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Malonic Anhydrides, Challenges from a Simple Structure

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Abstract

After many years of unsuccessful attempts, monomeric malonic anhydrides were prepared by ozonolysis of ketene dimers, a procedure validated by model studies. The structure proof relied most heavily on IR absorption at 1820 cm^{-1} and a Raman band at 1947 cm^{-1}. Malonic anhydrides are unstable, decomposing below room temperature to a ketene plus carbon dioxide. Surprisingly, according to kinetic studies, the dimethyl derivative is slightly less unstable than the parent, and the monomethyl is the fastest to decompose, with an enthalpy of activation of only 12.6 kcal/mol. Computations rationalize this behavior in terms of a concerted $[2_s+2_a]$ cycloreversion that requires a more highly organized transition state, as also manifested by a negative entropy of activation.

History

For many years malonic anhydrides (**1**), also known as 2,4-oxetanediones (the preferred name according to SciFinder), were classic unknown compounds, in contrast to their well-known homologs, succinic and glutaric anhydrides (**2**, **3**). This Perspective describes the long history of this simple structure, and the challenges it presented. A much condensed version of this story has been published.[1] We here begin with the many unsuccessful attempts to prepare such an anhydride.
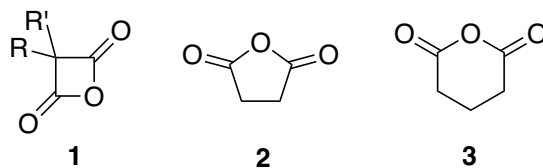
In 1906 Otto Diels (of future Diels-Alder fame) heated either malonic acid (HOCOCH$_2$COOH) or diethyl malonate with P$_2$O$_5$ and obtained a gas of formula C$_3$O$_2$ that could be hydrolyzed back to malonic acid.[2] In that respect it could be considered an anhydride of malonic acid, but it was carbon suboxide, of structure O=C=C=C=O, not **1**, R,R'=H.

The next report of a malonic anhydride was by Einhorn and von Diesbach.[3] They reacted diethylmalonyl chloride with aqueous pyridine and they could isolate an anhydride as an amorphous powder. It was an anhydride because it could be hydrolyzed back to the acid or converted with ammonia or diethylamine to diacid + diamide + acid amide. But according to melting-point depression, it did not have structure **1**, R,R' = C$_2$H$_5$, but was a 12-mer, presumably of (average) structure **4**. Besides, heating the 12-mer converted it to a tetrameric anhydride, perhaps cyclic (**5**).
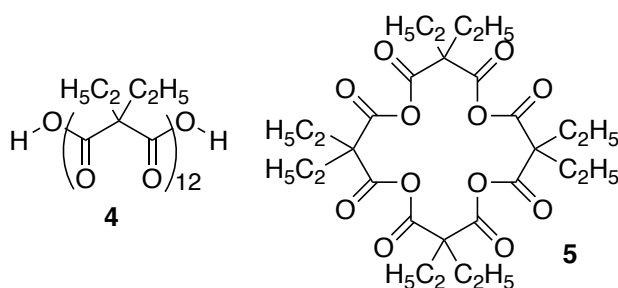
Hermann Staudinger questioned those measurements of molecular weight, especially because the values might have been low owing to the presence of impurities or decomposition products.[4] Indeed, after further purification molecular-weight determinations indicated a 17-
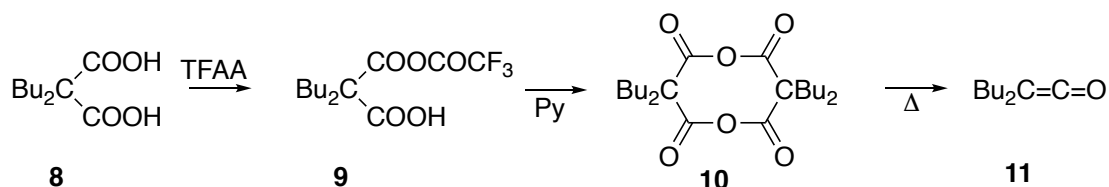
mer. An alternative synthesis used dimethylmalonic acid and acetic anhydride, toward

conversion to dimethylketene, a substance of more interest to him.[5] The resulting anhydride

was not soluble in most organic solvents, did not have a well-defined melting point, and was

acknowledged as polymeric. Staudinger was fascinated by such substances, which he called

"macromolecules" and which could be obtained by a reaction he called "polymerization". This

concept met much resistance from other chemists, who would not accept such large molecules,

with molecular weights above 5000. Of course, we know that eventually he triumphed, and, in

1953, he was awarded the Nobel Prize for Chemistry for his discoveries in the field of

macromolecular chemistry.[6]

Monomeric malonic anhydrides **1** continued to be sought. One example was the

treatment of α-phenyl-β-benzoylethylmalonic acid with $SOCl_2$ to form what was claimed to be a

crystalline anhydride, **6**.[7] However, as a result of a suggestion made at a meeting of the

