that the activation entropy for helix nucleation is most unfavorable at high salt concentration. Since the conformation of the product double helix should be invariant to changes in salt concentration, ΔS^* for forming a productlike transition state will alter

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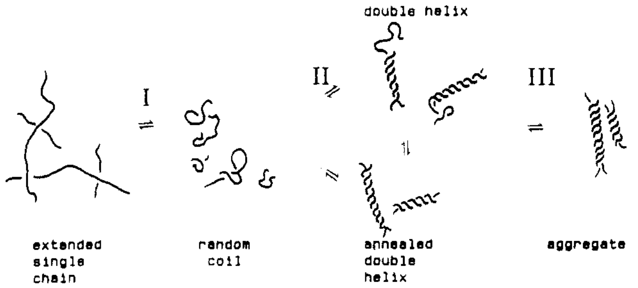

Figure 6. Sequence of reaction following a salt jump in dilute solutions of sulfated galactans. (Symbols for the reaction phases are the same as in Figure 4.)

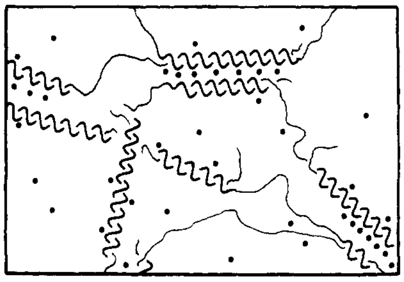

Figure 7. Schematic representation of the gel network in ι-carrageenan showing junction zones of dimers of double helices stabilized by cations (●) (after ref 26).

according to the entropy of the reactant single chains.[17a]

Aggregation and Gelation

Light-scattering measurements give evidence for substantial aggregation for κ-carrageenan in KCl, with M_w increasing by 2 orders of magnitude.[26] The thermal hysteresis observed between heating and cooling κ-carrageenan in 0.1 mol dm^{-3} KCl (Figure 4) is characteristic of aggregating polysaccharides, in which alignment of the isolated helices pulls the equilibrium toward the ordered state, thus driving the much faster coil–helix equilibrium and decreasing the coil concentration.

Light-scattering measurements made on agarose sulfate above and below the temperature range of the conformational transition indicate that aggregate formation involves an average of two to three helices.[19] Thermal hysteresis is observed for agarose sulfate, and conventional optical rotation measurements made on the slow movement across the hysteresis loop (cf. process III of Figure 4) show second-order kinetics with a rate constant 8 orders of magnitude slower then the initial dimerization monitored by the stopped-flow method.[19] We have attributed the process to sequential aggregation of the form helix + helix → dimer; helix + dimer → trimer, etc.

As in the case of primary conformational ordering, the nature and concentration of added salt influence the extent of aggregation, with the sequence of cation stabilization of aggregates being $Me_4N^+ < Na^+ < K^+$.[14] For ι-carrageenan segments in a solution containing Me_4NCl there is no aggregation of the double helices, and only a single process is observed[18a] on the stopped-flow time scale or longer after making a salt jump. With the less highly charged κ-carrageenan segments, primary conformational ordering in the Me_4N^+ salt solutions is followed by a secondary process, again second order, with a rate constant 2 orders of magnitude slower than the initial dimerization.[18b,c] Photon correlation spectroscopy showed that the diffusion coefficient did not change during the secondary process. This is consistent with either annealing of mismatched helices or limited side-by-side aggregation, which occurs without increasing the average diameter of the diffusing species. From our measurements of the time-resolved optical rotation changes (cf. Figure 4) occurring in dilute solutions of the sulfated galactans, we would propose that the sequence and mechanism of conformational ordering (illustrated in Figure 6) is a fast conformational change in the disordered, single-chain form (I) followed by formation of double-helix dimers (II), which may then anneal and undergo slow lateral association into a thermodynamically more stable aggregate structure (III).

Conformational ordering and aggregation are promoted by increasing the ionic strength and thereby screening interchain repulsions. The higher the degree of sulfation of the galactans, the less the tendency to aggregate. Specific ion effects on aggregation may be due in part to the ease of packing the cations into lateral aggregates of polyanion double helices.

Kinetic techniques are now being applied to gel formation in polysaccharides, and the results should help toward understanding the links between primary structure, solution conformations, aggregation, and gelation processes. A schematic picture of a gel network in ι-carrageenan is shown in Figure 7. The junction zones are based on the aggregates discussed earlier with lateral association of double helices stabilized by incorporation of cations from the added salt. Cross-linking within the gel comes from the ability of the polysaccharides to participate in a number of aggregates. The tendency to aggregate in this manner results from the presence of some chain-kinking residues[3] that act to prevent the idealized ordered helix structure (Figure 2) together with the normally low cooperativity for helix formation observed for the carrageenans.

