THE JOURNAL OF Organic Chemistry®

VOLUME 40, NUMBER 4 FEBRUARY 21, 1975

Mechanism of the Acyloin Condensation

Jordan J. Bloomfield* and Dennis C. Owsley*

Corporate Research Department, Monsanto Company, St. Louis, Missouri 63166

C. Ainsworth and R. E. Robertson

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521

Received August 1, 1974

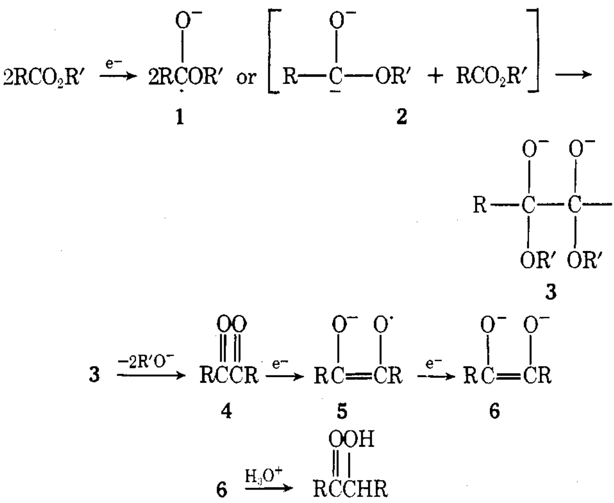
Anomalous results found in the acyloin condensation do not fit into the currently acceptable mechanistic schemes for this reaction. A new mechanism is proposed for the acyloin condensation that does not involve α-diketones as intermediates. This mechanism satisfactorily accounts for the wide variety of reaction products obtained in acyloin condensations conducted under different conditions.

The acyloin condensation is a particularly valuable synthetic tool in the construction of large rings[1a-g] and in the manufacture of perfumes.[1h] A thorough review of the literature concerning the acyloin condensation as a cyclization method was published in 1964.[2] More recently, Rühlmann has reviewed much of the work on the acyloin condensation conducted in the presence of trimethylchlorosilane.[3] During the preparation of an article on the acyloin condensation,[4] a number of anomalous results were found which were not explained by the published mechanistic schemes for the reaction.[1a,2,5-7] The mechanism(s) for any reaction should account for all reported results but, in the case of the acyloin condensation, the anomalous results have not been fitted into a coherent mechanistic scheme. This paper presents some conclusions as to the mechanism of the acyloin condensation in order to stimulate thought and experimentation on this reaction. We are presently unable to carry out any further work toward this end.

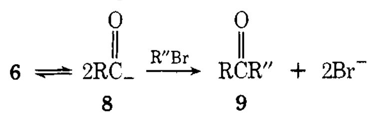
Currently Accepted Mechanistic Schemes

The currently accepted mechanism for the acyloin condensation involves production of the dianion **3** either (a) by coupling of two initially formed radical anions **1**[1a,2,5] or (b) by two-electron reduction of an ester to a dianion **2** followed by its addition to a second molecule of ester (Scheme I). The diketone **4** has been presumed to be an intermediate produced by loss of alkoxide from **3**. Subsequent two-electron reduction produces the acyloin enediolate **6** *via* the semidione **5**.[8] Neutralization of **6** gives the free acyloin **7**. The overall process requires two electrons for each molecule of ester reduced.

Scheme I

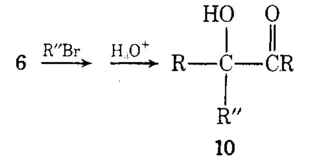


Alkylation experiments on several acyloin reaction mixtures in liquid ammonia produced ketone derivatives of the starting esters.[7] This result caused speculation that the enediolate **6** was in equilibrium with an acyl anion **8** (eq 1).



$$6 \rightleftharpoons 2\underset{\mathbf{8}}{\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}^{-}} \xrightarrow{\mathrm{R''Br}} \underset{\mathbf{9}}{\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{R''}} + 2\mathrm{Br}^- \qquad (1)$$

Despite the fact that others have obtained **10**, the normal product of simple enolate alkylation (eq 2),[9] the acyl anion



$$6 \xrightarrow{\mathrm{R''Br}} \xrightarrow{\mathrm{H_3O^+}} \underset{\mathbf{10}}{\mathrm{R}-\overset{\mathrm{HO}}{\overset{|}{\underset{\underset{\mathrm{R''}}{|}}{\mathrm{C}}}}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{R}} \qquad (2)$$

(or an alkoxide adduct of it), has been uncritically accepted by authors of reference works.[10] Furthermore, other experi-

For simplicity in presentation e⁻ is used as the indicated reductant in the mechanistic schemata. The metal employed certainly has some effect on the course of the reduction, partly through differences in ease of electron release to the ester and partly through differences in stability of intermediate salts and their degree of association. At present, however, there are no experimental data available on the latter effect and only inferences may be made about the former effect (*vide infra*).

mental work suggests that compounds of structure **10** may have decomposed under the drastic work-up conditions in use at that time,[7] which included base extractions in air and atmospheric pressure distillation.[11] Moreover, although no data are available to substantiate or disprove it, entropy considerations in an equilibrium between **6** and **8** in acyloin condensations of *diesters* should ultimately lead to polymer and not to the cyclic products which are observed.

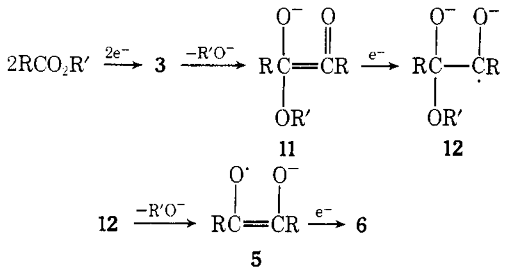
Evidence against the Mechanism of Scheme I

Perhaps the most compelling evidence against this mechanism is found in the reduction of esters in the presence of trimethylchlorosilane. Trimethylchlorosilane is an excellent trap for any alkoxides formed in the reaction. Although no kinetic data are available from the literature on the rate of reaction of Me_3SiCl with alkoxides, a second-order rate constant of 10^2–10^4 l. mol^{-1} sec^{-1} can be estimated for the rate of its reaction with alkoxide.[12] If intermediate **3** of Scheme I has any lifetime, it should be trapped when the acyloin condensation is conducted in the presence of Me_3SiCl. This has not been observed and therefore it is unlikely that **3** is an intermediate.

Furthermore, diketone **4** is excluded by the following experimental data. (1) Diketones are not found when oxygen is carefully excluded from reaction mixtures and work-up procedures.[3] (2) Diketones are reduced by sodium in the presence of Me_3SiCl to give mixtures which contain silylated **6** as only one of many products,[3,15] although α-diketones having no enolizable hydrogens reduce normally.[16a] Some diketones are not reduced at all in the absence of Me_3SiCl.[17] (3) Reduction of a mixture of methyl pivalate (1 mol) and di-*tert*-butyl diketone (1 mol) with 2 g-atoms of sodium (enough to reduce all the ester or all the dione but not both) in the presence of Me_3SiCl gave only trimethylsilylated enediolate and diketone with no recovered ester.[16] Reduction of methyl pivalate (1 mol) with 1 g-atom of sodium (enough to reduce only half the ester all the way or all of it to dione) gave recovered ester and silylated enediolate as the only products.[16] These two experiments should show the relative rates of reduction of ester and diketone if diketone were truly an intermediate. If diketone reduced faster or at the same rate as ester, then unreacted ester should have been found in the first experiment; or, alternatively, if ester is reduced faster than diketone, then diketone should have been found in the second experiment. These data strongly suggest that diketones **4** are not intermediates in the acyloin condensation.

An alternative mechanism to that of Scheme I is shown in Scheme II. Scheme II involves no diketone intermediates but assumes stepwise loss of alkoxide from **3**.