Chemical Society, it was found that the benzene ring in such materials could be hydrogenated

without hydrogenating a carbonyl group, so it was concluded that the material was instead the

dilactone **7** derived from the ketone hydrate.[8] One cryptic report showed the phosphorescence

spectrum of diphenylmalonic anhydride, but without any disclosure of its provenance or other

properties.[9]

6 **7**
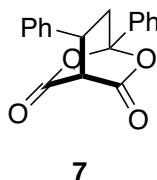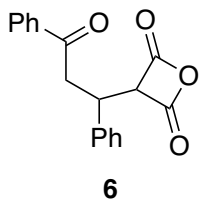
More recent claims for the preparation of monomeric malonic anhydrides **1** can be refuted by infrared evidence. Anhydrides show a characteristic pair of carbonyl bands, at high frequency, and the frequency increases with decreasing ring size. Linear extrapolation from the 1761- and 1802-cm^{-1} frequencies of glutaric anhydride (**3**) and the 1796- and 1872-cm^{-1} frequencies of succinic anhydride (**2**) suggests that malonic anhydrides ought to show carbonyl bands near 1830 and 1940 cm^{-1}.

In particular, the reaction of a dialkylmalonic acid, especially dibutyl **8**, with trifluoroacetic anhydride produced a mixed anhydride **9**.[10] Heating in vacuum or treatment with pyridine then produced a malonic anhydride **10** that could be pyrolyzed to a dialkylketene **11**. However, **10** showed IR bands at 1760 and 1824 cm^{-1}, characteristic of an oligomer. Consequently those bands were attributed to the cyclic dimer **10**.

Bu$_2$C(COOH)(COOH) —TFAA→ Bu$_2$C(COOCOCF$_3$)(COOH) —Py→ **10** (cyclic dimer, Bu$_2$C ... CBu$_2$) —Δ→ Bu$_2$C=C=O

| **8** | **9** | **10** | **11** |

Similarly, treatment of dibutylmalonyl peroxide **12** with Ph$_3$P, as well as of dibutylmalonic acid **8** with PhSO$_2$Cl in pyridine, produced that same anhydride, with IR bands at 1760 and 1815 cm^{-1},[11] and this was later acknowledged as polymeric.[12] More puzzlingly, treatment of diethylmalonic acid with dicyclohexylcarbodiimide produced material with IR bands of medium intensity at 1900 and 1980 cm^{-1}, with the former slightly more intense, and assigned as **1** (R,R' = C$_2$H$_5$), but not further characterized,[13] not even in the full paper.[14] More recently it was claimed that dehydration of dimethylmalonic acid with UF$_6$ produced dimethylmalonic anhydride (**1**, R,R'= CH$_3$), as characterized by GC but without any IR evidence.[15] In summary, monomeric malonic anhydrides were elusive.
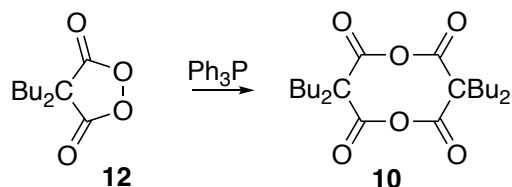
Successful Synthesis

Monomeric malonic anhydrides **1** were first prepared and characterized by a UCSD undergraduate working in my lab.[16] That undergraduate was Thomas Arrhenius, the great-grandson of Svante Arrhenius , so chemistry was in his genes. Thomas' grandfather was also a chemist. When he died, Thomas' father went back to Sweden to clean out his own father's lab. There he found a vial labeled malonic anhydride! But it turned out to be the polymeric form, like Staudinger's.

Our plan was to prepare malonic anhydrides **1** by ozonolysis of a ketene dimer (Scheme 1). Although the target malonic anhydrides look like such readily available materials, the proposed precursors look more complicated. Yet the parent (**13**, R,R'=H) is diketene, long sold by Tennessee Eastman by the tankcar lot.[17] And the dimethyl derivative (**13**, R,R'=CH₃) had been available from Aldrich and was an Org. Syn. prep.[18] This procedure has the advantage of starting with a strained four-membered ring, rather than trying to close it as in the many unsuccessful attempts.

Scheme 1. Malonic Anhydrides **1** by ozonolysis of ketene dimers **13**.
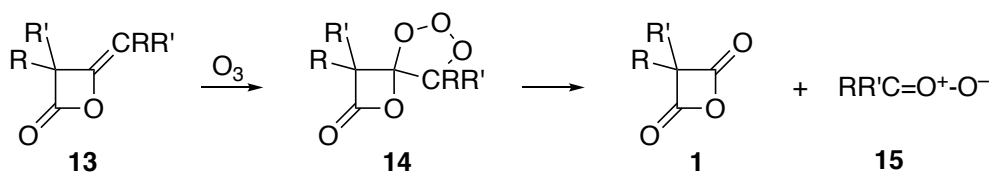
No one had ever synthesized anhydrides by ozonolysis, presumably because nearly all

anhydrides are more readily available than the enol esters and enol lactones that might serve

as their ozonolysis precursors. Malonic anhydrides are an exception! Besides, in ozonolysis

there is always the dilemma of where the third oxygen goes when the ozonide **14** fragments.

