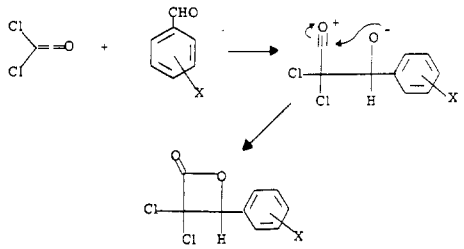
Scheme XII



substituted benzaldehydes and the product yields increase as the benzaldehyde substituent becomes more electron releasing. (2) The reaction appears to be completely stereospecific. (3) The same product and stereochemistry are observed from the azidofuranone decomposition as from the cycloadditions themselves. (4) Generation of chlorocyanoketene in the presence of a 1:10 ratio of *p*-methoxybenzaldehyde and benzaldehyde gave a 0.8:1.0 mixture of, respectively, the *p*-methoxyphenyl- and phenylethene products. On the other hand, when the *p*-methoxyphenylfuranone **45** was decomposed in the presence of 10 molar equiv of benzaldehyde, this ratio increased to 1.4:1.0. Thus the zwitterion **46** is reasonably assumed to partition between alkene product formation and cleavage to chlorocyanoketene and *p*-methoxybenzaldehyde.

These results are of particular interest when they are compared to other reported ketene/aldehyde cycloadditions. For example, dichloro-, methyl-, chloro-, isopropoxy-, and phenoxyketene do cycloadd to aldehydes, but unlike chlorocyanoketene, they react rapidly with electron-deficient aldehydes and slowly or not at all with electron-rich analogues.[28] As mentioned, the opposite is true for chlorocyanoketene. One such study of particular note was recently reported by Krabbenhoft[28e] who reported an investigation of the cycloaddition of dichloroketene with a series of substituted benzaldehydes, including many of the same derivatives we used in the analogous chlorocyanoketene study. Here it was observed that the reaction is most facile with the more electropositive benzaldehyde derivatives. Although the mechanism of these cycloadditions was not established, an extreme dipolar process which reflects the nucleophilic character of dichloroketene is outlined in Scheme XII. Thus, one comes to the rather startling conclusion that dichloroketene functions as a nucleophile in its reactions with benzaldehydes while chlorocyanoketene functions as an electrophile.

A final few brief comments regarding cyanoketene chemistry should be made in order that one is not left with the conclusion that all of their cycloadditions are nonconcerted. Results outlined here clearly show their reactions with imidates, ketenes, and benzaldehydes to be nonconcerted. The same is undoubtedly true for the reactions of *tert*-butylcyanoketene with enol ethers.[4d] Allenes, on the other hand, readily cycloadd to *tert*-butylcyanoketene, but the mechanism appears to vary between a concerted and dipolar process depending upon the allene substituents.[4a,c,i] Alkynes are proposed to react with this ketene by a concerted process,[4g] and alkenes have been documented to react by a ($_{\pi}2_s + {}_{\pi}2_a$) concerted mechanism.[4a,h]

Conclusions

In conclusion, I wish to summarize some significant points resulting from the studies outlined here. (1) For the first time the zwitterions resulting from the interaction of a ketene with an imidate or another ketene or an aldehyde have been independently generated and shown to give the same products as the cycloadditions themselves. (2) The fact that zwitterions are formed in the thermolyses of **18**, **39**, and **45** establishes the mechanism of the zwittazido cleavage, and thus a powerful predictive model is at hand. (3) A new β-lactam synthesis has been discovered, and many of the new cyano-substituted β-lactams show antimicrobial as well as antifungal activity. (4) Finally, a potentially generally mechanistic probe for the investigation of the cycloadditions of a variety of cyano-substituted substrates results from these investigations.

I wish to extend a special thanks to my graduate students and postdoctoral associates whose names appear in the literature cited. They, along with the generous financial support of the National Science Foundation and the National Institutes of Health, have made this research possible.

(28) (a) W. T. Brady and L. Smith, *J. Org. Chem.*, **36**, 1637 (1971); (b) D. Borrman and R. Wegler, *Chem. Ber.*, **99**, 1245 (1966); (c) D. Borrman and R. Wegler, *ibid.*, **102**, 64 (1969); (d) D. Borrman and R. Wegler, *ibid.*, **100**, 1575 (1967); (e) H. O. Krabbenhoft, *J. Org. Chem.*, **43**, 1305 (1978).