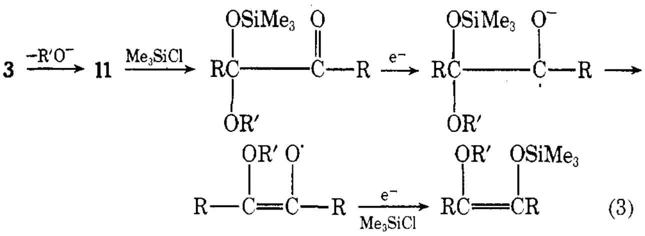
Scheme II



$$2RCO_2R' \xrightarrow{2e^-} 3 \xrightarrow{-R'O^-} \underset{11}{RC(O^-)(OR')=C(=O)R} \xrightarrow{e^-} \underset{12}{RC(O^-)(OR')-\dot{C}(O^-)R}$$

$$12 \xrightarrow{-R'O^-} \underset{5}{RC(O^\cdot)=CR(O^-)} \xrightarrow{e^-} 6$$

This scheme can also be ruled out on the basis of experiments conducted in the presence of Me_3SiCl. If dialkoxy intermediate **3** is not trapped by Me_3SiCl, then **11** should be trapped because it also is a molecule that should have some stability. However, because trimethylsilanol is a stronger acid[18] than either methanol or ethanol (and trimethylsilyl oxide is therefore likely to be a better leaving group), at least some of the final product should have the structure shown in eq 3.



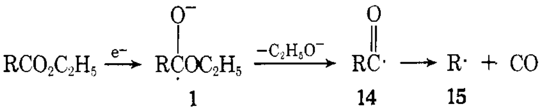
$$3 \xrightarrow{-R'O^-} 11 \xrightarrow{Me_3SiCl} RC(OSiMe_3)(OR')-C(=O)-R \xrightarrow{e^-} RC(OSiMe_3)(OR')-\dot{C}(O^-)-R \longrightarrow R-C(OR')=C(O^\cdot)-R \xrightarrow[Me_3SiCl]{e^-} RC(OR')=CR(OSiMe_3) \qquad (3)$$

All data that have been found to date on reductions of esters point to the conclusion that the acyloin condensation mechanism does not involve the formation of dialkoxy derivative **3** and diketone **4** and therefore *must not involve the dimerization of two initially formed radical anions or the addition of an ester dianion to a second mole of ester.* Moreover, the schemes presented above do not account for reductions in liquid ammonia[7,19-22] and in hydrocarbon solvents[23-25] where acids, alcohols, and other anomalous products are found. (References 7 and 19–25 are only a few representative examples.)

Initial Radical Nature of the Reaction

That the initial step in the acyloin condensation involves the addition of one electron to the ester forming the radical anion **1** does not seem arguable. What subsequently occurs may still be open to considerable debate.

Evidence which supported the initial radical nature of the reaction was obtained from reductions in which an initially formed radical anion could decompose to carbon monoxide, alkoxide, and a resonance-stabilized tertiary radical.[26] Reduction of the esters $RCO_2C_2H_5$ [R = 1-phenylcyclopentyl, 1-phenylcyclohexyl, and 2,3,4-trimethyl-3-pentenyl] produced acyloin, RH, RR, and RCOR. The sequence of reactions suggested to account for these results was



$$RCO_2C_2H_5 \xrightarrow{e^-} \underset{1}{R\dot{C}(O^-)OC_2H_5} \xrightarrow{-C_2H_5O^-} \underset{14}{R\dot{C}=O} \longrightarrow \underset{15}{R\cdot} + CO \qquad (4)$$

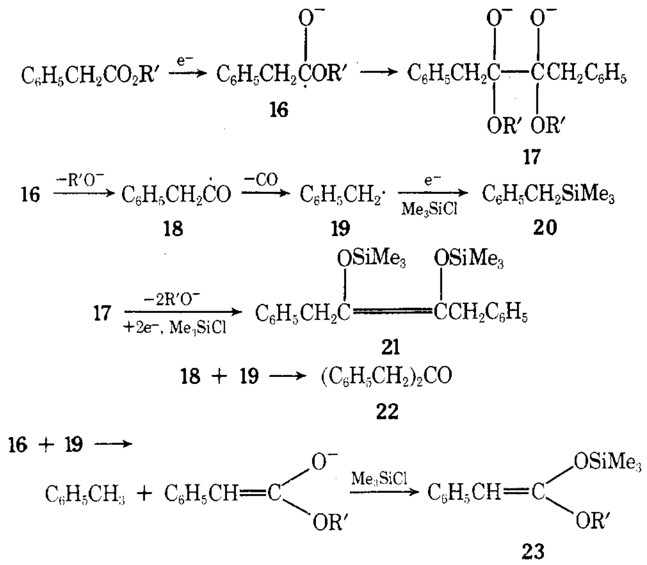
The radical **15** was presumed to dimerize to form R–R, react with **14** to produce ketone, or abstract a hydrogen atom from solvent to produce RH. The acyloin was supposed to be formed by dimerization of **1** or **14** followed by reduction.

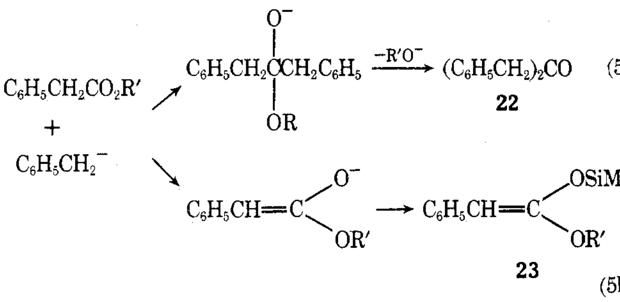
Recently, the reduction of phenylacetic esters in the presence of Me_3SiCl was also explained in terms of free radical intermediates (Scheme III).[3] Bibenzyl, which is found in reactions involving benzyl radicals, is surprisingly absent from the reaction mixture. This suggests that the benzyl radical might not be present at all. This point is discussed in more detail below.

Compound **23**, the silylated derivative of the original ester was also isolated. It was suggested that this product was formed by hydrogen atom abstraction from **16** to give the enolate corresponding to **23** which was rapidly silylated.

An alternative explanation involving benzyl anions could explain all the results of Scheme III. Benzyl anion could attack starting ester at carbonyl to produce ketone, or it could abstract a proton to give enolate of starting ester (eq 5). A pathway by which benzyl anions can form is discussed below.

Scheme III





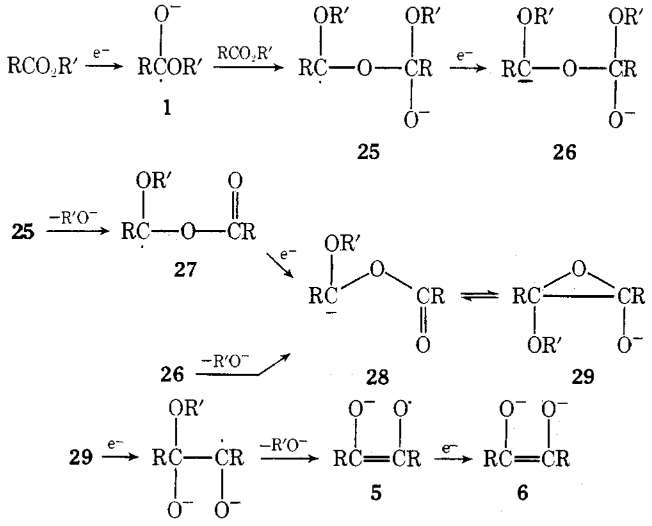
(5a)

(5b)

Unified Acyloin Condensation Mechanism

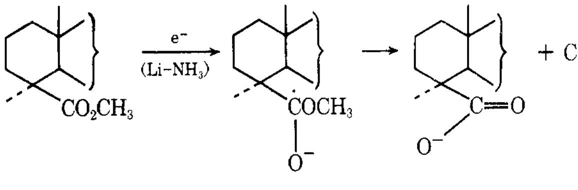
Scheme IV describes an alternative to the currently accepted acyloin condensation mechanism. This section will describe precedents for the formation and fate of each intermediate and will attempt to show how the sequence can be interrupted at many points to give the anomalous products which have been found. Next, the outlines of Scheme IV will be used to describe the products of the reduction of dimethyl dimethylmalonate[22] in which a large number of anomalous products are found. Finally, two cases will be described which are difficult to explain by any mechanism at all. Note that the proposed mechanism of Scheme IV involves no ketone (either mono- or di-) and involves discrete steps in which one electron is added at each juncture.

Scheme IV



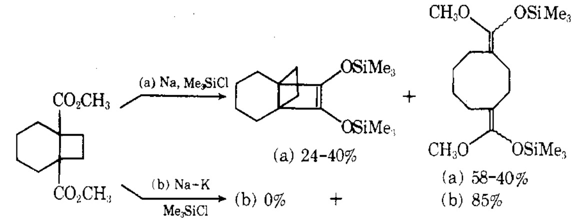
(I) The Initially Formed Radical Anion (1). The initially formed radical anion can have three possible fates: (1) addition to a second molecule of ester to give the first oxy-bridged intermediate **25** (see below), (2) β scission to produce a carboxylate anion and an alkyl radical, and (3) in the case of substituted succinic esters, fragmentation to produce (finally) two enolate anions.