As suggested in Scheme 1, it seemed likely that that oxygen would go to the unoxygenated

carbon. In that way the oxygenated carbon would be stabilized by ester resonance and not

react further with the carbonyl oxide **15**. In support of this hypothesis, ozonolysis of

dihydropyran **16** was known to produce a formate ester and an aldehyde oxide RCH=O$^+$-O that

is converted by methanol to a hydroperoxide.[19]

16
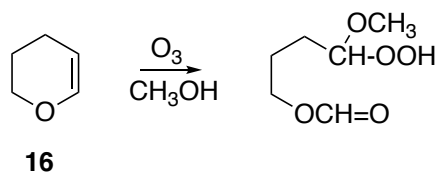
Indeed, Thomas showed that isopropenyl acetate could be ozonized to acetic anhydride

(Scheme 2a) and that 6-phenyl-5-hydroxy-5-hexenoic acid δ-lactone could be ozonized to

glutaric anhydride (**3**, Scheme 2b).[16] Both of these are present as such in the reaction mixture

while the aldehyde oxide dimerizes or trimerizes. Therefore, ozonolysis of an enol ester or enol

lactone is indeed a feasible method for synthesis of anhydrides, as was subsequently

confirmed, without acknowledgment, by ozonolysis of vinyl acetate.[20]

Scheme 2. Ozonolytic preparation of (a) acetic anhydride and (b) glutaric anhydride (**3**).

(a)   (b)
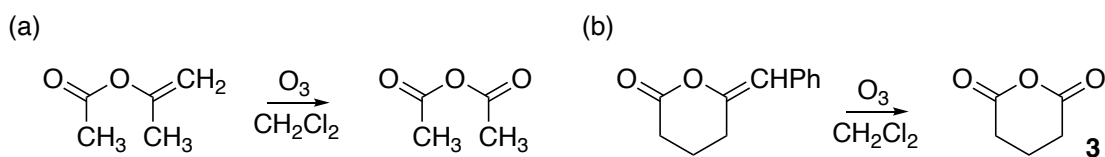
Our initial studies had used a ozonator purchased from a pet store and intended for a home aquarium. Then after pilot studies that promised feasibility we bought a higher-capacity OREC ozone generator and calibrated its output so as to introduce one equivalent of O_3, as signaled by its blue color, and then disperse any excess with a stream of O_2.

Ozonolyses of diketene (**13**, R,R'=H) and of the enol lactone dimer of dimethylketene (**13**, R,R' = CH$_3$) in CH$_2$Cl$_2$ or CDCl$_3$ at -78 C produced material whose NMR spectra, both ^{1}H and ^{13}C, were consistent with formation of malonic anhydride (**1**, R,R' = H) or dimethylmalonic anhydride (**1**, R,R'=CH$_3$), respectively (Scheme 1).[16] However, those spectra were not particularly diagnostic, because they showed very ordinary chemical shifts that would not distinguish a monomeric malonic anhydride from an oligomer. More convincingly, the malonic anhydrides could be converted with aniline or phenol to known derivatives that could be characterized by melting point. The yields of those derivatives, as well as of monoethyl esters, were nearly quantitative, inconsistent with oligomeric anhydrides that would hydrolyze to a mixture of products.

One eminent synthetic-organicker told me that he could have kicked himself for not thinking of such a simple, one-step procedure. But he decided that if the synthesis of malonic anhydrides were so simple, then someone like R. B. Woodward would have thought of it. And since no one had reported the synthesis of a monomeric malonic anhydride, the procedure must not work. But it does.

The IR spectra of the products from ozonolyses of **13** were diagnostic.[16] They showed a strong doublet at 1820 and 1830 cm^{-1} for R,R' = H and a strong absorption at 1820 cm^{-1} for R,R' = CH$_3$. Such high frequencies are in excellent agreement with the extrapolated frequency of

1830 cm^{-1}. Nevertheless, the expected band at 1940 cm^{-1} was absent, and there was no absorption between 1850 and 2000 cm^{-1}.

