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Addition Reactions with Intramolecular Cyclisation

V.I.Staninets and E.A.Shilov (deceased)

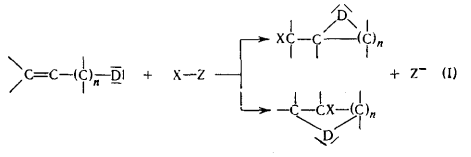
Heterolytic addition reactions in which the effect of the electrophilic agent on a double or triple bond leads to intramolecular cyclisation via an electron-donating group ("the AC reaction") are discussed. These reactions almost always give rise to five- and six-membered rings. Weak electrophilic agents form only cyclic adducts under the conditions of AC reactions, while strong electrophilic agents form, together with cyclic compounds, simple and mixed acyclic addition products. The formation of cyclic adducts is also promoted by the rigid structure of the unsaturated molecule and the nucleophilic properties of the electron-donating group.
The AC reactions obey the kinetic equations for second-order processes. They are distinguished from the analogous trimolecular acceptor-donor addition reactions by the synchronous occurrence of the electrophilic and nucleophilic stages in the elementary step, which is related to the steric conditions of ring formation.
The bibliography includes 124 references.

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I. INTRODUCTION. THE CONCEPT OF ADDITION REACTIONS WITH CYCLISATION

Reactions where the addition of an electrophilic agent X–Z to an unsaturated molecule containing an electron-donating group D is accompanied by the formation of a heterocycle via the mechanism (two possible modes of these reactions are shown)



(I)

are of particular interest. Unsaturated molecules in which the double bond is incorporated into a cyclic system and also compounds with a triple bond or with heteroatoms in the carbon chain react via mechanism (I). Addition reactions with cyclisation of this type will be referred to as AC reactions.

On the one hand AC reactions have found practical application in the synthesis of a wide variety of heterocyclic compounds. On the other hand, they are of considerable theoretical interest because their study can yield certain new information about heterolytic addition reactions.

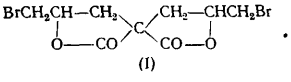
In the literature there are no reviews of reactions of this type—only individual cases and special relations in such reactions are noted in reviews on other topics, in particular those where the problem of "the effect of neighbouring groups" is discussed[1-5].

This review deals with the effect of the structure of the reactants on the nature of AC reactions, the relevant kinetic data are presented, and a general theoretical interpretation of these reactions is given.

The formation of lactones and other cyclisation reactions under the influence of acids are not discussed because they have been partly reviewed elsewhere[3,4] and because the extensive literature data on these reactions merit a discussion in a separate article.

II. STRUCTURAL FACTORS IN ADDITION REACTIONS WITH CYCLISATION

The intramolecular formation of cyclic species in addition reactions was first observed by Fittig and Hjelt[6] in the bromination of diallylacetic and diallylmalonic acids. Structural formulae with a five-membered ring were ascribed to the resulting bromolactones, for example structure (I) for the bromination product of diallylmalonic acid:

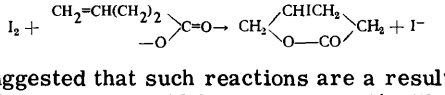


(I)

In order to account for the formation of bromolactones, Fittig and Hjelt assumed the intermediate formation of unstable dibromides, which cyclise with elimination of hydrogen bromide. We may note that similar hypotheses were also put forward subsequently in the discussion of the mechanism of AC reactions.

The intramolecular formation of cyclic species was observed also in the study of the reactions of allylureas and allylthioureas. When these compounds were brominated or iodinated, bromomethyl- or iodomethyl-oxazolidines and thiazolidines were obtained[7,11].

Bougault[12-14] made a detailed and systematic study of the formation of iodine-substituted lactones in the iodination of unsaturated carboxylic acids in aqueous potassium iodide and sodium bicarbonate solutions, i.e. under conditions where the acids are present in the form of anions, for example:



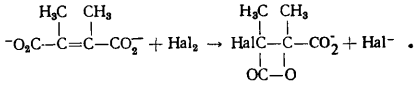
He also suggested that such reactions are a result of the addition of hypoiodous acid *in statu nascendi* with subsequent lactonisation of the resulting iodoxy-acid. He showed that only those unsaturated compounds whose structure allows the formation of a five- or six-membered

ring are capable of iodolactonisation reactions. Subsequently numerous examples showed that this rule is extremely general for AC reactions.

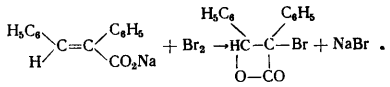
If the structure of the unsaturated molecule does not allow the formation of a five- or six-membered ring, then iodination under the conditions of the Bougault reaction does not occur at all or leads to unstable non-cyclic adducts—di-iodides and iodohydrins.

In particular, acrylate and crotonate anions and their substituted derivatives, the structure of which allows the formation of only four-membered rings, do not react with iodine. Octenic acids, and probably other unsaturated acids in which the electron-donating group is separated from the double bond by more than six atoms, do not form iodolactones [13,15].

However, it is noteworthy that the bromination or chlorination of unsaturated dimethylmaleate and dimethylfumarate anions leads to the rare case of the formation of a four-membered lactone [16]:

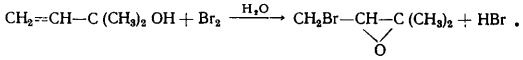


A similar four-membered lactone was obtained recently [7] by the bromination of the sodium and silver salts of *cis*- and *trans*-stilbene-2-carboxylic acids in carbon tetrachloride:



The reaction is accompanied by the formation of polymers and side products. The configuration of the resulting lactone was not indicated.

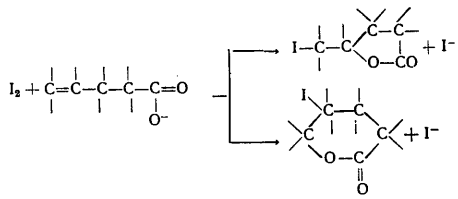
The formation of a three-membered ring was observed in the bromination of dimethylvinylmethanol [18]:



The exclusive formation of five- and six-membered rings in AC reactions has been used for the iodometric determination of $\beta\gamma$- and $\gamma\delta$-unsaturated acids in mixtures with acids having other structures [19]. The composition of mixtures of compounds containing *endo*- and *exo*-bridges (in the form of CH_2 and CH_2CH_2 groups) has been determined similarly [20-22]. Under certain conditions of analysis, only the *endo*-compounds are iodinated.