The β scission reaction takes place with esters which are so hindered that they are not hydrolyzed by base. Thus, reaction 6 probably occurs.[19] Note that in this case, the ester is so highly hindered that approach of a second ester to form the oxy-bridged intermediate **25** cannot readily occur.



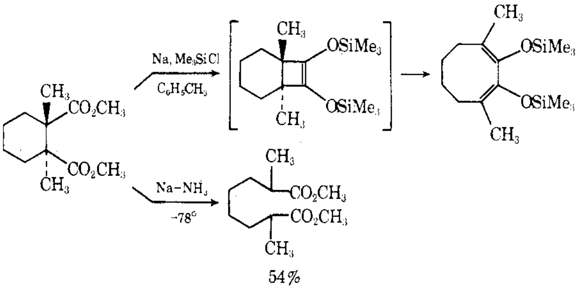
(6)

The fragmentation reaction of succinic esters is exemplified by two cases: eq 7[27] and 8.[28a] Three factors seem to facilitate fragmentation: (1) exceptional strain in the potential cyclic product, (2) increased reducing power of the metal–medium, and (3) in liquid ammonia, solvation of the initially formed radical anion. This means that there are at least two alternate pathways that can occur *before* closure



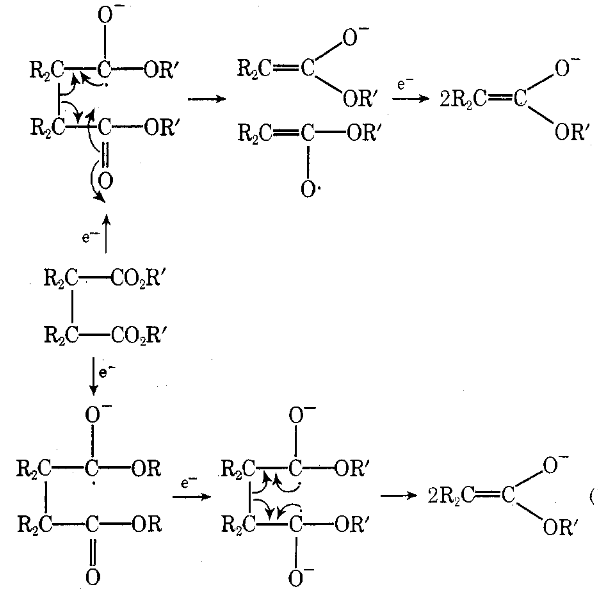
(7a)

(7b)



(8a)

(8b)

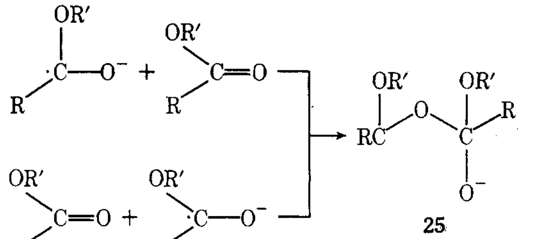


(9)

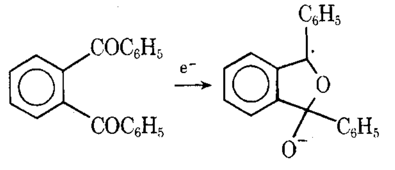
(10)

to the oxy-bridged radical anion **25** (eq 9, 10). It is quite possible that fragmentations of succinic esters in liquid ammonia[28] involve an apparent two-electron reduction of the diester by a very fast addition of a second electron to the initially formed radical anion (eq 10). The timing of the addition is the most important step in the acyloin condensation mechanism (*vide infra*).

(II) Oxy-Bridged Radical Anion 25. The oxy-bridged radical anion **25** can be formed either by attack of the oxygen of an ester radical anion on carbonyl carbon of an unreduced ester or by attack of the carbon of the radical anion on carbonyl oxygen of unreduced ester (eq 11). The first mode of attack needs no further comment while the second is found in trialkyltin hydride reductions of acid chlorides and ketones.[29] In addition, the esr spectrum of the oxy-bridged radical anion **30** has been recently observed (eq 12).[30]



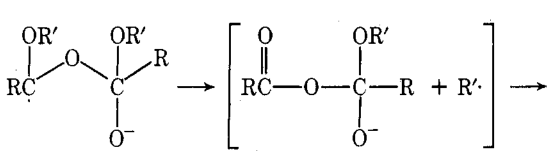
(11)



(12)

30

Oxy-bridged radical anion **25** could have three fates: (1) β scission and decomposition to produce ester, carboxylate anion, and a radical (eq 13), (2) addition of a second electron to form dianion **26**, and (3) loss of alkoxide to form radical **27**. The β scission and fragmentation reaction may have been observed in the case of some benzoic esters of alcohols such as benzyl, allyl, cinnamyl, etc.[25] (*vide infra*).



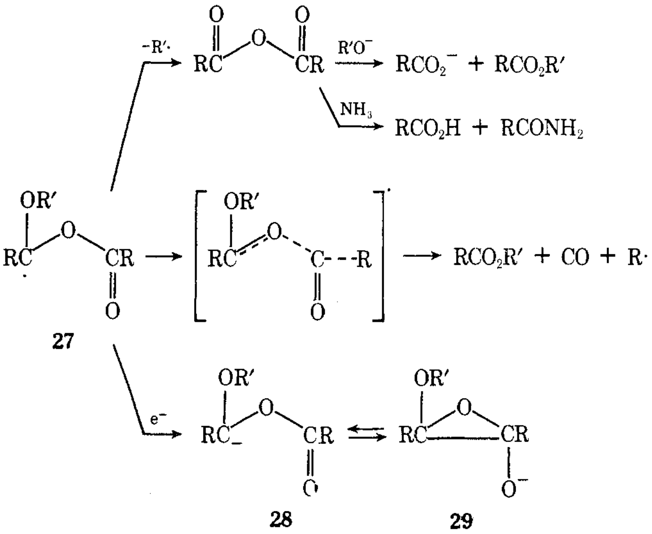
25

$RCO_2^- + RCO_2R' + R'\cdot$ (13)

(III) Radical 27. Discussion of the formation and fate of dianion **26** will be passed over for the moment and instead the fate of radical **27** will be discussed because it is here that an earlier point concerning the timing of the addition of the second electron becomes very important. The various fates of radical **27** are summarized in Scheme V.

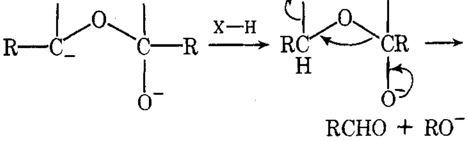
Scheme V offers another pathway for formation of acids in hydrocarbon solvents. Such a reaction was noted in the reduction of benzoic esters using large particle size sodium.[25] This result was quite puzzling until a simple calculation was carried out on surface area per unit volume for sodium particles of 1-mm and 1-μ particle size. Comparison of these two surfaces showed that the 1-μ particle size sodium had a surface area 10^3 times greater than that of the 1-mm particle size sodium. This means that in a given unit volume, the ratio of molecules of unreacted ester to available sodium atoms in the large particle size case is 10^3 times greater than in the small particle size case. This indicates that there is a greater chance of electron release to the ester (giving **25** or **27**) with the large particle size sodium. Once one electron is released to the ester, giving one molecule of **25** or **27**, the situation is now reversed, for the ratio of available sodium atoms to **25** or **27** molecules is now 10^3 times greater with the small particle size sodium than with the large particle size sodium. This means that the second one-electron reduction to **26** or **27** is more favorable in the small particle size case. These calculations suggest that *the most important step in the acyloin condensation mechanism is the timing of the transfer of the second electron to the substrate and that this step determines to a great extent what course the reaction will take.* This timing is a function of both the reducing power of the metal–medium and the various steric and electronic factors in the substrate.

Scheme V



For reactions conducted in liquid ammonia Scheme V offers one pathway for the formation of amides.[7] Scheme V also provides a pathway for the formation of radicals in the reduction of those esters where resonance-stabilized tertiary radicals can be formed.[26] We believe that Scheme V better accounts for the radical products (R–R and R–H) found than the α elimination previously proposed[26] (see eq 4).