The absence of the high-frequency band had us puzzled for a while, until we remembered the selection rues for infrared spectroscopy. The high-frequency mode in malonic anhydrides is the symmetric, in-phase carbonyl stretch. It is expected to be weak inasmuch as the carbonyls are opposed and the symmetric mode does not change the dipole moment appreciably. In support, it is a general observation that although the high-frequency carbonyl band is the more intense one in acyclic anhydrides, it is the less intense one in cyclic anhydrides.[21] Indeed, if a malonic-anhydride molecule were highly symmetric, with carbonyls exactly opposed, then the in-phase stretch would be totally forbidden. In support of this principle neither 1,3-cyclobutanedione (**17**, R = H) nor tetramethyl-1,3-cyclobutanedione (**17**, R = CH$_3$) shows a high-frequency carbonyl absorption.[22] Therefore, we can conclude that our lone high-frequency carbonyl frequency is consistent with malonic anhydrides. A similar feature, strong IR absorptions at both 1760 and 1890 cm^{-1}, is seen in the less symmetrical and more electron-rich *N*-methyl-2-pyrrolidinylidenemalonic anhydride **18**.[23] Moreover, this analysis shows that the claim of a malonic anhydride with IR absorptions at both 1900 and 1980 cm^{-1} cannot be valid. [13]

17   **18**   **19**
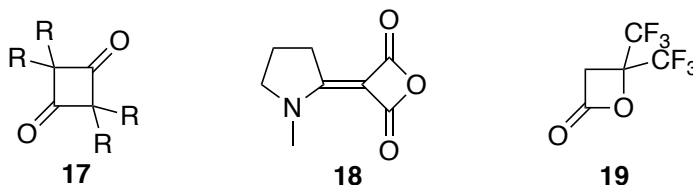
We never tried to take a mass spectrum of a malonic anhydride as part of a structure proof. Cyclic anhydrides are very polar, with high boiling points, and malonic anhydride would

be difficult to vaporize. However, with modern ionization techniques, someone might be able to take its mass spectrum and determine whether its molecular ion can be detected or whether it fragments.

Selection rules are reversed in the Raman spectrum, such that the symmetric, in-phase carbonyl stretch becomes allowed. Indeed, the Raman spectrum of dimethylmalonic anhydride shows a prominent line at 1947 cm⁻¹,[24] in excellent agreement with the other extrapolated frequency of 1940 cm⁻¹. This observed frequency is a champion among all organic carbonyl compounds.[25] It is so high and so unusual that it constitutes our best structure proof for the elusive monomeric malonic anhydride. The only other organic carbonyl compound with such a high-frequency vibration is β,β-bis(trifluoromethyl)-β-butyrolactone **19**, with λ_{max} claimed at 5.29 and 5.13 μ,[26] or 1890 and 1949 cm⁻¹, which are much too high for a four-membered-ring lactone.

There is a prior report on the ozonolysis of diketene, a study undertaken in order to decide whether its structure was **20** or **21**. Because a material of mp 144-145º was obtained after derivatization with PhNHNH₂, that material was assigned as the osazone of CH_3COCHO, so the structure of diketene was assigned as **20**.[27] Unfortunately formaldehyde phenylhydrazone, $CH_2=NNHPH$, also melts at 145º, and subsequent ozonolyses of diketene showed that $CH_2=O$ was indeed the product and that the structure of diketene is **13** (R,R'=H), not **20**.[28] The possible intermediacy of malonic anhydride was not addressed.


20   **21**
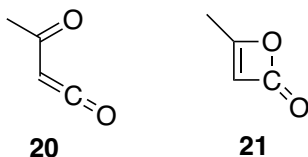
Malonic anhydrides might be useful for synthesizing new penicillin and cephalosporin

derivatives **22** and **23**. They would permit attaching a malonyl residue onto those β-lactam

antibiotics, which might confer resistance to hydrolysis by bacterial β-lactamases. Consequently

the University patented the synthetic procedure.[29] Unfortunately the peroxide byproducts from

the ozonolysis (Scheme 1) discourage large-scale production. I would have been content with

riches within the dreams of avarice, but no pharmaceutical company took advantage of this

synthesis.

22   **23**
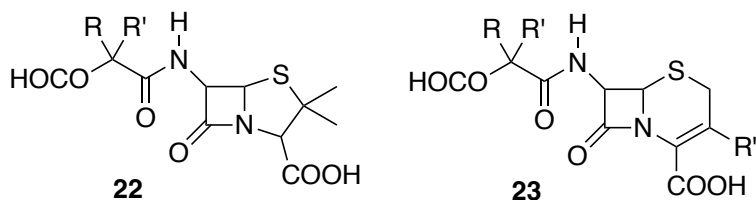
Decomposition

Malonic anhydrides **1** are unstable! We reached this conclusion when we took the ^{13}C

NMR spectrum.[16] As a precaution, we had lowered the temperature to -30º C. But in 1978

NMR spectrophotometers were much less sensitive than today. Before acquiring the final

spectrum it was necessary to check the settings by acquiring a fifteen-minute spectrum. The

two spectra differed! Over the course of an hour some of the malonic anhydride decomposed

to ketene and carbon dioxide (Scheme 3, R,R'=H), both of which have very characteristic ^{13}C

chemical shifts. At 0º C the ketene could be confirmed in the effluent by trapping it as

acetanilide, $CH_3CONHPh$. Likewise, isobutryranilide, $(CH_3)_2CHCONHPh$, could be isolated by

trapping dimethylketene in the effluent following ozonolytic generation of dimethylmalonic

anhydride (Scheme 3, R,R' = CH_3).