Bougault established that the derivatives of but-3-enoic acid (4-ethyl, 4-phenyl, 4-benzyl, 4-anisyl, 2,2-dimethyl, 2,4-diphenyl-, 2,2,4-trimethyl-, and other derivatives) form only five-membered iodolactones, in accordance with their structures [13]. Subsequently analogous iodolactones were obtained from 4-methyl-, 4-vinyl-, and 4-ethyl-pent-3-enoic acids [15,23,24]. However, unsubstituted but-3-enoic (vinylacetic) acid reacts with difficulty and, as shown recently [24], forms iodine-free furanones (4-hydroxy-2-oxotetrahydrofuran, its vinylacetic ester, and 2-oxo-3,4-dihydrofuran). These compounds are probably formed as a result of the hydrolysis and elimination of hydrogen iodide from the intermediate iodo-adducts.

Compounds with the structure of pent-4-enoic (allylacetic) acid can form both five- and six-membered rings:



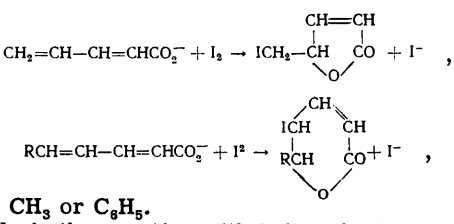
Few reliable data have been published on the mode of cyclisation in those reactions where there is a possibility of the formation of both five- and six-membered rings. In many cases the structures of the resulting cyclic adducts were not established or are only tentatively indicated. This is because the chemical methods for distinguishing five- and six-membered rings are fairly laborious. At the present time spectroscopic methods (infrared and NMR spectroscopy) are being used with great success [25-27].

It has been shown [23] that on iodination unsubstituted pent-4-enoic acid forms only a five-membered iodolactone†. Five-membered iodolactones are also formed from 1- and 3-cyclohexenylacetic acids [23]. However, hex-4-enoic acid gives rise to a six-membered iodolactone [24]. Iodination of *cis*-cinnamylacetic acid results in the formation of a five-membered lactone, while its *trans*-isomer gives a mixture of compounds with five- and six-membered rings [28].

The addition of electrophilic agents in AC reactions involving the competing formation of five- or six-membered rings in general takes place in accordance with the Markovnikov rule. However, the mode of reaction depends not only on the electronic nature of the substituents at the C=C bond but also on the steric effects of these substituent on the stabilisation of the cyclic transition state and on the nucleophilic properties of the electron-donating end of the unsaturated molecule. Therefore an exact prediction of the structure of the AC reaction product is not always possible.

Especially little is known about the effect of electron-accepting groups at the C=C bond on the mode of cyclisation. This is because electron-accepting substituents greatly hinder or even prevent the addition of weak electrophilic agents via the AC reaction mechanism.

If the unsaturated chain of the compound iodinated contains two conjugated double bonds, the rule of the formation of a five- or six-membered ring holds, but the iodocyclisation reaction is retarded [24]. The vinylacrylate anion gives the iodolactone with the dihydrofuran structure and hexa-2,4-dienate (sorbate) and 5-phenylpenta-2,4-dienate anions form six-membered rings on iodination [24]:



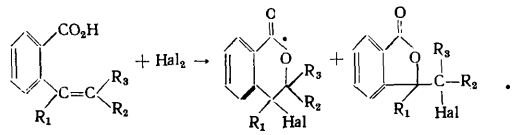
where R = CH_3 or C_6H_5.

Evidently in the reaction with iodine the terminal carbon atom is more active in the CH_2=CH group, while in the RCH=CH group the electrophilic agent acts upon the

† Bougault suggested that the iodolactone from allylacetic acid has a pyran structure [13]. This error was amended by van Tamelen and Shamma [23].

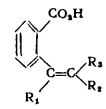
neighbouring carbon atom and ring closure occurs at the atom linked to the R group. Thus the rule established for allyl derivatives holds for compounds with conjugated double bonds.

If the hydrogen atoms in *o*-vinylbenzoic acid are substituted by alkyl groups, iodination results in the formation of both five- and six-membered iodolactones or their mixture:



Berti and coworkers[29-35] investigated the chlorination of 2-vinylbenzoic acids in carbon tetrachloride and in water and their bromination in chloroform and acetic acid. Their results are presented in Table 1, which shows that the accumulation of substituents at the terminal atom of the vinyl group leads to the formation of a six-membered ring, while substitution at the neighbouring atom promotes the formation of the furan ring.

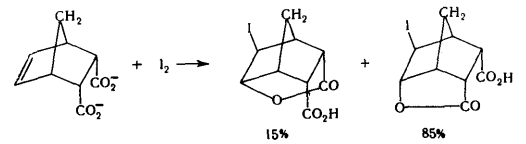
Table 1. Mode of halogenocyclisation of 2-vinylbenzoic acids[35]



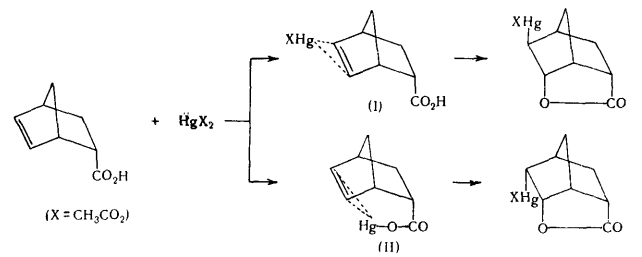
R_1	R_2	R_3	No. of units in ring after reaction with Cl_2	No. of units in ring after reaction with Br_2	R_1	R_2	R_3	No. of units in ring after reaction with Cl_2	No. of units in ring after reaction with Br_2
CH_3	H	H	5	5	H	CH_3	CH_3	6	—
C_6H_5	CH_3	H	5	5	H	C_6H_5	H	6	6
iso-C_3H_7	CH_3	CH_3	6	6	CH_3	C_6H_5	H	5+6	—

The effect of geometrical isomerism on the formation of five- and six-membered iodolactones was investigated in the iodocyclisation of cinnamylacetic acid and its $\beta\beta'$-disubstituted derivative[28]. *cis*-Cinnamyl acetic acid forms only a five-membered adduct, while the *trans*-isomer gives a mixture of five- and six-membered iodolactones; *cis*-$\beta\beta'$-dimethylcinnamylacetic acids gives rise to a mixture of both products and the *trans*-isomer only the six-membered iodolactone.