Gelation of carrageenans has been studied[27] by measuring the time required for the molecules to cross-link to a point where the molecular weight diverges to infinity to produce a three-dimensional network, which when inverted within a container has enough structure to resist the shear forces and remains intact. By analysis of the data in terms of initial rates, the dependence of the time taken to reach this point on the polysaccharide concentration can give the reaction order, n, in terms of number of chains involved in a junction zone. These are found to be 4 for ι-carrageenan and 16 for κ-carrageenan. A severe problem with these results is that the point at which a three-dimensional structure exists can correspond to a high extent of reaction for the particular concentration and temperature conditions. We are at present investigating whether these measurements have any significance and whether they can be related back to the molecules and molecular changes that occur on the milliseconds or seconds time scale. Time-resolved studies using light scattering and other physical techniques should yield evidence which will help in tying together these extremes of length and time scales.

Xanthan has been observed to aggregate at temperatures below T_m for conformational ordering, with an approximate doubling of M_w.[11] We have suggested that

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(26) Morris, E. R.; Rees, D. A.; Robinson, G. *J. Mol. Biol.* **1980**, *138*, 349.

(27) Oakenfull, D.; Scott, A., In ref 1, p 465.

the gel-like properties of these xanthan solutions may arise from lateral association of ordered chain sequences to form extended junction zones analogous to those in "true gels" but much weaker, so that the network structure is broken down under stress, allowing the solution to flow. It is interesting to speculate whether the cellulose backbone predisposes xanthan to single-helix formation in the process of primary conformational ordering and to rigid-rod-like behavior over a persistence length of more than 40 residues.[7,8] This would lead to an essentially one-dimensional structure even in a dimeric aggregate.

Conclusion

Scattering and rheological methods do not allow unambiguous determination of solution conformations of the ordered forms of aggregating polysaccharides used as food hydrocolloids. Kinetic studies of salt-induced transitions of these anionic biopolymers show that the primary process of conformational ordering can be readily separated from secondary aggregation and gelation. For the algal polysaccharides ι- and κ-carrageenan and agarose sulfate, ordering is a cooperative dimerization, with activation parameters for double-helix nucleation influenced by salt effects on the disordered form of the reactant. For the bacterial polysaccharide xanthan, both conformational equilibria and kinetics show that ordering is intramolecular and that single-helix and coil regions can be present at equilibrium within a single chain. Slow, secondary processes lead to sequential buildup of aggregates by lateral association of helices. Kinetic behavior may be correlated with primary structure, with the 1,3-glycosidic linkages in the algal polysaccharides predisposing the polymers to formation of hollow helices, and the β-1,4 link in xanthan to an extended ribbon structure.

Controlled Carbometalation as a New Tool for Carbon–Carbon Bond Formation and Its Application to Cyclization†

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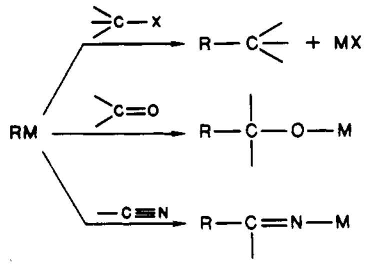
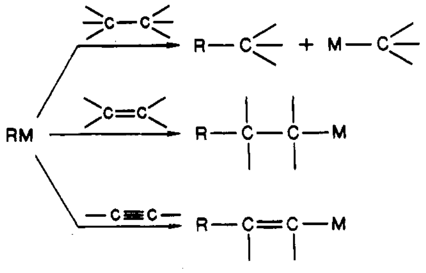
Carbon–carbon bond formation by means of organometallics has most commonly been achieved by their reactions with polar carbon electrophiles, such as those shown in Scheme I.[1] In search for new types of selective organometallic carbon–carbon bond forming reactions, it is of interest to consider the corresponding reactions of carbon–carbon bonds (Scheme II). In this Account, we are concerned about the addition reactions of organometallics with alkenes and alkynes, for which the term *carbometalation* has been suggested[2] and widely adopted.[3]

In principle, carbometalation may involve carbon–metal double and triple bonds, i.e., metal–carbene and metal–carbyne complexes, as well as metallacycles, such as metallacyclopropanes and metallacyclopropenes. Their carbometalation reactions with alkenes and alkynes are expected to proceed as shown in Scheme III. The products in Scheme III may further undergo carbometalation to produce 6-, 7-, and even higher membered metallacycles.

Scheme I



Scheme II



In fact, most of the processes shown in Schemes II and III have been observed and/or proposed, and carbometalation is indeed ubiquitous in organotransition-metal chemistry.[4] The Ziegler–Natta polymerization reaction[5] of alkenes catalyzed by an organoalane and titanium chloride, for example, is thought to be a car-

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† This Account is dedicated to Professor George Zweifel on the occasion of his 60th birthday.

(1) For a review, see: Negishi, E. *Organometallics in Organic Synthesis*; Wiley-Interscience: New York, 1980; Vol. 1.

(2) (a) Van Horn, D. E.; Negihsi, E. *J. Am. Chem. Soc.* 1978, *100*, 2252. (b) Negishi, E. *Pure Appl. Chem.* 1981, *53*, 2333.

(3) See, for example: Normant, J. F.; Alexakis, A. *Synthesis* 1981, 841.

(4) See, for example: Collman, J. P.; Hegedus, L. S. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valey, CA, 1980.

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