Scheme 3. Decomposition of malonic anhydrides.

$$RR'C=C=O$$
$$O=C=O$$
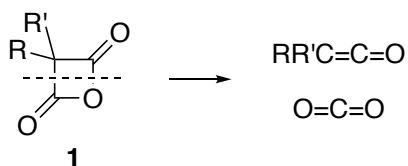
This decomposition documents the falsity of those previously claimed syntheses. Malonic anhydrides do not survive even room temperature. We really were the first to succeed at their synthesis and characterization. The ozonolytic method of Scheme 2 has the advantage that the ketene dimer **13** is so reactive toward electrophilic ozone that it reacts at a temperature low enough that the anhydride survives.

Moreover, the instability of malonic anhydrides demonstrates the fraudulence or imprecision of some recent publications that claimed malonic anhydride as a reactant,[30] and a corrigendum was published for another such report.[31] In addition, it calls into question the four chemical-supply companies that SciFinder lists as offering malonic anhydride or dimethyl malonic anhydride for sale.[32] Three of them did not respond to an e-mail inquiry about availability, while the fourth admitted that it was not in stock.

Why is this decomposition so facile, proceeding even below room temperature? It is much faster than for other four-membered rings. For example, diketene **13** (R,R'=H) decomposes at 548 ºC,[33] cyclobutane **24** decomposes at 449 ºC,[34] cyclobutanone **25** decomposes ~ 350 ºC,[35] β-propiolactone **26** decomposes ~250 ºC,[36] and cyclobutane-1,3-dione **27** at 120ºC.[37] Certainly one reason for the facility of malonic anhydride decomposition is the great stability of CO_2, which confers stabilization on the transition state through product-

development control. But that is not sufficient, inasmuch as β-propiolactone **26** is much slower

to decompose even though it too produces CO_2.

     13   **24**   **25**   **26**   **27**
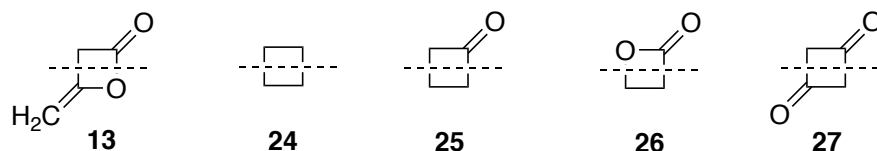
What is the mechanism of the decomposition and how does that account for its facility?

It is certainly a 2+2 cycloreversion, but is it concerted or stepwise? This is a common dichotomy

in 2+2 cycloreversions and cycloadditions.[38] Yet it is difficult to imagine a bond that is so weak

that it can be broken at such a low temperature. Instead, so low an activation energy is

consistent only with a concerted cycloreversion, where a stabilization due to formation of the

new bonds compensates for the energy cost of breaking the old ones.

A further puzzle is that the parent malonic anhydride (**1**, R,R' = H) decomposes at a

slightly lower temperature than does dimethylmalonic anhydride (**1**, R,R' = CH3). This is contrary

to an expectation that the additional methyls ought to stabilize the incipient sp^2-hybridized

carbons and promote a faster reaction, as in β-eliminations,[39] although admittedly not in

ketenes.[40]

To understand the mechanism of decomposition we resorted to computation.[41]

Structures of malonic anhydride (**1**, R,R'=H), ketene (CH_2=C=O), CO_2, and transition state were

optimized at the UBPW91/6-311+G(3df,2p) level, including zero-point energy. The calculated

energy of activation was a low 22.98 kcal/mol.

According to the calculations, the reaction is concerted, with no intermediate to be

found. Moreover, the transition state has Möbius topology, with the positive lobe of one

atomic orbital overlapping with the negative lobe of another, as suggested in Fig. 1. Such a

topology is generally designated as $2_s + 2_a$, indicating that the reaction is suprafacial across the

C=C but antarafacial across the C=O. (An alternative designation is [2s + (2s + 2s)], applicable to

some other cycloadditions,[42] but we shall ignore this distinction.) This requires a twisting, as can

be seen in the calculated structure of the transition state,[41] with an OCCC dihedral angle of 32º

(Fig. 2). The Möbius topology is most clearly seen in the highest-occupied MO, with an

antarafacial interaction of one oxygen of the CO_2 with the carbonyl carbon of the ketene (Fig.

3). Thus, the facility of the decomposition is due not only to the great stability of CO_2 but also

to the involvement of ketene, which allows antarafacial coordination across its C=C.[43] It should

be recognized though that although this is a concerted process, it is asynchronous, with C−O

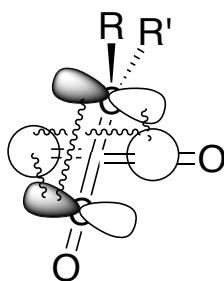cleavage occurring in advance of C−C cleavage.