AC-reactions have the same fundamental mechanism (I) also in those cases where the double bond is in a ring, provided that the formation of a five- or six-membered ring is possible. Examples of such reactions are known for tetrahydrobenzoic[19,21-23,36] and tetrahydrophthalic acids; their bridged derivatives[37-51], and dihydronaphthoic[52] and cyclohexenylacetic acids[13,23,53]. Iodination and mercuration of these compounds in an aqueous medium usually results in the formation of five-membered rings even in those cases where the structure of the compounds allows the formation of a six-membered ring[24]. A mixture of five- and six-membered iodolactones is obtained in the iodination of *cis*-3,6-*endo*-methylene-Δ^4-tetrahydrophthalate salts[49]:

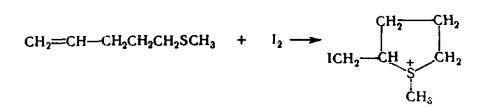


The formation of a mixture of stereoisomeric five-membered lactones in the mercuration of 2,5-*endo*-methylene-Δ^3-tetrahydrobenzoic acid with mercury acetate was noted[54]. The authors explained the formation of the five-membered *cis*-mercurilactone by the intermediate formation of the complex (II):



In contrast to the *endo*-series, unsaturated acids of the *exo*-series do not form lactones on iodination or mercuration, probably because the carboxylate ion is sterically hindered by the methylene group[21,22,43,49,54].

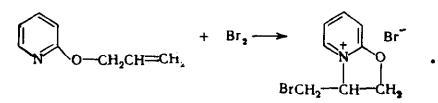
The general rules for AC reactions operate also in those cases where the ring closure does not take place via the carboxylate group but via another electron-donating group. $\gamma\delta$-Unsaturated alcohols, sulphides, and amines give rise on iodination or bromination to five-membered tetrahydrofuran, tetrahydrothiophen, and tetrahydropyrrole derivatives[15,55,56], for example:



o-Allylphenol and 2-allyl-4,6-dichlorophenol form iodomethylbenzotetrahydrofurans. α-(ω-Butenyl)pyridine is converted into 2-iodomethyl-1,5-pyridopyrrolidinium iodide[56].

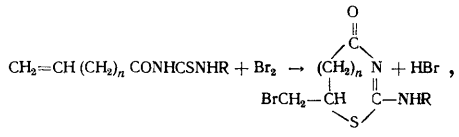
When the chain of the unsaturated molecule contains a heteroatom or a group Δ = O, S, or NH, the iodocyclisation reactions become relatively hindered and in many cases acyclic addition or substitution takes place[57-60]. The compounds $CH_2{=}CHCH_2{-}\Delta{-}CH_2CO_2^-$ and $CH_2{=}CHCH_2{-}\Delta{-}CH_2CH_2N(CH_3)_2$ give rise only to six-membered adducts[57]. It is interesting that a seven-membered ring is not formed on iodination even in those cases where the structure of the initial compound promotes its formation. Thus iodination of the allyloxy-β-propionate ion does not give a cyclic adduct, which could have been only seven-membered in this case[57]. Allyloxymethylamines are iodinated with formation of five-membered rings[61].

When α-allyloxy- and α-allyl-aminopyridines are brominated[56], the closure of the five-membered ring takes place at the nitrogen atom:



There exist examples of ring closure in addition reactions at chains containing several heteroatoms. Thioureas

acylated by residues of $\alpha\beta$-, $\beta\gamma$-, and $\gamma\delta$-unsaturated carboxylic acids react with bromine in carbon tetrachloride and chloroform via the mechanism[62,63]

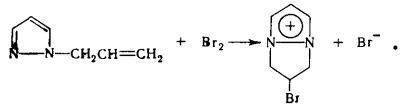


where R=H, alkyl, or aryl and n = 0, 1, or 2.

An interesting case of the formation of a seven-membered ring[63,64] (4-thiazepinone) with n = 2 has been described.

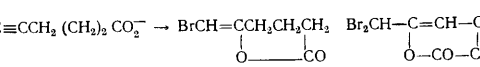
These bromocyclisation reactions are accompanied by the addition of bromine at the double bond, but in the formation of a five-membered thiazoline ring (n = 0) there are no dibromides in the reaction products or their amount is very small, while in the case of larger rings the yield of dibromide is appreciable.

The bromination of 1-allylpyrazole results in a derivative of 3a,6a-diazapentalene[65,66]:

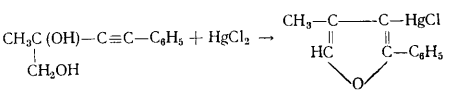


Not many AC reactions for compounds with a triple bond are known. The replacement of a double bond by a triple bond leads to the retardation of the reaction, but in all probability the general rules of AC reactions remain in force. As a result of addition, a compound with an electron-donating group at the double bond is formed in the first stage. This frequently leads to further reactions.

The iodination of propargylacetic and propargylmalonic acids stops at the stage involving the formation of an unsaturated, probably five-membered, lactone[15,67]. In the bromination of hex-5-ynoic acid[68] the reaction proceeds further and yields an unsaturated dibromide:



Primary-tertiary and secondary-tertiary butynediols are converted by mercury(II) chloride into chloromercurifurans[69-72]:



Amines and oxamines containing the propargyl group, $HC\equiv C-CH_2OCH_2NHR$, $HC\equiv C-CH_2OCH_2NR_2$, and $HC\equiv C-CH_2(CH_2)_2NR_2$, also cyclise to five-membered ring compounds on bromination and iodination[61].

III. EFFECT OF THE NATURE OF ELECTRON-DONATING GROUPS AND X–Z ELECTROPHILIC AGENTS IN ADDITION REACTIONS WITH CYCLISATION

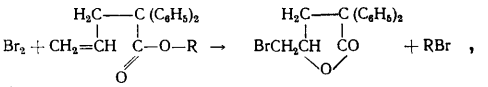
1. Electron-donating Groups

Ring closure in addition reactions takes place with participation of various electron-donating groups: OH, RO^-, NH_2, NHR, NR_2, –SR, CO_2^-, CO_2H, COOR, $\rangle C{=}O$, $CONR_2$, $CSNR_2$, etc. The capacity of these groups for ring closure depends on their nucleophilic properties. Weakly nucleophilic electron-donating groups, for example RSO_3^-, are incapable of ring closure on iodination[15,73]. However, under the influence of powerful electrophilic agents (bromine and chlorine), the same unsaturated sulphonate salts form sultones[74].

Unsaturated amines cyclise only in the form of the free bases with formation of ammonium salts[15,75].

Phenoxides react much more readily than the free phenols[15,76,77], but in the case of unsaturated alkoxides ring closure was not observed, probably owing to the low concentration of the alkoxides in aqueous solutions at low pH.[76,78,79] The free carboxy-group can participate in ring closure, but the conjugate carboxylate anions react much more readily. Therefore it sometimes happens that in aqueous solutions of unsaturated acids the anion and not the undissociated acid itself reacts with the electrophilic agent.