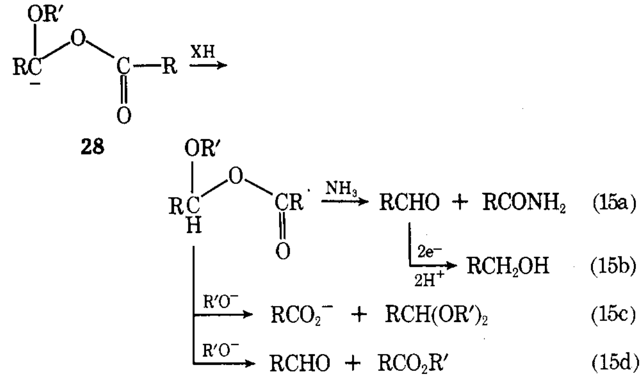
(IV) Dianion 26. Dianion **26** has two possible pathways for decomposition: (1) loss of alkoxide to give oxy-bridged anion **28** and (2) in ammonia or at high concentrations of starting ester,[24] protonation and fragmentation to aldehyde and ester (eq 14). Further reduction of the aldehyde would lead to alcohol if sufficient reducing agent were present. This reaction would take place in a situation where R is very sterically crowded and thus cannot go further to **28** ⇄ **29**, because the bonding distance cannot be attained. This is, in fact, the result obtained in the reduction of methyl mesitoate by lithium in liquid ammonia.[19]



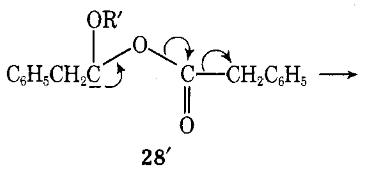
$RCHO + RO^- + RCO_2R'$ (14)

(V) Oxy-Bridged Anion 28. The entire concept of an oxy-bridged anion is hoary. It was first suggested by Favorsky[31] as providing possible intermediates for the Cannizzaro reaction, benzilic acid rearrangement, and acyloin rearrangement, as well as the reaction that now bears his name.

In ammonia, protonation of **28** could occur, leading to amide, alcohol, and even aldehyde if insufficient reducing agent were present (eq 15).[7,20,22]



Further examination of transformations of **28** shows that it can account for the reduction products of phenylacetic esters[3] in a way that explains the absence of bibenzyl but without invoking free radicals other than as transient radical-anion intermediates (eq 16). Thus, **28′** can fragment, producing a resonance-stabilized anion and starting ester.

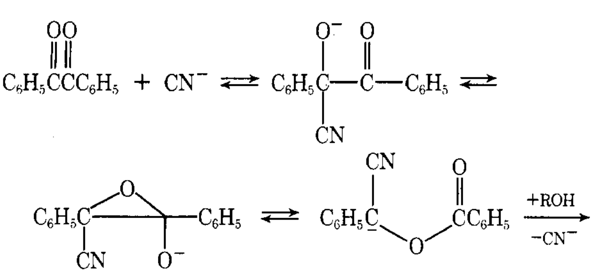


28′

$$C_6H_5CH_2CO_2R + CO + C_6H_5CH_2^- \quad (16)$$

In the presence of Me$_3$SiCl, the anion can be trapped to produce benzyltrimethylsilane (**20**) or it can attack the starting ester (perhaps in a "cage" reaction). Attack at carbonyl would produce dibenzyl ketone (**22**) while attack at the benzylic hydrogen would produce enolate of the starting ester which is subsequently silylated to give **23.** No bibenzyl is predicted by this scheme. A similar fragmentation pathway in the reactions involving tertiary benzylic or allylic compounds[26] also produces resonance-stabilized anions which account for all products except dimer hydrocarbons.

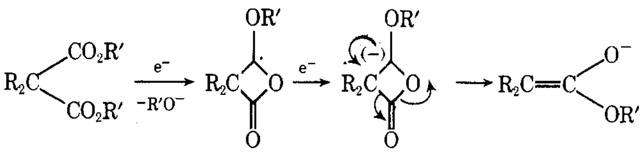
The steps involving the conversion of **28** to **29** parallel very closely, in reverse, the pathways suggested for cleavage of benzils by cyanide ion (eq 17)[32] or by methylsulfinyl carbanion.[33] The anion **31** is comparable to **29** while **32** is comparable to **28.** Furthermore, an intermediate very much like **29** was proposed to account for products from the peracid oxidation of β-diketones.[34] A very similar structure is also found in the hydrate of 1,2-cyclohexanedione which is formulated as a dihydroxyepoxycyclohexane.[35]



31 **32**

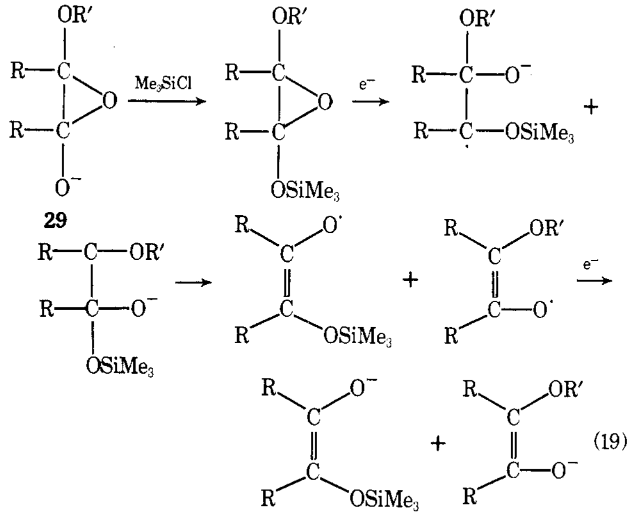
$$C_6H_5CO_2R + C_6H_5CHO \quad (17)$$

Malonic esters undergo a reaction in which the elements of carbon monoxide and alkoxide are lost to give the substituted acetic ester (eq 18).[22,36] Note that the closure of **28″** to the epoxide derivative would produce a 2-oxabicyclo[1.1.0]butane. An alternate pathway open to **28″** is expulsion of carbon monoxide and formation of ester enolate, which is the result observed in hydrocarbon solvents at room temperature and above. This result fits with the previously stated concept that most of the anomalous products of the acyloin condensation can be explained most readily as results of anionic reactions.

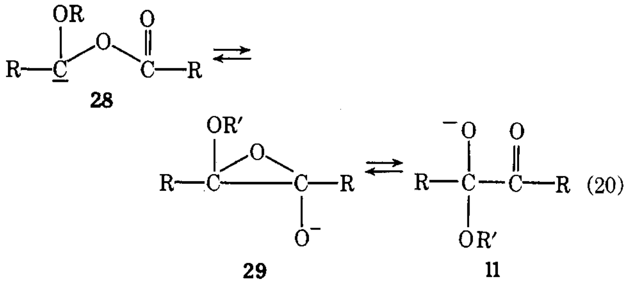


28″ (18)