Figure 1. Transition-state structure for [$2_s + 2_a$] cycloreversion of malonic anhydrides, with

atomic-orbital overlaps indicated by wavy lines.[reprinted from ref 41. Copyright 2012
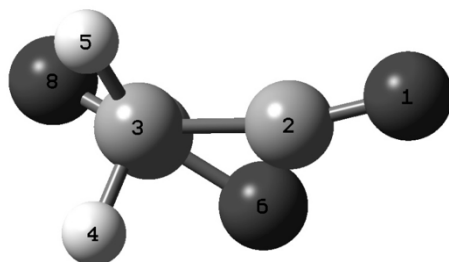
American Chemical Society.]]

Figure 2. Transition-state structure for decomposition of malonic anhydrides, as calculated at the MP2/6-31G(d) level.[reprinted from ref 41. Copyright 2012 American Chemical Society.]]
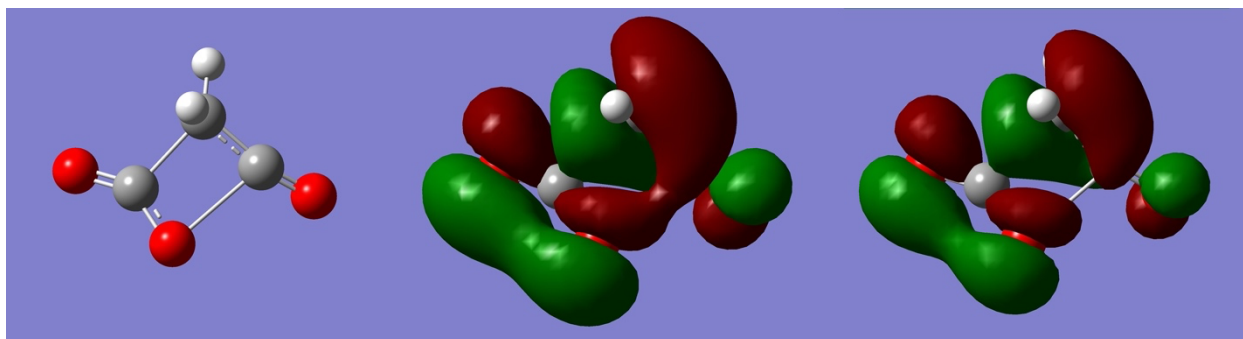

Figure 3. Atomic framework and two contours of the HOMO of the transition state for decomposition of malonic anhydrides, as calculated at the B3LYP/6-31G(d) level.[reprinted from ref 41. Copyright 2012 American Chemical Society.]]

Kinetics of Decomposition

Further insight into why decomposition is so fast and why the parent is faster than the dimethyl comes from experimental measurements of the rates of decomposition. For many years we were unable to study those kinetics, because of the presence of the peroxide byproduct (Scheme 3). Indeed, in the synthesis of dimethymalonic anhydride, the byproduct is the trimer, triacetone triperoxide (TATP, the Shoe Bomber's explosive, which was also used by suicide bombers in Paris in 2015 and in Brusssels in 2016). It is highly susceptible to accidental detonation, leading to its nickname "Mother of Satan". It is not a wise idea to place such materials in the NMR probe.

More recently we returned to this question now that NMR instrumentation has become sensitive enough to permit concentrations low enough that the peroxide byproducts do not

endanger the researcher or the spectrometer probe. We could follow the disappearance of

malonic anhydride by monitoring the intensity of the CH_2 or $C(CH_3)_2$ singlet of **1** (R,R' = H or CH_3)

or the $CHCH_3$ doublet of **1** (R = H, R' = CH_3).[41] The kinetics in $CDCl_3$ follow simple first-order

decay. Figure 4 shows the Eyring plot for the three sets of rate constants. Activation

parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ could be derived from the temperature dependences of those rate
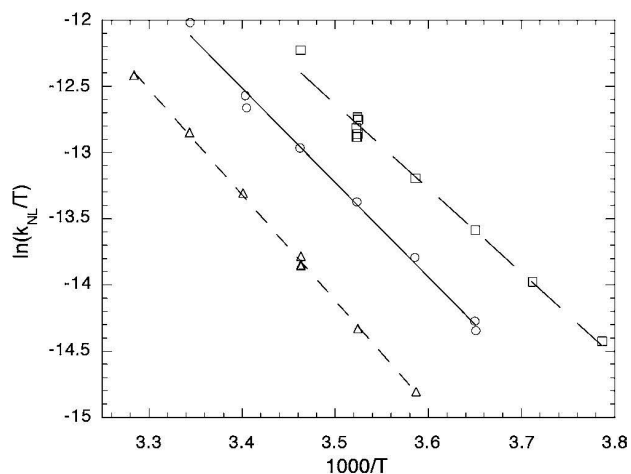
constants.