It is remarkable that, under the influence of powerful electrophilic agents, even the ester group can form a lactone with elimination of an alkyl halide[80-83]:



The iodination of the amides of unsaturated carboxylic acids in acidic and neutral aqueous solutions results in the formation of lactims, while in alkaline solutions the products are lactams[15,84-87]. When 2,2-disubstituted allylacetonitriles are brominated in chloroform, lactims are formed together with dibromides[85]. On bromination, allylacetamidomalonic ester yields 6-bromomethyl-4,4-diethoxycarbonyl-2-methyl-5,6-dihydro-1,3-oxazine dibromide[86].

The bromination of allylureas gives 5-bromomethyl-Δ^2-oxazolines together with dibromides[9,88-91]. In contrast, allylthioureas form on bromination and iodination only 5-bromomethyl-Δ^2-thiazolines[7,8,10,11,92-94].

Probably many other electron-donating groups can also participate in AC reactions (for example the epoxy-, N-oxide, oxime, etc. groups, which have not yet been investigated).

Williams et al.[95] recently published a paper in which the results of a study of the bromination and iodination of the alcohols $CH_2{=}CH(CH_2)_nOH$, where n = 1, 2, 3, or 4, are presented. They show a close analogy between the reactions of these alcohols and the halogenation of the acids $CH_2{=}CH(CH_2)_{n-1}CO_2H$. In particular, the maximum rate occurs with n = 3, which corresponds to the formation of a five-membered ring. Bromination results in a mixture of cyclic and non-cyclic addition products (50–60% of cyclic products with n = 3, 5–10% with n = 4, and 0% with n = 1 or 2). Iodination of the alcohols with n = 3 and 4 gives only the cyclic adducts. The quantitative characteristics of the involvement of electron-donating groups in ring closure will be presented in the discussion of the kinetic relations in AC reactions.

2. Electrophilic Agents

Among the known electrophilic agents, iodine, bromine, chlorine, iodine chloride, cyanogen iodide, hypochlorous acid, mercury salts, peracids, 2,4-dinitrosulphenyl chloride, and tellurium and selenium compounds have been investigated in AC reactions. Strong acids can also behave as electrophilic agents in AC reactions but, as already stated, such reactions are not discussed in this review.

Certain electrophilic agents, for example $SnCl_4$, ArN_2^+, etc., have not been tested in AC reactions.

The mode of addition depends on the differences between the electrophilicities of the reactants. Weak electrophilic agents (I_2, $HgCl_2$) often react wholly via the AC reaction mechanism. This applies particularly to those cases where the electrophilic agent (for example I_2 in aqueous KI solutions) is altogether incapable of adding to unsaturated molecules via the usual mechanism. Strong electrophilic agents show a greater tendency to form non-cyclic adducts, particularly in non-aqueous solvents.

According to the literature, in the bromination of many unsaturated acids in non-ionising solvents only the dibromides were isolated even in those cases where bromolactones could have been formed. Incidentally, it is possible that in some cases small amounts of cyclic adducts escaped the notice of investigators.

According to Berti's data, the bromination of *cis*- and *trans*-stilbene-2-carboxylic acids gives a mixture of dibromides and bromolactones. The mixture compositions are different for the two stereoisomers and depend on the nature of the solvent. In particular, the reaction of the *cis*-acid with bromine in carbon tetrachloride results in the almost exclusive formation of the dibromide, while in chloroform the product is mainly the bromolactone.

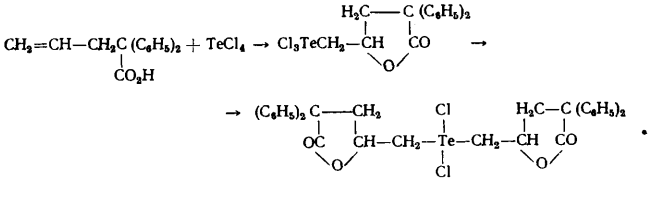
It is interesting that the chlorination of these acids in acetic acid as well as in chloroform and carbon tetrachloride leads to quantitative formation of the chlorolactones.

Data are available on the relative amounts of the cyclic and non-cyclic adducts in the chlorination and bromination products of certain unsaturated compounds in an aqueous medium[96]. Table 2 shows that, when salts of unsaturated acids are brominated and chlorinated, the yield of the halogenolactones is much lower than in iodination, since their iodination takes place with quantitative formation of iodolactones alone. In the reactions with chlorine the amount of lactones formed is much less than in the reactions with bromine (in contrast to Berti's observations in non-aqueous solvents).

Table 2 also shows that compounds with rigidly fixed reaction centres such as the anions of 3,6-*endo*-methylene-Δ^4-cyclohexene-1,2-dicarboxylic acids give higher yields of halogenolactones on chlorination and bromination than the anions of Δ^4-cyclohexene-1,2-dicarboxylic acids, the structure of which permits the inversion of the cyclohexene ring.

Electrophilic agents can participate in AC reactions in different forms. Thus it has been shown that mercury(II) chloride reacts both as $HgCl_2$ and $HgCl^+$, the chloromercury cation being 120 000 times more active than the neutral molecule[97,98]. Moreover, iodine never participates in AC reactions as the iodine cation (more precisely its complex with the substrate molecule), although this form of iodine is the most important active agent in aromatic substitution reactions[99].

Among complex electrophilic agents, 2,4-dinitrobenzenesulphenyl chloride, which readily adds to unsaturated molecules via the usual mechanism but can participate also in AC reactions, is of interest. Tellurium tetrachloride forms 1 : 2 cyclic adducts with $\alpha\alpha'$-diphenylallylacetic acid:



Unsaturated carboxylic acids also cyclise when acted upon by ring-substituted phenylselenium bromides and β-naphthyltellurium iodides[100,101].

In the reaction with peracids as electrophilic agents *cis*- and *trans*-stilbene-2-carboxylic acids are converted into mixtures of epimeric five- and six-membered hydroxylactones[32], for example:

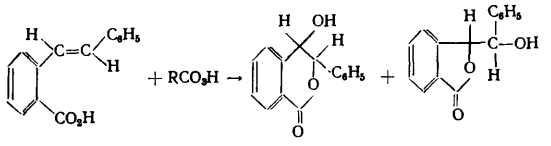
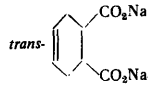
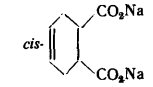
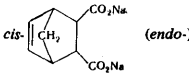
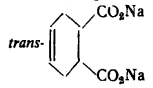
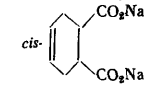
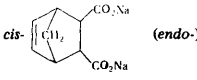


Table 2. Composition of the halogenation products of the sodium salts of unsaturated carboxylic acids in aqueous solutions at 25 °C (according to the data of Staninets et al.[96]).