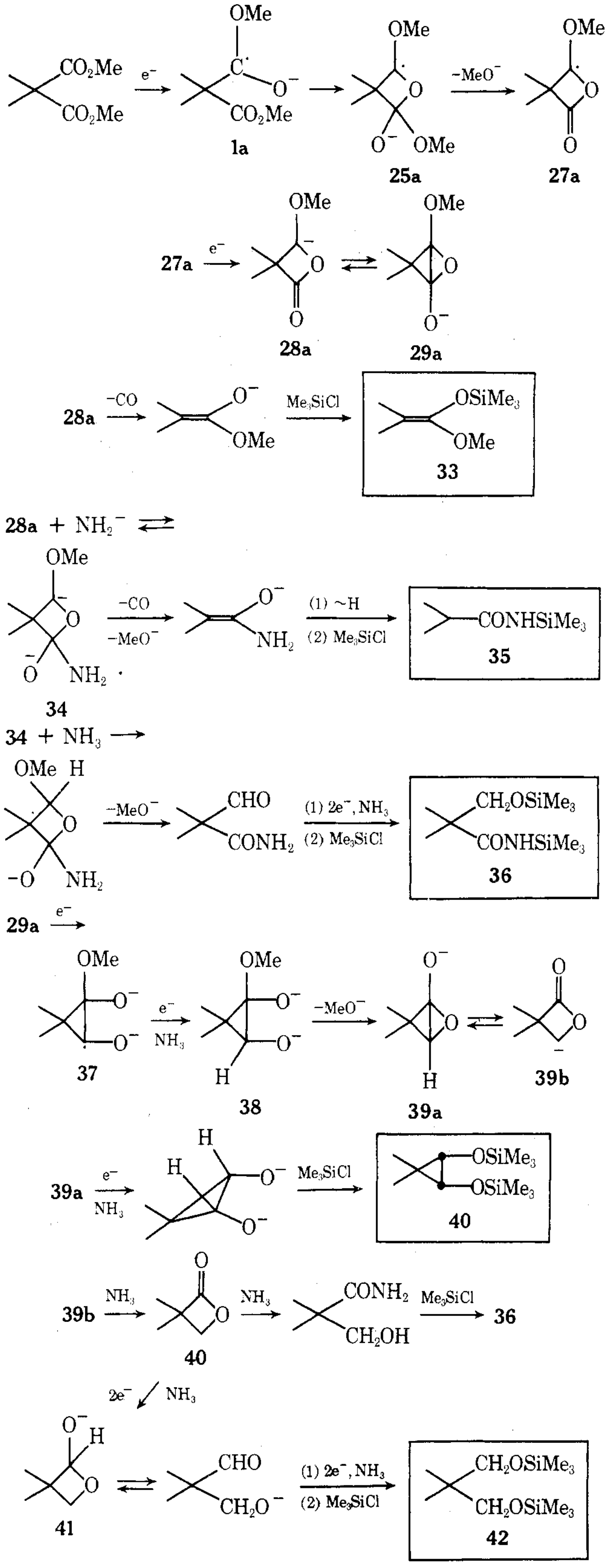
(VI) Epoxide 29. The formation of epoxy intermediate **29** was just discussed. The reduction of epoxides by alkali metals in both hydrocarbon solvents and liquid ammonia has been carefully investigated.[37] Thus conversion of **29** to semidione **5** and subsequent reduction to endiolate **6** is easily understood. However, if Me$_3$SiCl is present, **29** should have sufficient lifetime to be silylated before reduction to a silylated semidione. Silylated **29** is a nearly symmetrical intermediate and reduction could occur in either of two directions (eq 19). No mixed silylated–alkylated enediolates are found. The ring opening of silylated **29** in one direction only may be rationalized in the following way. Comparison of *tert*-butyl methyl ether with trimethylsilyl methyl ether by nmr shows that the oxygen of the trimethylsilyl methyl ether is more electronegative than that in *tert*-butyl methyl ether.[38] The reason for this is participation of the vacant silicon d orbitals in delocalizing the lone pairs on oxygen to a certain extent. Thus, inductively, the carbon next to the silyloxy group in silylated **29** can more readily accept an electron than the carbon next to the alkoxy group.



One other intermediate could be involved in the equilibrium **28** ⇄ **29** of Scheme IV. This is intermediate **11** of Scheme II (eq 20). For the reasons stated previously under Scheme II it is felt that **11** is not involved in the acyloin condensation mechanism because no mixed silyloxy-alkoxy alkenes are found when the reaction is conducted in the presence of Me$_3$SiCl.



Scheme VI



One final piece of evidence is now offered which strongly implies that the mechanism for the acyloin condensation is not the "classical" one of Scheme I. Figure 1A is a plot of yield vs. ring size for the acyloin condensation, the Dieckmann condensation, and the Thorpe–Ziegler condensation.[39] Note that the rapid drop in yield for the acyloin condensation falls at the eight-membered ring while in both the Dieckmann and the Thorpe–Ziegler reactions, the drop is at the nine-membered ring. Entropy considerations should govern the formation of a given size ring, no matter how it was formed. Figure IB is a plot of the size of the first formed intermediate vs. yield for all three condensation reactions. Note that in the "unified" mechanism discussed above, the oxy-bridged intermediates are one member larger than the ring size of the final product. The plots of intermediate size vs. yield correspond well for all three cases.

Reduction of Dimethyl Dimethylmalonate

The variety of products issuing from the reduction of dimethyl dimethylmalonate by sodium in liquid ammonia[22] offers an example in which the generality of the "unified" acyloin mechanism can explain all products. Scheme VI gives pathways to these products in terms of intermediates **25–29** of Scheme IV. In these reactions, Me_3SiCl was added at the end of the reduction to facilitate isolation of the products.[22]

Table I is a compilation of the yields of the various products as the reaction conditions were changed. Examination of this table shows that there are probably two independent groups of products. The yields of **40** and **42** are nearly independent of all changes in conditions, while those of **33**, **35**, and **36** change as the temperature is lowered from −34 to −78°. Note also that at −34° the total yield of **33**, **35**, and **36** is 56% while at −78° the yield of **33** is 57% and **35** and **36** completely disappear. This suggests that **33**, **35**, and **36** arise from a common intermediate.

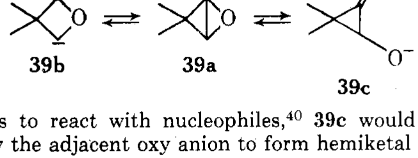
Scheme VI is consistent with this view. Compound **33** is formed by fragmentation of intermediate **28a**, as shown in eq 18. Compounds **35** and **36** are formed from **34**, an ammonolysis product of **28a**. If dianion **34** decomposes with loss of carbon monoxide and methoxide, the precursor to **35** is formed. On the other hand, if **34** is protonated before decomposition, then a pathway to **36** is now opened. The disappearance of **35** and **36** as the temperature is lowered suggests that the ammonolysis of **28a** (to **34**) is much slower at −78° and that at −78° **28a** can fragment or be reduced further. This is consistent with the expectation of a lower activation energy for fragmentation or reduction of **28a** than for its ammonolysis.

The independence of the yield of **40** and **42** from all changes in conditions also suggests a common precursor, intermediate **39**. Intermediate **39** is formed in preference to a cyclopropene semidione. Instead, **37** undergoes further reduction and protonation to give **39a** ⇄ **39b**. Reduction of **39a** to the *cis*-cyclopropanediolate precursor of **40** is easily explained in terms of the known metal–amine reduction of epoxides which proceeds with inversion of configuration at carbon.[37b,c]

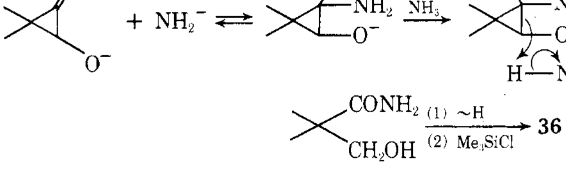
The pathway from **39b** to the silylated diol **42** involves the cyclic hemiacetal **41**, produced by reduction of 2,2-dimethylpropiolactone (**40**). The suggestion of the hemiacetal **41** is particularly plausible because a cyclic hemiacetal *has been* identified among the products of an acyloin condensation conducted in liquid ammonia.[20] Diols have also been found in other acyloin condensations.[23,24]

Ammonolysis of **40** could also produce the amide alcohol **36**. However, if this were the major pathway to **36**, then a concomitant rise in the yield of **42** should be noted as the temperature is lowered. Since **42** is found in such small yields (3–4%), any contribution by this pathway to the overall yield of **36** must be negligible.

A cyclopropanone derivative **39c** is also possible in the equilibria represented by **39a–c**. Because of the known propensity of cyclopropanones to react with nucleophiles,[40] **39c** would be rapidly trapped by the adjacent oxy anion to form hemiketal **39a**. Attack of ammonia (or amide) on **39c** could lead to **36** (eq 21), but again a



39b **39a** **39c**



(21)