Revival of Troponoid Chemistry

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The chemistry of tropone (cycloheptatrienone) and its derivatives began as natural product chemistry.[1] In 1945, the tropolone (2-hydroxytropone) structure was first suggested for stipitatic acid (**1**), a mould metabolite of the Penicillium family, and colchicine (**2**), an alkaloid of the Liliaceae,[2] was recognized as a tropone derivative.

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The author wishes to dedicate this work to Professor E. Havinga on the occasion of his 70th birthday.

(1) (a) T. Nozoe, *Fortschr. Chem. Org. Naturst.*, **13**, 232 (1956); J. G. Buta, J. L. Flippen, and W. R. Lubsy, *J. Org. Chem.*, **43**, 1002 (1978); (b) T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds", Academic Press, New York: Vol. I, 1975, p 398; Vol. II, 1972, pp 43–44.

(2) M. J. S. Dewar, *Nature (London)*, **155**, 50, 141, 479 (1945).

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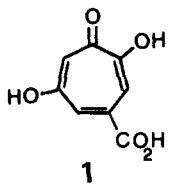
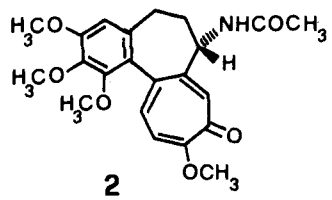
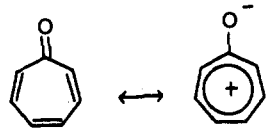


1



2



3a 3b

These suggestions led to recognition of the troponoidal structure for other natural products previously isolated, in particular for antifungal alkyl- and alkenyltropolones from conifers of the family of Cupressaceae,[1,3] which is the third main source of natural troponoids.

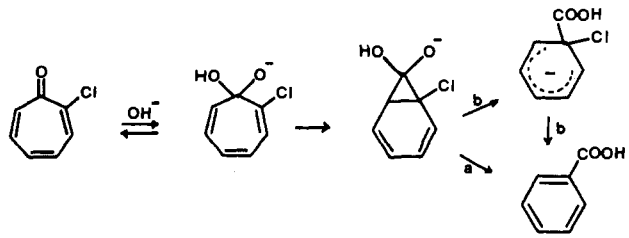
A peculiarity of the tropone structure, 3, namely that it allows writing a plausible tropenylium oxide form (**3b**) with a Hückel sextet of electrons, with implied aromatic properties, aroused general interest. The late forties and the early fifties saw studies on the synthesis, structure, and reactivity of troponoids, and these have been reviewed.[3b] However, probably because the wealth of facts brought to light by these studies was impressively large, suggestive of exhaustiveness, the impression was created that there was no longer anything new to learn in this area. Studies on troponoids were then for some while confined to minor aspects and were pursued mainly in laboratories where such chemistry had started.

Renewed progress came in the late sixties when the time was ripe for appreciating both the shortcomings of some previous conclusions and the fact that some areas had not actually been very thoroughly investigated. With regard to the first point, evidence was obtained that the contribution of form **3b** had been overestimated. Neither the planarity of the cycloheptatrienone nucleus nor the tendency of many of its derivatives toward substitution reactions is now considered to be of aromatic origin.[4] With regard to the second point, extensive research has been conducted in recent years on the behavior of troponoids in basic media and on utilization of the troponoidal skeleton in organic synthesis. This Account is concerned with the latter two aspects of troponoid chemistry.

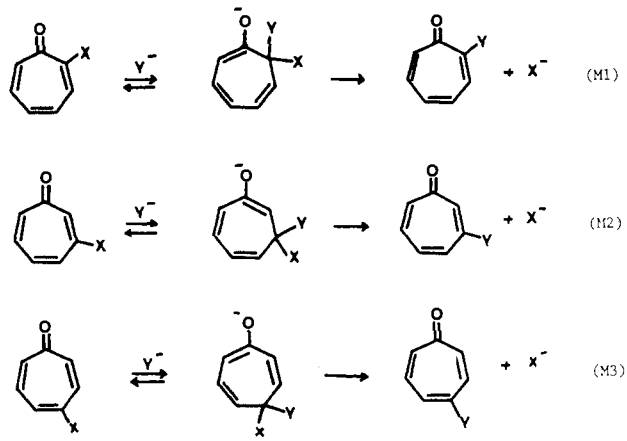
Interaction with Bases and Nucleophiles

Chemists have long been intrigued by the transformation of tropones that carry a nucleofugal substituent into benzene derivatives on treatment with alkali. A representative example is shown in Scheme I. A key step in rearrangement to benzoic acid is disrotatory electrocyclic ring closure in the initial hydroxide ion adduct. It should also be noted that breaking of the