Halogenating agent and unsaturated acid salt	Yield, %		
	halogeno-lactone	dihalide	halogeno-hydrin
Br, Br_2			
CH_2=CHCH$_2$CH$_2$CO$_2$Na	38	4	58
CH_2=CHCH$_2$CH$_2$CH$_2$CO$_2$Na	19	5	76
CH_2=CHCH$_2$OCH$_2$CO$_2$Na	7	8	85
trans-C_6H_5CH=CHCH=CHCO$_2$Na	0	8	92
trans- 	23	3	74
cis- 	64	3	33
cis-  (*endo*-)	86	7	7
Cl, Cl_2			
trans- 	5	4	91
cis- 	45	—	55
cis-  (*endo*-)	83	8	9

Under the influence of peracids, unsaturated polycyclic carboxylic acids and *o*-allylphenol also participate in AC reactions[102-106].

IV. KINETICS OF ADDITION REACTIONS WITH CYCLISATION

Among AC reactions, the kinetics of iodocyclisation have been investigated in greatest detail. This reaction is very convenient for kinetic studies because it occurs at a measurable and readily controlled rate, is not accompanied by side reactions, and its rate can be readily followed by measuring the decrease in the iodine titre.

The rate of AC reactions with bromine and chlorine are usually too high for measurements by the usual kinetic methods and, moreover, they are accompanied by addition and substitution side processes.

The qualitative kinetic characteristics of iodocyclisation were obtained comparatively long ago. In 1960 de Moura Campos published a series of studies on the rates of iodination of alkyl- and allyl-substituted allylacetic acids [83,107]. However, these were preliminary investigations.

The kinetics of the iodocyclisation of unsaturated compounds of different structures and containing electron-donating groups have been investigated very thoroughly by Shilov and coworkers [15,49,58-61,62,75-77,108-112]. These kinetic measurements were made largely in aqueous solutions.

It was established that all the iodocyclisation reactions investigated obey the simple equation for second-order processes:

$$-\frac{d[I]}{dt} = k[M][I_2] \ ,$$

where [M] is the concentration of the unsaturated compound in its active form, (I) is the analytical concentration of iodine, and $[I_2]$ is the concentration of molecular iodine not bound in the complex I_3^-.

Table 3. The rate constants $k_{20°}$, activation energies $\Delta E^{\neq}$, and the logarithms of the pre-exponential factor $\lg A$ for the iodolactonisation of acid anions with a single multiple bond [15].

Substrate	$k_{20°}$, litre mole^{-1} s^{-1}	$\Delta E^{\neq}$, kcal mole^{-1}	$\lg A$
(I) $CH_2{=}CHCO_2^-$	0	—	—
(II) $CH_3CH{=}CHCO_2^-$	0	—	—
(III) $CH_3{=}CHCH_2CO_2^-$	(0.01)	21	14
(IV) $CH_2{=}CH(CH_2)_2CO_2^-$	84	13.5	11.8
(V) $CH_2{=}CH(CH_2)_3CO_2^-$	10.9	13.2	10.9
(VI) $CH_2{=}CH(CH_2)_4CO_2^-$	0.17	13.2	9.1
(VII) $CH_2{=}CH(CH_2)_5CO_2^-$	0	—	—
(VIII) $CH_3CH{=}CHCH_2CH_2CO_2^-$	142	12.3	12.3
(IX) $C_6H_5CH{=}CHCH_2CH_2CO_2^-$	61	14.8	12.8
(X) o-$CH_2{=}CHC_6H_4CO_2^-$	3.1	16.4	13
(XI) o-$CH_3CH{=}CHC_6H_4CO_2^-$	5.3	16.3	13
(XII) $CH_2{=}CHCH_2CH(CO_2)_2^-$	169	13.5	12
(XIII) $CH{\equiv}C(CH_2)_2CO_2^-$	1.2	14.1	11
(XIV) $CH{\equiv}CCH_2CH(CO_2)_2^-$	3.6	13.9	10
(XV) $CHCl{=}CH(CH_2)_3CO_2^-$	0.025	17.2	11

The constant k depends on the structure, configuration, and conformation of the molecule cyclised, on the reactivity of the multiple bond in relation to electrophilic agents, and on the nucleophilic properties of the electron-donating group D.

Table 3 demonstrates the effect of structural factors in the iodocyclisation of unsaturated carboxylic acid anions‡ in aqueous potassium iodide solutions. It shows that the tendency towards iodocyclisation is shown almost exclusively by compounds with a structure which can give rise to five- and six-membered rings. The formation of the seven-membered iodolactone (VI) is already 70 times slower than that of the six-membered lactone (V) and the rate of formation of rings with more than seven members or less than five members is virtually zero.

The replacement of a hydrogen atom at the extreme carbon atom in the $CH_2{=}CH$-group by an alkyl group appreciably accelerates the iodination [compounds(IV)–(VIII)], while substitution in C_6H_5 has only a slight effect [compound (IX)]. When the benzene ring is incorporated in the chain undergoing closure, the reaction is greatly retarded [compounds (X) and (XI)]. A chlorine located at the double bond also greatly retards the reaction [compound (XV)].

Table 4. The rate constants $k_{20°}$, activation energies $\Delta E^{\neq}$, and the logarithms of the pre-exponential factor $\lg A$ for the iodolactonisation of the anions of alkenoic and alkadienoic acids [112].

Iodinated anion	$k_{20°}$, litre mole^{-1} s^{-1}	$\Delta E^{\neq}$, kcal mole^{-1}	$\lg A$
$CH_2{=}CHCH{=}CHCO_2^-$	0.034	18.5	15.3
$CH_2{=}CHCH_2CH_2CO_2^-$	84	13.5	12.0
$CH_3CH{=}CHCH{=}CHCO_2^-$ (*trans, trans*)	0.062	17.2	14.6
$CH_3CH{=}CHCH{=}CHCO_2^-$ (*trans, cis*)	6.6	14.0	11.1
$CH_3CH{=}CHCH_2CH_2CO_2^-$	142	12.3	12.3
$C_6H_5CH{=}CHCH{=}CHCO_2^-$	0.027	20	15.4
$C_6H_5CH{=}CHCH_2CH_2CO_2^-$	61	14.8	12.8
$CH_2{=}CHCH{=}CHCH_2CO_2^-$	0.95	16.2	12.1
$CH_2{=}CHCH_2CH_2CH_2CO_2^-$	12	13.6	11.1

The experimental data in Table 4 make it possible to estimate the effects of conjugated double bonds on reactivity. Comparison of the rate constants k for the iodocyclisation of acids with a single double bond in Table 3 with the rate constants for the reactions of compounds with analogous structures listed in Table 4 shows that the compounds containing conjugated double bonds are less active by approximately three powers of 10 than their non-conjugated analogues. This retardation is associated with the increase of activation energy. The compensation by the entropy factor is insufficient.