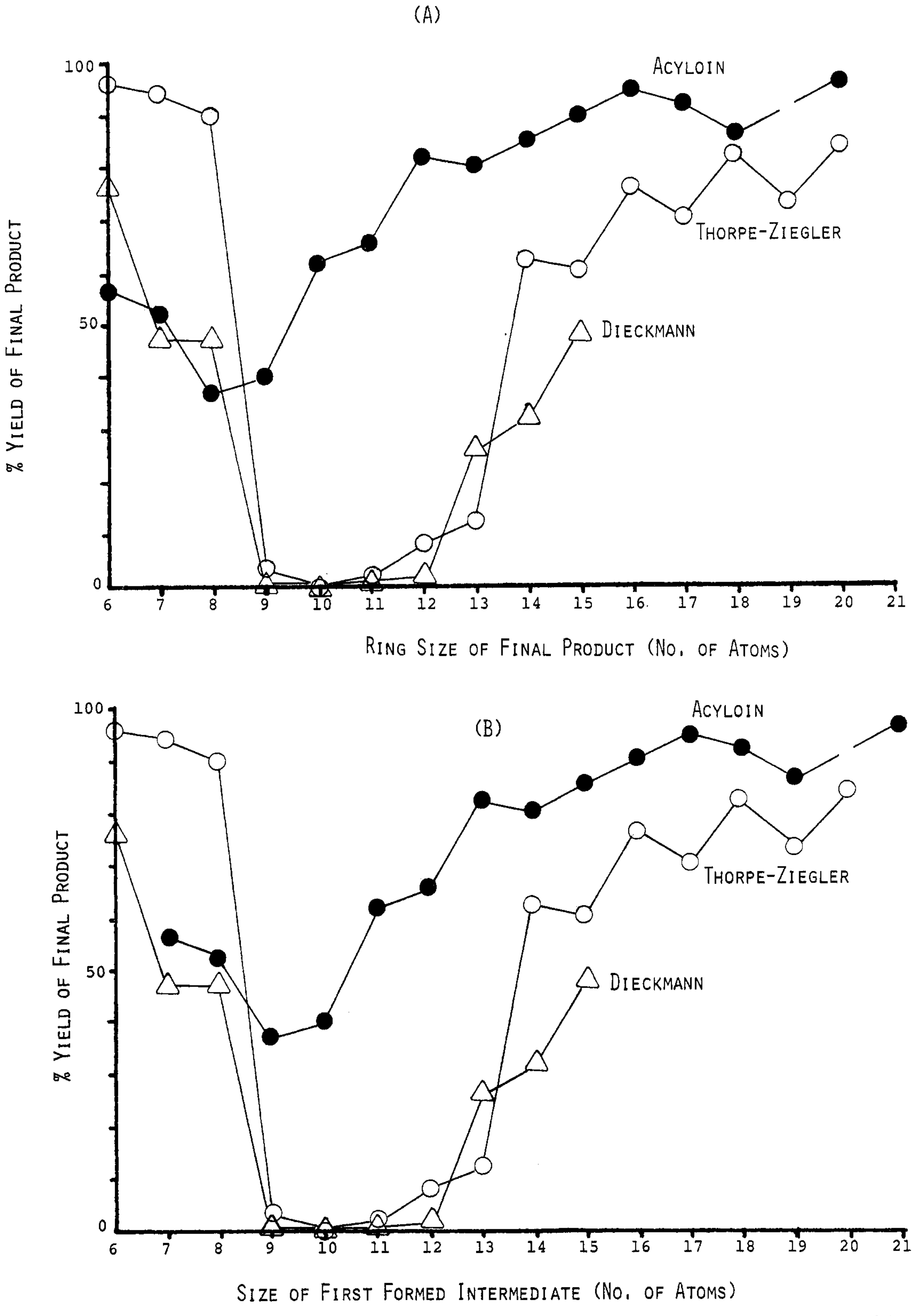
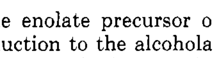


Figure 1. Dependence of yield of various cyclization processes on product ring size (A) and on the size of the hypothetical first formed cyclic intermediate (B) [adapted from J. Sicher, *Progr. Stereochem.*, **3**, 215 (1962)].

decrease in yield of **36** with decreasing temperature should produce a rise in the yield of **40** and **42** if eq 21 described the major pathway to **36**. Furthermore, reduction of **39c** should produce a *trans*-cyclopropanediolate on the grounds of greater charge separation in this molecule over that in the *cis*-cyclopropanediolate (eq 22). These complications make any substantial contribution of **39c** very unlikely as no products derived from it are found.

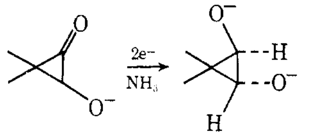
The proposed intermediacy of the 2-oxabicyclo[1.1.0]butane intermediates **29a** and **39a** leads to predictions of a variety of products *via* a combination of thermal rearrangements[41] and reductions. One such rearrangement is shown in eq 23. Compound **44** has been tentatively identified in these reactions.

When the reduction of dimethyl dimethylmalonate in liquid ammonia is conducted in the presence of methanol **43** is produced on subsequent treatment with Me_3SiCl. This is easily accounted for

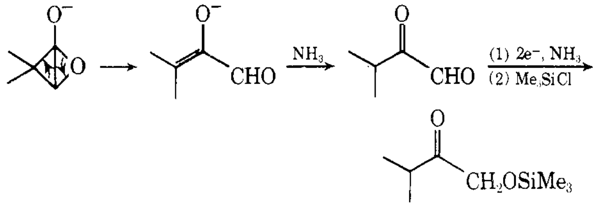


43

by methanolysis of the enolate precursor of **33** and subsequent Bouveault–Blanc[41] reduction to the alcoholate of **43**. In fact, it is likely that the mechanism of the Bouveault–Blanc reduction is a variant of the acyloin condensation mechanism (see eq 15d).



(22)

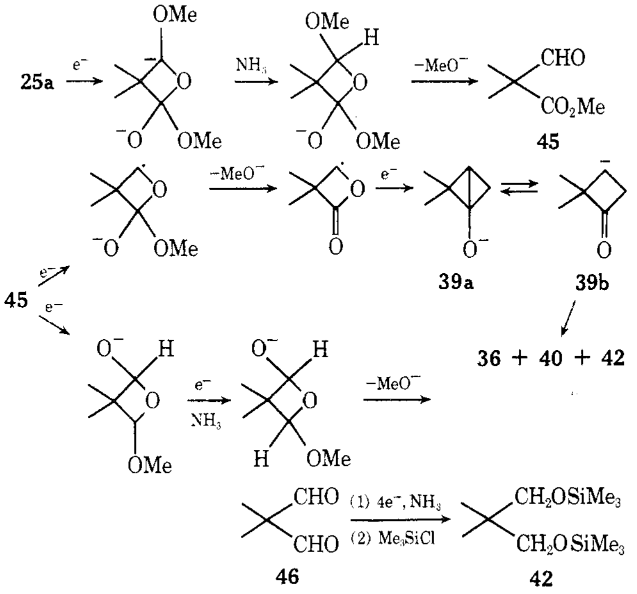


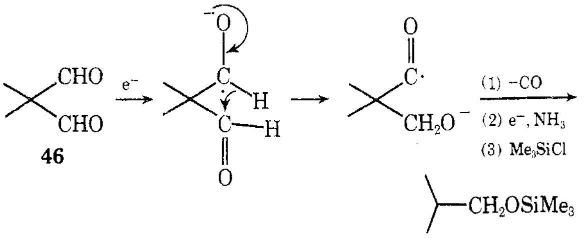
(23)

44

Scheme VI did not include an exposition of the fate of a possible dianion intermediate (**26a**) resulting from reduction of **25a**. It is not likely that **26a** is in the pathway for this reduction. Scheme VII summarizes the possible fates for **26a**, in which the intermediacy of aldehyde ester **45** is predicted. However, reduction of **45** under the acyloin reaction conditions produced a mixture which consisted of **35** (6%), **40** (25%), **42** (25%), and **43** (45%).[22] These results suggest that any pathway for the reduction of the diester that goes through **26a** must be negligible. The production of **43** from **46** could involve a type of internal Cannizzaro reaction (eq 24).

Scheme VII





(24)