Figure 4. Eyring plot for decomposition of malonic anhydrides **1**: (○) parent, (□) methyl, and (△) dimethyl.[reprinted from ref 41. Copyright 2012 American Chemical Society.]

We could document quantitatively that dimethylmalonic anhydride **1**, R,R' = CH_3,

decomposes more slowly than parent malonic anhydride, **1**, R,R' = H. Thus, decomposition of

the parent can be followed conveniently in the range from 0 to 25 ºC, whereas that range is 5

to 30 ºC for the dimethyl. More quantitatively, $\Delta H^{\ddagger}$ is 15.9±0.2 kcal/mol for **1**, R,R' = CH_3, but

only 14.2±0.4 kcal/mol for **1**, R,R'=H. Besides, those enthalpies of activation conclusively

exclude the possibility of a stepwise reaction, because there is no bond in the molecule whose

bond strength is so low.

The computed activation energy of 23 kcal/mol for **1**, R,R' = H, is considerably higher

than the experimental 14 kcal/mol. The discrepancy can be attributed not only to the level of

theory used but also to the neglect of solvation, because when solvation is modeled with PCM, the activation energy decreases.

To help understand why dimethylmalonic anhydride **1**, R,R' = CH$_3$, decomposes more slowly than parent malonic anhydride **1**, R,R' = H, we also studied the kinetics of decomposition of monomethyl malonic anhydride **1** (R = H, R' = CH$_3$). It is the fastest of all three! All the activation parameters are listed in Table 1. Remarkably, neither the enthalpies of activation nor the free energies of activation are monotonic in *n*, the number of methyl groups. For the monomethyl anhydride $\Delta H^{\ddagger}$ is an unusually low 12.6 kcal/mol.

Table 1. Activation parameters for decomposition of malonic anhydrides, (CH$_3$)$_n$CH$_{2-n}$(CO)$_2$O.

n_{CH3}	$\Delta H^{\ddagger}$,kcal/mol	$\Delta S^{\ddagger}$,cal/mol-deg	$\Delta G^{\ddagger}$,kcal/mol
0	14.2±0.4	-23.9±1.5	21.06±0.04
1	12.6±0.5	-28.1±1.7	20.73±0.05
2	15.9±0.2	-19.8±0.8	21.55±0.02

A clue to understanding the sequence of reactivities comes from the entropies of activation, also listed in Table 1. For all malonic anhydrides $\Delta S^{\ddagger}$ is negative, opposite to what might be expected for a fragmentation reaction of one molecule into two (which proceeds with a $\Delta S^{o} > 0$) but consistent with a concerted [2+2] process that requires a more organized antarafacial transition-state structure that permits the necessary orbital overlaps. Like $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ the values of $\Delta S^{\ddagger}$ are not monotonic in the number of methyl substituents, and $\Delta S^{\ddagger}$ is most negative for *n*=1. According to the calculations, a methyl retards decomposition through steric destabilization of the twisted transition-state structure (Figures 1-3), which brings one methyl group closer to one of the oxygens of the CO$_2$. According to the B3LYP/cc-pVTZ calculation on

the parent (**1**, R,R'=H), the distances between an H and the oxygens of the CO_2 have shortened

from 2.889 and 3.043 Å in the anhydride to 2.647 and 2.925 Å in the transition-state structure.

For the dimethyl anhydride **1**, R,R'=CH$_3$, the distances between an H on each methyl and one or

the other oxygen of CO_2 have shortened from >3.2 Å to 2.664 and 2.783 Å in the transition-

state structure. One of those distances is within 2.72 Å, the sum of the van der Waals radii for

H and O.[44] This is an unusual situation for the transition state in a fragmentation because the

twisting brings a methyl closer to an oxygen, not farther as might be expected.

The least negative $\Delta S^{\ddagger}$ is for n_{CH3} = 2 (**1**, R,R' = CH$_3$). This may be a consequence of the

steric repulsion, whereby the transition-state structure has a more pronounced character of

fragmentation and therefore less organization. The more interesting result is the 4.2 ± 2.3

cal/mol-deg more negative $\Delta S^{\ddagger}$ for n_{CH3} = 1 (**1**, R = H, R' = CH$_3$) than for n_{CH3} = 0 (**1**, R,R' = H). This

is consistent with a contribution of $R \ln 2$, arising from the ability of the latter to twist in two

directions to reach the transition-state structure, whereas **1** (R = H, R' = CH$_3$) can twist in only

one way to avoid methyl repulsion.