In a series of studies [19,109-111] the changes in reactivity with increase of the rigidity of the molecular structure were investigated. The mono- and di-anions of Δ^4-tetrahydrophthalic acids (I) and (V) and their bridged derivatives (II)–(VII) were iodinated under identical conditions (Table 5).

In almost all cases the reaction leads to the formation of a five-membered iodolactone. The dianion of unsubstituted tetrahydrophthalic acid is iodinated 50 times faster than the monoanion but more slowly than the allylacetate anion (Table 2). When the molecule contains an *endo*-ethylene group [compounds (II) and (VI)], the rate of iodination of the monoanion is 85 times higher than that of its analogue without an inner bond. If the molecule contains a methylene bridge [compounds (III) and (IV)], the rate of iodination increases very greatly: by 4 powers of 10 for the *trans*-isomer and even more for the *cis*-derivative.

We may note that the activation energies in iodolactonisation reactions of monoanions for compounds with a

‡ With the exception of α-alkyl-substituted allylacetate ions discussed in a separate section below.

methylene bridge are lower by 3 kcal mole^{-1} than for the monoanions of compounds without a bridge or with an *endo*-ethylene bridge. The activation energy falls to the same extent on passing from monoanions to dianions [compounds (I)–(V) and (II)–(VI) in Table 5].

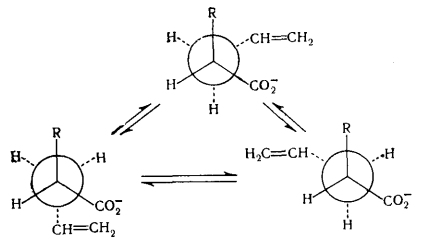
The increase of the rate of iodocyclisation is caused both by the decrease of $\Delta E^{\neq}$ and the increase of the entropy of activation. Consequently there is no "compensation effect" in these systems.

Table 5. Kinetic data for the iodolactonisation of Δ^4-tetrahydrophthalate anions and their bridged derivatives [110].

Compound iodinated	Reaction rate constant $k_{20°}$, litre mole^{-1} s^{-1}	Activation energy $\Delta E^{\neq}$, kcal mole^{-1}	Activation entropy $\Delta S^{\neq}$, e.u.
Acid monoanions			
(I) *cis*-Δ^4-Tetrahydrophthalate	0.4	13.8	24.5
(II) *cis*-3,6-*endo*-Ethylene-Δ^4-tetrahydrophthalate	34	13.7	15.8
(III) *trans*-3,6-*endo*-Methylene-Δ^4-tetrahydrophthalate	4340	10.6	7.6
(IV) *cis*-3,6-*endo*-Methylene-Δ^4-tetrahydrophthalate	15 200	10.9	4.2
Acid dianions			
(V) *cis*-Δ^4-Tetrahydrophthalate	21	10.6	18.4
(VI) *cis*-3,6-*endo*-Ethylene-Δ^4-tetrahydrophthalate	350	10.8	11.8
(VII) 3,6-*exo*-Methylene-Δ^4-tetrahydrophthalate	0	-	-

The *exo*-isomer (VII) is not iodinated at all, which can be readily accounted for by the steric hindrance at the carboxylate ion due to the bridge.

A relation between the rate of iodolactonisation and the proportions of the conformers of the compounds has been established for the anions of α-alkyl-ω-pentenoic acids. These acids exist in cisoid and transoid forms, between which an equilibrium is established, whose position depends on the structure of the compound:



cisoid form transoid form

The constants for the equilibrium between the conformers were calculated using an additive method [112]. The rates of iodolactonisation were measured in the usual way for a number of acids [111]. The results of the kinetic measurements and calculations are presented in Table 6.

Evidently the introduction of an alkyl group in the α-position of allylacetic acid increases the rate of iodination and to a greater extent the more branched is the group. This acceleration corresponds to the content of the *cisoid* conformer in the equilibrium mixture. If the iodination rate constant is referred to the content of the *cisoid* conformer, the calculated values of k_{cis} are found to be constant for all the acids investigated.

Evidently the anions of unsaturated carboxylic acids are iodolactonised only in the cisoid form.

The study of the kinetics of the iodocyclisation of compounds with a heteroatom Δ = O, S, or NH in the unsaturated chain showed that the replacement of a CH_2 group by O, S, or NH retards the reaction (Table 7). [57,59]

Table 6. Dependence of the rate constant for the iodolactonisation of α-R-allylacetate anions on the concentration of their cisoid conformers.

R	$k_{20°}$, litre mole^{-1} s^{-1}	Cisoid conformer, %	$10^{-3}k_{cis}$, litre mole^{-1} s^{-1}
H	84	7	1.21
CH_3	420	35	1.20
C_2H_5	500	40	1.25
n-C_3H_7	500	40	1.25
CH_2=$CHCH_2$	440	40	1.10
n-C_4H_9	560	46	1.22
i-C_3H_7	940	75	1.25
sec.-C_4H_9	980	80	1.28
tert.-C_4H_9	1340	88	1.37
		Mean	1.2

Shilov and Tsegel'nyuk [59] explained these changes in reactivity by the lowering of the mobility of the chain undergoing ring closure in the series O < S < NH < CH_2. The absolute values of k and $\Delta E^{\neq}$ naturally depend also on the electronic effects of the heteroatom.

Table 7. Rate constants and activation energies for the iodocyclisation of compounds with the structure [59]

$$CH_2{=}CHCH_2{-}\Delta{-}CH_2CO_2^-.$$

Δ	$k_{30°}$, litre mole^{-1} s^{-1}	$\Delta E^{\neq}$, kcal mole^{-1}	lg$A$	$\Delta S^{\neq}$
O	0.14	14.5	8.63	−3.28
S	0.45	15.8	11.1	−9.79
NH	6.98	17.1	14.3	+4.58
CH_2	22.4	13.1	10.0	−10.9

The most important characteristic of the electron-donating group in the kinetics of AC reactions is its nucleophilicity. This relation can be followed in a series of kinetic experiments on the iodination of unsaturated compounds the chain structure of which remains unchanged and only the component D is varied [15,61,75,77].

Table 8 presents the results of the measurements of the rate constants for iodocyclisation in a group of unsaturated compounds, which leads to the formation of five-membered heterocycles.