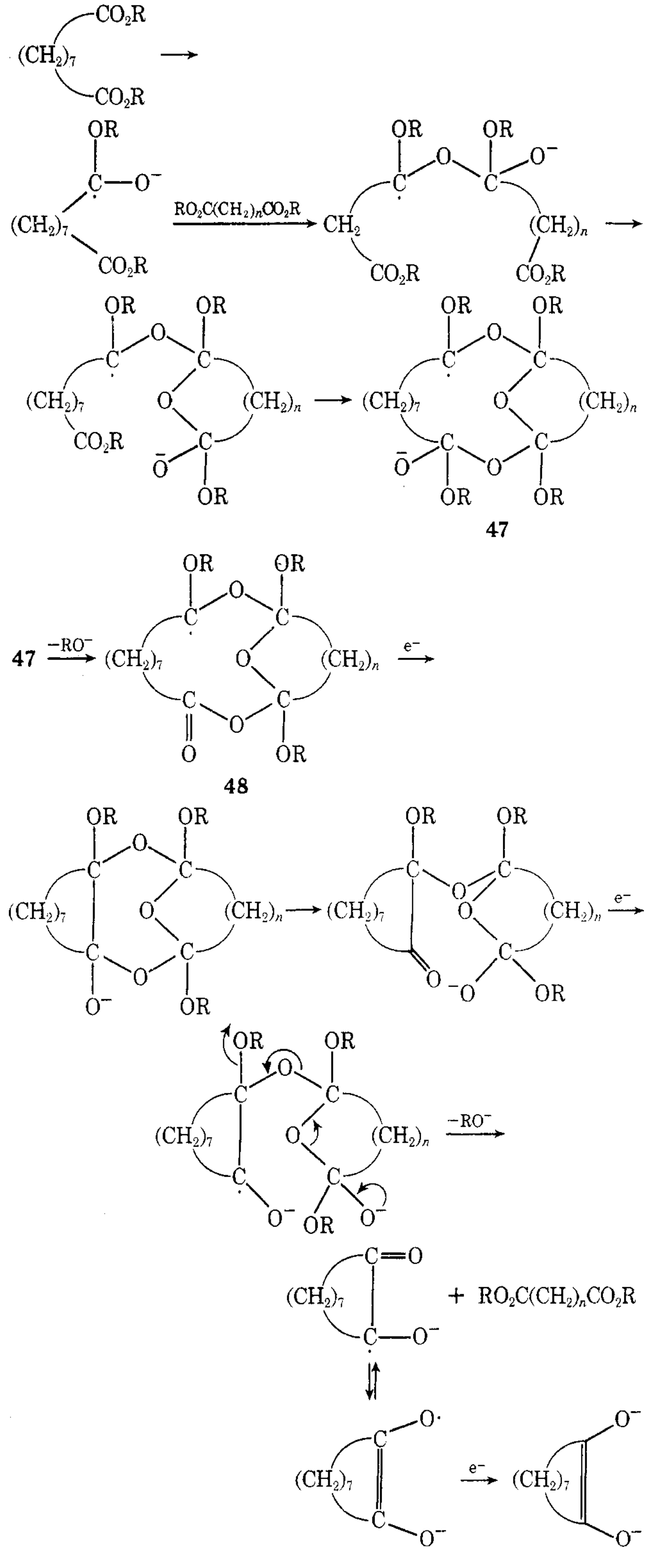
43

Results Difficult to Explain

The simultaneous reduction of a mixture of two different long-chain diesters gives very peculiar results.[43] When dimethyl nonanedioate is reduced alone, the yield of acyloin is 16%. In the presence of an equimolar amount of another long-chain diester, a yield of nine-membered acyloin of 52–62% is obtained![43]

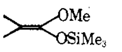
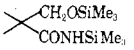
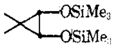
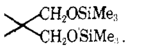
Table II presents a comparison of some results obtained in both the Dieckmann and acyloin condensations. Note that the Dieckmann cyclization is worthless for monomer in the C_9–C_{12} range but that cyclic dimer is produced. In the acyloin condensation with added Me_3SiCl, the yield for all ring sizes ranges from fair to excellent.[4] Related data are plotted in Figure 1A and B.

Scheme VIII



Compare the two cases in Table II in which the acyloin condensation was carried out in the presence of Me_3SiCl under both normal and high-dilution conditions. Under normal conditions, the yield of dimer is considerable. The mixed-ester reactions[43] were carried out without added Me_3SiCl under normal conditions. Under high-dilution conditions, the reaction becomes monomolecular and the

Table I
Yields of Various Products from the Reduction of Dimethyl Dimethylmalonate by Sodium in Liquid Ammonia[22]

Conditions	 33	 35	 36	 40	 42
(1) Na–NH_3, ether, –34° (2) Me_3SiCl	6	25	25	25	3
(1) Na–NH_3, ether, –78° (2) Me_3SiCl	57			25	3
(1) K–NH_3, ether, –78° (2) Me_3SiCl	38		7	25	5
(1) Na–NH_3, CH_3OH, ether, –34° (2) Me_3SiCl		10		22	3

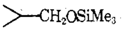
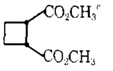
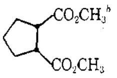
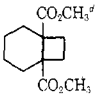
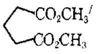
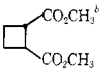
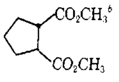
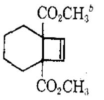
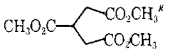
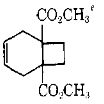
also  (43) (55%)

Table II
Comparison of Yields (%) for Cyclization of $RO_2C(CH_2)_nCO_2R$ under Various Conditions

		Acyloin			
N = final ring size	Dieckmann[a,b]	Ref 43[c]	Ref 43[d]	Me_3SiCl (A)[e]	Me_3SiCl (B)[f]
8	15 (dimer = 11)				72–85
9	0 (dimer = 28)	5	5 (16)	22 (dimer = 62)	68
10	0 (dimer = 12)	52	69 (52)	53 (dimer = 20) 22 (dimer = 73)	58–69
11	0.5 (dimer = 23)	60	62 (69)		48
12	0.5 (dimer = 16)	57	84 (72)		68
13	24 (dimer = 19)	62	52 (64)		84
14	32 (dimer = 2)	58	87 (84)		67

[a] Taken from Table II in J. P. Schaefer and J. J. Bloomfield, *Org. React.*, 15 (1967). [b] Note that for the Dieckmann reaction the value of n to obtain a given size ring must be 1 larger than in the acyloin condensation. [c] Yield of C_9 cycle when 0.01 mol of C_9 diester is cyclized with 0.01 mol of the diester for which $n = N - 2$. [d] Yield of C_N cycle when 0.01 mol of C_N is cyclized with 0.01 mol of C_9 diester. The number in parentheses is the yield when no other ester is present. [e] Reference 3, ester added fairly rapidly. [f] Reference 44, ester slowly added *via* high-dilution cycle.

Table III
Esters Which Are Not Reduced

Reduced ↑	$C_2H_5O_2CCO_2C_2H_5$[a]				
Not reduced ↓	$CH_3O_2CCO_2CH_3$[b]				
					

[a] Reference 36b. [b] Reference 44. [c] Reference 45. [d] Reference 27. [e] Reference 46. [f] Reference 47. [g] Reference 48.

yield of monomer goes up, although reaction rates are slow. [The relative rates in parentheses are C_9 (16), C_{10} (6), C_{11} (6.6), C_{12} (2), and C_{14} (1.7).[43]]

Study of Table II provides a clue to what might occur when two long-chain esters are reduced simultaneously.[43] The relative rate studies show that the C_9 diester is reduced at a much faster rate than the other esters studied. Therefore, could the initially formed radical anion from the C_9 diester be trapped by a higher carbon numbered diester to produce an intermediate bimolecular product which decomposes to two monomolecular products? Scheme VIII offers a very speculative suggestion. Note that in intermediates **47** and **48**, the ends of the C_9 diester are now held in a 14-membered ring, and the C_n diester is held in a C_{n+3} size ring (the size of the intermediate in the unimolecular acyloin condensation). If $n + 2 = 9$, then a 10-membered ring is formed which results in no net gain in ring size and dimer is formed. With $n + 2 > 9$, then going to such structures as **47** and **48** might be favored, opening a pathway to higher yields of the C_9 monomolecular acyloin.

In Table III are collected a number of other anomalies in the acyloin condensation. For these examples there can be no mechanism because the diesters are not reduced at all! For comparison some diesters are included which are reduced and have structures similar to those of the diesters which are not reduced. (Not all the known examples of nonreduction are recorded in Table III. For more complete listing see ref 4.)

This paper has presented a number of conclusions about the acyloin condensation mechanism which are at variance with the generally accepted mechanism of the reaction. It is hoped that further discussion and experimentation will result which will either prove or disprove these conclusions. Furthermore, because of the importance of the acyloin reaction as a synthetic tool in organic chemistry, more work is needed to describe (1) adsorption and desorption of organic molecules on alkali metal surfaces and (2) steric, conformational, and electronic effects on the electron transfer to esters.

References and Notes

(1) See reviews: (a) V. Prelog, *J. Chem. Soc.*, 420 (1950); (b) M. Stoll, *Chimia*, **2**, 217 (1948); (c) K. Ziegler in Houben-Weyl, "Methoden der Organischen Chemie," Vol. 4/2, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1955, pp 739, 755; (d) L. I. Belen'kii, *Russ. Chem. Rev.*, **33**, 551 (1964); (e) D. J. Cram, *Record Chem. Progr.*, **20**, 71 (1959); (f) N. J. Leonard, *ibid.*, **17**, 243 (1956); (g) B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, N.Y., 1964, pp 27–42; (h) J. A. Van Allan, *Amer. Perfum. Essent. Oil Rev.*, 33 (1949).

(2) K. T. Finley, *Chem. Rev.*, **64**, 573 (1964).

(3) K. Rühlmann, *Synthesis*, 236 (1971).

(4) J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. React.*, in press.

(5) S. M. McElvain, *Org. React.*, **4**, 256 (1948).