Why though is the monomethyl anhydride **1** (R = H, R' = CH$_3$) the fastest of all three? It

must be that a methyl group stabilizes the transition state, even though it does not stabilize an

sp^2 carbon in a ketene. We suggest that there is delocalized charge in in the transition state,

and a methyl group stabilizes that by hyperconjugation. In support, the calculated total charge

on the methyl group in the transition-state structure is greater than the total charge on the

methyl in either reactant **1** (R = H, R' = CH$_3$) or in product methylketene. However, a second

methyl does not provide enough hyperconjugative stabilization to outweigh its steric

retardation. Consequently dimethylmalonic anhydride **1**, R,R' = CH$_3$, is the slowest of all three,

with the highest $\Delta H^{\ddagger}$, because its transition state suffers steric repulsion regardless of which way it is twisted.

Further Challenges

How acidic are malonic anhydrides **1**? By analogy to diethyl malonate, it ought to be reasonably acidic. Encouragingly, the calculated pK_a of the parent (**1**, R,R' = H) is 7.3.[45] Then if the conjugate base is reasonably stable, its reaction with electrophiles might provide a synthetic entry to more highly substituted malonic anhydrides, many of which are not readily available by ozonolysis of a ketene dimer. However, we anticipate that the anion **28** might undergo decomposition (stepwise!) even faster than the anhydride, because it does not require the geometric constraints and steric repulson of an antarafacial 2+2 cycloreversion (Figs. 1-3). If so, the resulting alkynolate **29** can then react with anhydride, either as base or as nucleophile, so that the reaction would become autocatalytic in added base.
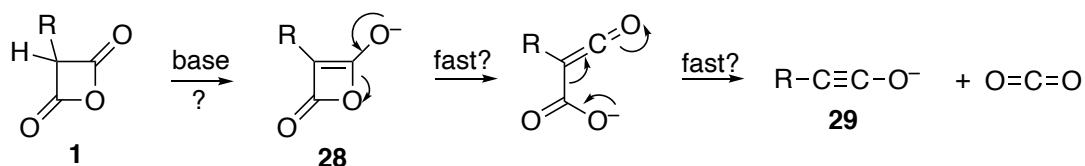
An alternative CH acid is a malonimide **30** ("azetidine-2,4-dione"). It can be prepared by [2+2] cycloaddition of ketene plus isocyanate, as was shown by Staudinger,[46] and also by reaction of an amine with a malonyl dichloride.[47] In contrast to malonic anhydrides, a malonimide does not undergo [2+2] cycloreversion, because R'NCO is so much less stable than CO_2. Moreover, its conjugate base **31** is also stable to [2+2] cycloreversion, because ynolate

anions **29** can be added across isocyanates to give malonimides.[48] Therefore, alkylation of **31**

might be an entry into more highly substituted malonimides.
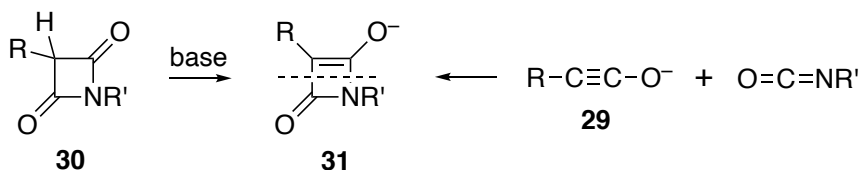
Summary

The topic of malonic anhydrides has been fascinating, with many surprises and

challenges. After more than 70 years of futile attempts, malonic anhydrides were successfully

prepared in 1978 by Thomas Arrhenius, an undergraduate working in my lab. The synthesis is

remarkably easy, just ozonolysis of a readily available ketene dimer. The best evidence for the

monomer was the combination of IR and Raman spectral data, including a record carbonyl

frequency of 1947 cm^{-1}.

Malonic anhydrides are unstable, decomposing below room temperature to a ketene

and CO_2. Therefore, other claims of monomeric malonic anhydrides must be erroneous because

they do not survive room temperature. We were truly the first to succeed at this long-sought

material.

The instability raised further questions, of why decomposition is so facile, and why the

dimethyl derivative is slower to decompose. Computations documented that the

decomposition is a concerted $[2_s+2_a]$ cycloreversion, antarafacial across the C=C of the ketene

product, and not stepwise. Kinetic studies revealed that the monomethyl anhydride is faster

than either the parent or the dimethyl, because a methyl group stabilizes the transition state

electronically but can interfere sterically. In support, the entropy of activation is negative for all,

unusual for a fragmentation but consistent with a twisted transition state that requires organization to minimize steric repulsion.

Author Information

Born in Pittsburgh, Charles L. Perrin graduated from Harvard College in 1959 and received his PhD in 1963 from Harvard University, under the direction of F. H. Westheimer. Following an NSF Postdoctoral Fellowship at UC Berkeley, he joined the founders of the new campus at UC San Diego, where he is now Distinguished Professor of Chemistry (emeritus, recalled to active service). His research spans a broad range of structural and mechanistic chemistry, including malonic anhydrides, anomeric effects, stereoelectronic control, isotope effects, dynamic NMR, solvation, hydrogen bonding, and *p*-benzynes. This is his third Perspective.

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