Table 9 presents data on the kinetics of the iodination of substituted 2-allylphenols via the mechanism

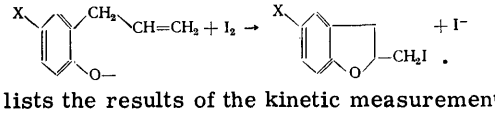


Table 10 lists the results of the kinetic measurements for the iodocyclisation of unsaturated compounds in which the electron-donating groups differ markedly not only in basicity but also in chemical structure. Tables 8–10 list

the pK_a values for the compounds undergoing iodocyclisation as the characteristics of their nucleophilic properties. Evidently the reactivity of the molecules increases with the pK_a.

While the weakly basic SO_3^- group in butene-ω-sulphonate does not participate in the iodocyclisation reaction, the rate constants for the iodination of the strongly basic ω-pentenylamines reach values of 10^5 litre $mole^{-1}$ s^{-1}. For substituted allylphenols, where the variation of basicity is not so great (Table 9), the correlation between the iodocyclisation rate constants and the pK_a is described by the Hammett equation.

Table 8. Rate constants for the iodination of the ω-butenyl derivative[15]

$CH_2=CHCH_2CH_2-R.$

R	$k_{20°}$, litre $mole^{-1}$ s^{-1}	$\Delta E^{\neq}$, kcal $mole^{-1}$	lgA	pK_a
SO_3^-	0	—	—	—
CH_2SCH_3	0.003	17.3	8.0	—
$CONH_2$	0.67	12.2	8.9	−0.4
CH_2OH	1.47	8.9	7.8	—
CH_2NH_2	$1.4\cdot10^5$	2.8	7.2	10.5
CH_2NHCH_3	$2.3\cdot10^5$	1.6	6.7	10.1
$CH_2N(CH_3)_2$	$1.8\cdot10^5$	1.9	7.2	10.3

At the same time comparison of the above tables shows that some of the compounds iodinated have the same or similar pK_a's but the rates of their cyclisation differ markedly. This is not surprising, since the rate of AC reactions does not depend on the basicity of the D component alone.

Other factors which determine the reactivity of the electron-donating component of unsaturated compounds in AC reactions are polarisation, steric, etc. factors which characterise its intrinsic nucleophilicity.

Table 9. Rate constants for the iodination of the ions of X-2-allylphenols[77].

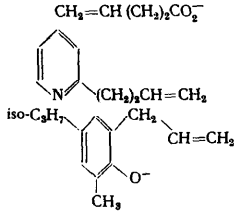
X	$k_{20°}$, litre $mole^{-1}$ s^{-1}	$\Delta E^{\neq}$, kcal $mole^{-1}$	lgA	pK_a
4-Nitro	46	5.2	5.5	7.1
4-Phenylazo	80	5.0	5.5	7.4
4,6-Dichloro	170	3.2	4.6	8.5
4-Chloro	176	3.8	5.3	9.3
4-Bromo	180	4.0	5.5	9.4
4-Methyl	360	3.4	5.2	10.1
4-Methoxy	420	3.2	5.1	10.3

Tables 8 and 9 show that, for the same or similar reaction series, the observed variation of the iodocyclisation rate constant depend mainly on the activation energy, since the activation entropy and the corresponding frequency factors are fairly constant, particularly for allylphenols. For a given reaction series, the relation between the cyclisation rate constant and the nucleophilicity of the electron-donating component is expressed in the fact that the more nucleophilic is the electron-donating component of the unsaturated molecule, the higher is the rate constant and the lower the activation energy.

In the cyclisation of unsaturated compounds the electron-donating components of which differ greatly in chemical structure (Table 10), this relation is less distinct.

Analogous kinetic relations are observed also in the chloromercuration of 2-allylphenols and unsaturated alcohols[97,98]. Phenoxide anions are more reactive in these processes by three powers of 10 than the free phenols.

Table 10. Activation parameters and rate constants for AC reactions.

Compound iodinated	$k_{20°}$, litre $mole^{-1}$ s^{-1}	$\Delta E^{\neq}$, kcal $mole^{-1}$	$\Delta S^{\neq}$, e.u.	lgA	pK_a	Refs.
$CH_2=CH(CH_2)_2CO_2^-$	84	13.5	−5.58	11.2	4.68	15
	173	7.2	−23.7	7.8	8.03	75
	7770	1.7	−35.8	5.1	10.1	77

Interesting experimental data have been obtained, which make it possible to compare the rates of chloromercuration in AC reaction and non-cyclic addition reactions. It has been established that the rate constant k for chloromercuration at 25°C by $HgCl_2$ is 450 times higher for pent-1-en-5-ol than for its methyl ether[98].

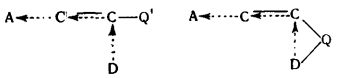
V. THEORETICAL DISCUSSION OF ADDITION REACTIONS WITH CYCLISATION

AC reactions are a variety of addition reactions of a general type involving, apart from the unsaturated molecule, electron-accepting and electron-donating agents, the transition state of which may be described by the scheme D → M → A.[113-115] A characteristic feature of AC reactions is that the nucleophilic component D is linked by a valence bond to the M molecule and therefore the reaction is bimolecular in relation to the addition of the electrophilic agent and intramolecular in relation to the nucleophilic agent§.

§ Previously it was postulated (see, for example, Refs. 6 and 13) that the formation of a ring in addition reactions takes place in two consecutive stages: the product of direct addition of the electrophilic agent to the multiple bond is formed initially and then ring closure takes place as a result of an exchange reaction between the added atom and the electron-donating end of the molecule.

Linstead and May[19] were the first to point out that the mechanism involving simultaneous addition and ring closure is more likely. It is not difficult to demonstrate that the hypothesis of a general two-stage exchange cyclisation mechanism is erroneous. In fact in many cases analogous intermolecular reactions involving addition to multiple bonds do not occur at all and, when direct addition products can be observed (for example, vicinal dibromo-substituted acids), they prove to be stable and their cyclisation is much slower than the corresponding AC reaction. In particular, certain characteristics of chloromercury-cyclisation suggest this hypothesis[69,97,98]. Such reactions evidently cannot be included in the category of AC reactions.

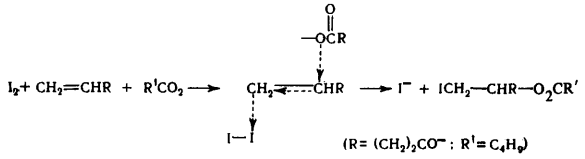
This difference between the transition states can be represented by the scheme



intermolecular reaction AC reaction

As a result of the intramolecular addition mechanism, AC reactions (in which five- or six-membered rings may be formed) sometimes take place much faster than the analogous trimolecular reactions[114-116]¶.