(6) F. F. Blicke, *J. Amer. Chem. Soc.*, **47**, 229 (1925).

(7) M. S. Kharasch, E. Sternfeld, and F. R. Mayo, *J. Org. Chem.*, **5**, 362 (1940).

(8) G. A. Russell and P. R. Whittle, *J. Amer. Chem. Soc.*, **89**, 6781 (1967), reported formation of semidiones under the conditions of the acyloin condensation.

(9) (a) J. C. Speck, Jr., and R. W. Bost, *J. Org. Chem.*, **11**, 788 (1946); (b) J. H. Van de Sande and K. R. Kopecky, *Can. J. Chem.*, **47**, 163 (1969); (c) J. Cologne and P. Brison, *Bull. Soc. Chim. Fr.*, 175 (1962); (d) F. Chen, R. E. Robertson, and C. Ainsworth, *J. Chem. Eng. Data*, **16**, 121 (1971).

(10) *Cf.* (a) H. Smith "Chemistry in Non Aqueous Ionizing Solvents," Vol. I, Interscience, New York, N.Y., 1963, Part II, p 174; (b) C. Walling, "Free Radicals in Solution," Wiley, New York, N.Y., 1957, p 585; (c) A. J. Birch, *Quart. Rev., Chem. Soc.*, **4**, 69 (1950).

(11) D. B. Sharp and E. L. Miller, *J. Amer. Chem. Soc.*, **74**, 5643 (1952).

(12) The second-order rate constant for the reaction of methanol with triisopropylchlorosilane is $\sim 1.5 \times 10^{-4}$ l. mol^{-1} sec^{-1}.[13] We estimate that the rate of the reaction of Me_3SiCl with methanol would be at least an order of magnitude greater. Furthermore, the reaction of triphenylfluorosilane with hydroxide is 10^6 times faster than with water.[14] Thus, we estimate that the reaction of methoxide with Me_3SiCl would be at least these orders of magnitude greater than that of methanol with Me_3SiCl.

(13) A. D. Allan, J. C. Charlton, C. E. Eaborn, and G. Modena, *J. Chem. Soc.*, 3688 (1957).

(14) C. G. Swain, R. M. Esteve, Jr., and R. H. Jones, *J. Amer. Chem. Soc.*, **71**, 965 (1949).

(15) K. Rühlmann, B. Fichte, T. Kiriakidis, C. Michael, G. Michael, and E. Gründemann, *J. Organometal. Chem.*, **34**, 41 (1972).

(16) (a) R. E. Robertson, M.S. Thesis, Colorado State University, 1971. (b) Control experiments in which Me_3SiCl either was present initially or was added at the end of the reduction gave essentially the same results.

(17) E. L. Totton, R. C. Freeman, H. Powell, and T. L. Yarboro, *J. Org. Chem.*, **26**, 343 (1961).

(18) (a) L. H. Sommer, E. W. Pietrusza, and F. C. Whitmore, *J. Amer. Chem. Soc.*, **68**, 2282 (1946); (b) R. West and R. H. Baney, *ibid.*, **81**, 6145 (1959).

(19) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **80**, 217 (1958).

(20) J. J. Bloomfield and J. R. S. Irelan, *J. Org. Chem.*, **31**, 2017 (1966).

(21) T. Okubo and S. Tsutsumi, *Technol. Rep. Osaka Univ.*, **12**, 457 (1962) [*Chem. Abstr.*, **59**, 7422*g* (1963)].

(22) F. Chen and C. Ainsworth, *J. Amer. Chem. Soc.*, **94**, 4037 (1972).

(23) A. E. Kober and T. L. Westmann, *J. Org. Chem.*, **35**, 4161 (1970).

(24) D. Machtinger, *Bull. Soc. Chim. Fr.*, 1341 (1961).

(25) H. Stetter and K.-A. Lehmann, *Justus Liebigs Ann. Chem.*, 499 (1973).

(26) (a) E. Van Heyningen, *J. Amer. Chem. Soc.*, **74**, 4861 (1952); (b) E. Van Heyningen, *ibid.*, **77**, 4016 (1955).

(27) J. J. Bloomfield, R. A. Martin, and J. M. Nelke, *J. Chem. Soc., Chem. Commun.*, 96 (1972).

(28) (a) P. G. Gassman and X. Creary, *J. Chem. Soc., Chem. Commun.*, 1214 (1972); (b) E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem.*, **76**, 281 (1964).

(29) H. G. Kuivula, *Synthesis*, 499 (1970).

(30) J. A. Campbell, R. W. Koch, J. V. Hay, M. A. Ogliaruso, and J. F. Wolfe, *J. Org. Chem.*, **39**, 146 (1974).

(31) Al. Favorsky, *Bull. Soc. Chim. Fr.*, [4] **43**, 551 (1928).

(32) H. Kwart and M. M. Baevsky, *J. Amer. Chem. Soc., Soc.*, **80**, 580 (1958).

(33) J. C. Trisler, J. K. Doty, and J. M. Robinson, *J. Org. Chem.*, **34**, 3421 (1969).

(34) H. O. House and W. F. Gannon, *J. Org. Chem.*, **23**, 879 (1958).

(35) L. De Borger, M. Anteunis, H. Lammens, and M. Verzale, *Bull. Soc. Chim. Belg.*, **73**, 73 (1964).

(36) (a) F. Krollpfeiffer and A. Rosenberg, *Chem. Ber.*, **69**, 465 (1936); (b) Y. N. Kuo, F. Chen, C. Ainsworth, and J. J. Bloomfield, *Chem. Commun.*, 136 (1971).

(37) (a) M. Mousseron, R. Richard, R. Granger, F. Winternitz, G. Combes, E. Cavals, L. Souche, M. Cabanes, and P. Froger, *Bull. Soc. Chim. Fr.*, **51**, 629 (1946); (b) A. S. Hallsworth and H. B. Henbest, *J. Chem. Soc.*, 4604 (1957); (c) G. Nomine, D. Bertin, and A. Pierdet, *Tetrahedron*, **8**, 217 (1960).

(38) (a) H. A. Brune, *Chem. Ber.*, **97**, 2829 (1964); (b) T. Ostdick and P. A. McKusker, *Inorg. Chem.*, **6**, 98 (1967).

(39) See reviews: (a) E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles," Interscience, New York, N.Y., 1970, Chapter 1; (b) J. P. Schaefer and J. J. Bloomfield, *Org. React.*, **15**, 28 (1964).

(40) N. J. Turro and W. B. Hammond, *Tetrahedron*, **24**, 6029 (1968).

(41) *Cf.* J. Ciabattoni, *J. Amer. Chem. Soc.*, **93**, 4902 (1971), and references therein.

(42) L. Bouvealt and G. Blanc, *C. R. Acad. Sci.*, **136**, 1676 (1903).

(43) K. T. Finley and N. A. Sasaki, *J. Amer. Chem. Soc.*, **88**, 4267 (1966).

(44) J. J. Bloomfield, unpublished work.

(45) J. J. Bloomfield, R. G. Todd, and L. T. Takahashi, *J. Org. Chem.*, **28**, 1474 (1963).

(46) D. Ginsburg, *Accounts Chem. Res.*, **7**, 249 (1972).

(47) U. Schräpler and K. Rühlmann, *Chem. Ber.*, **97**, 1383 (1964).

(48) P. E. Eaton, private communication.

A Suggestion for the Revision of Mechanistic Designations

Robert D. Guthrie

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

Received July 18, 1974

A simple system for the designation of chemical reaction mechanisms is suggested. The new system represents each bond-making and bond-breaking step in symbolic form and requires only two symbols plus atomic symbols for the elements to represent all heterolytic and homolytic reactions including electron-transfer reactions. Minor modification of the system allows the designation of ion-paired intermediates and caged radical pairs. An approach to the designation of photochemical reaction mechanisms is also suggested. The new system can serve as a digital code which, when applied to a set of reagents, will generate both mechanism and products. Its application to information retrieval is anticipated.

In the past 30 years chemistry has become increasingly mechanistic. The term mechanism has many peripherally different definitions but basically means a description of the sequence of bond-making and bond-breaking steps occurring as a set of starting molecules, atoms, or ions is converted to a new set. When mechanisms are grouped for classification, extramechanistic information is included to indicate the outcome of the reaction, *i.e.*, substitution, elimination, or addition. This procedure gives more information than would be available from the purely mechanistic part of the classification symbols, but it still leaves important parts of the known details of the mechanism to be associated with the symbols by memorization.

As an example, consider the classification S$_N$2. The most