The addition reactions occurring under the influence of weak electrophilic agents, in particular iodine, are especially instructive in this respect. In many such cases trimolecular addition reactions do not occur at all. For example, as already noted, the allylacetate ion readily forms 5-iodo-4-valerolactone under the influence of iodine in aqueous potassium iodide solution. This reaction would correspond to a trimolecular mixed compound involving the anion of allylacetic or other carboxylic acid formed via the mechanism



$(R = (CH_2)_2CO^-;\ R' = C_4H_9)$

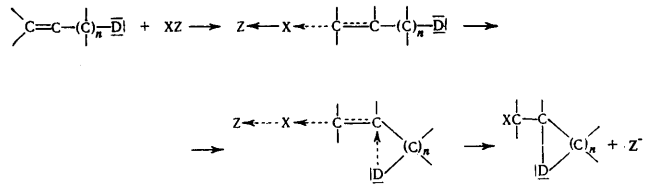
However, even at high concentration of the added anions, for example butyrate anions, this type of reaction does not occur and the rate of iodocyclisation does not change[67].

Competition between cyclic and non-cyclic addition takes place when the reactivity of the ring-closure group is reduced[57] or when more vigorous electrophilic agents are employed, as shown above for bromination and chlorination.

Another characteristic feature of AC reactions is that they are much more sensitive to the nucleophilic properties of the electron-donating component than non-cyclic addition reactions[114,115]. We have seen that the rate constant for iodocyclisation can change by many powers of 10 as the nucleophilic properties of the D component are altered. In reactions involving mixed trimolecular additions, this type of relation is much weaker or is altogether absent. For example, there are data for the rates of chlorination of olefins in the presence of various electron-donating agents in acetic acid[119,120]. The increase of the rate of these reactions is proportional to the concentration of donors in the mixture but a definite relation between the rate constant and the nucleophilicity of the anion is not found.

When allyl alcohol is iodinated, the effect of the nucleophilic properties of the electron-donating agent is appreciable but is nevertheless inferior to that observed in iodocyclisation reactions[121,122].

The above characteristics of AC reactions indicate the particular importance of nucleophilic attack in such processes, in contrast to noncyclic addition reactions. In AC reactions the electron-donating group evidently reacts with the primary weakly polarised complex formed by the electrophilic agent molecule with the multiple bond. The reaction occurs as a synchronous process in which the complex bond is converted into a valence bond and ring closure takes place:



The synchronous effect of the electron-accepting and electron-donating groups on the multiple bond in the molecules in AC reactions can appreciably lower their activation energy. AC reactions proceed with negative activation entropies, the absolute values of which fall from several tens to several entropy units for unsaturated compounds with rigidly fixed reaction centres[49].

The presence in one molecule of two reaction centres (the C=C bond and the electron-donating group) capable of interacting synchronously with the electrophilic agent is also favourable from the standpoint of the entropy change, since such reaction requires a relatively lower structural rearrangement in the reaction system than, for example, in intermolecular acyclic addition.

Acyclic trimolecular addition of iodine occurs only in the presence of powerful nucleophilic agents in view of the weak polarisation by iodine of the multiple bond in the π complex. Weak nucleophilic agents cannot interact effectively with the multiple bond of the weakly polarised π complex of iodine.

If, however, a powerful electrophilic agent, for example bromine, is involved in the intermolecular reaction, a highly polarised complex (probably an ion pair or a σ complex) is formed and is so active that the nucleophilic cooperation of the electron-donating component loses its importance to a considerable degree[96]. AC reactions can also proceed via a σ-complex but only in competition with non-cyclic addition. Although non-cyclic bromination reactions are somewhat accelerated by nucleophilic agents, the nucleophilic properties of strong acid anions are sufficient to complete the addition.

The role of nucleophilic cooperation in AC reactions increases when there is a possibility of the formation of five- and six-membered rings. In the case of small rings (three- and four-membered) there is no nucleophilic cooperation or it is hindered by virtue of certain steric effects. For larger rings, there is a decrease of the probability of a favourable disposition of the multiple bond and the electron-donating end of the molecule as a result of the increase of the number of conformations which the reacting molecule may assume.

These factors operate also in many other chemical reactions, promoting the formation of five- and six-membered rings. In this respect AC reactions constitute a special case obeying the general principle.

As a favourable disposition of the reaction centres—the double bond and the electron-donating group D—is more firmly fixed in the unsaturated molecule M, the AC reaction is facilitated to a greater extent. Therefore in very rigid systems, for example the anions of *endo*-methylenetetrahydrophthalic acids, high rates of ring closure are observed. Conversely, the more mobile is the chain of the reacting molecule, the slower is the AC reaction[49,57,110]. These relations are reflected to some degree in the parameters of the Arrhenius equation when similar series of compounds are considered.

¶ This ease of formation of five- and six-membered rings serves as a confirmation of the old idea that cyclic transition complexes play a major role in heterolytic reactions[117,118].

Thus we find that the differences between the rates of iodination in the series of acid anions with the structure $CH_2=CH(CH_2)_nCO_2^-$ are related to the changes in activation entropy, while the values of $E^{\neq}$ are fairly close (Table 3). Conversely the dependence of the rate of reaction on the nucleophilic properties of D is related to the activation energy and only to a lesser extent to the activation entropy. The acceleration of AC reactions for rigid *endo*-methylene and *endo*-ethylene systems depends both on the lowering of $E^{\neq}$ and the increase of entropy (Table 5). Examination of a large number of the thermodynamic parameters of activation of AC reactions reveals a superposition of various electronic and steric effects, which hinder the isolation of a particular factor in a pure form.

In particular, one can show that the presence of a methylene bridge, which makes the molecule very rigid, is associated with a considerable strain of the double bond, which is estimated as 6 kcal mole^{-1} relative to the unstrained double bond in the cyclohexene ring or the double bond in the same ring with an internal *endo*-ethylene bridge[123]. Thus in AC reactions of molecules with methylene bridges there is, in addition to the steric effect, also the electronic effect associated with the double bond strain. We may note that the products of AC reactions are thermally and chemically more stable than the analogous non-cyclic adducts.

The importance of the formation of five-, six-, and seven-membered active complexes in organic reactions was discussed by Syrkin 10 years ago[124]. He put forward the idea that the electronic perturbations in these processes entail a lowering of the activation energy owing to the formation of more stable quasi-aromatic systems. The idea of the aromaticity of the cyclic complex apparently was not developed further and its applications have been by no means always correct. However, the general assertion of "a kind of parallelism between thermodynamics and kinetics" in chemical reactions is probably valid.

It appears that in AC reactions we have a kind of combination of steric and energetic conditions whereby the electron-donating group is maintained in contact with the polarised atom of the multiple bond. The active electron-donating atom remains at the multiple bond for a longer period than in trimolecular reactions and this corresponds to a lowering of the chemical potential necessary for the formation of stable reaction products.

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