Scheme I



Scheme II



norcaradiene intermediate into products can occur concertedly with loss of the nucleofugal substituent (path a) or a discrete species may be involved resembling the anionic σ-complex intermediate in S_NAr reactions of benzene derivatives (path b).[5] As one might therefore expect, the troponoid to benzenoid rearrangement is accelerated by substituents such as nitro that can accommodate the negative charge of the σ-complex intermediate. Competitively, ring contraction of 2-chlorotropone to salicylaldehyde by alkali was also observed.[3a]

Although there were some early examples, it was only in recent years that one came properly to realize that nucleophilic replacement of nucleofugal substituents with maintenance of the troponoid structure can also occur. As indicated in Scheme II, the carbonyl group of the tropone system activates nucleophilic attack on any of the other six-ring carbon atoms.

Furthermore, cases have recently been found in which nucleophilic attack on a 2- (or α-) substituted tropone effects introduction of the nucleophile at the 7 (or α') position with loss of the 2-substituent, that is, telesubstitution. Clearly some sort of hydrogen shift or exchange is also involved. Instances of the replacement of hydrogen, initiated by nucleophilic attack, have also been found.

Further variety is provided by the occasional incidence of substitution via aryne analogues and by the direct observation of covalent adducts such as those shown in Schemes I and II.

When so many different reaction pathways are available, questions arise as to what happens in a particular case and what principles govern the incidence of one reaction mode or another. Those questions are the focus of attention in this Account.

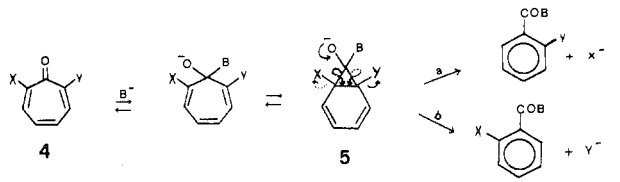
Extrusion of C-1. Extrusion of C-1 from troponoids by bases, such as hydroxide or alkoxide ions in lyate

(3) (a) F. Pietra, *Chem. Rev.*, **73**, 293 (1973); (b) P. L. Pauson, *ibid.*, **55**, 9 (1955).

(4) D. J. Bertelli, T. G. Andrews, Jr., and P. O. Crews, *J. Am. Chem. Soc.*, **91**, 5286 (1969); C. A. Veracini and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 1262 (1972); M. J. Barrow, O. S. Mills, and G. Filippini, *ibid.*, 66 (1973).

(5) R. M. Magid, C. R. Grayson, and D. R. Cowsar, *Tetrahedron Lett.*, 4819, 4877 (1968); R. M. Magid, Ph.D. Thesis, Yale, 1964.

Scheme III



4a, X = Cl; Y = H
4b, X = OMe; Y = Br; NO_2 at C-5; path a (dotted arrows)
4c, X = OMe; Y = Br; CO_2Me at C-4; path b (heavy arrows)

solvents, or amines, occurs easily (in competition with extrusion of other ring carbons or replacement of a mobile α-substituent) for tropones carrying an electron-attracting, mobile group at the α carbon, such as **4a**. Here C-1 extrusion was evidenced by ^{14}C-1 labeling[5] (Scheme III). Such a facile attack at the "hard" carbonyl carbon by "hard" nucleophiles is in line with current views on the factors determining nucleophilicities.[6]

With a strongly bound, mesomerically electron-donating group, such as methoxy, at the α carbon, C-1 extrusion is much more difficult (in competition with a slow replacement of methoxy) unless electron-attracting substituents are present at suitable ring positions.[5] Thus, in contrast with 2-methoxytropone, for both **4b** and **4c** C-1 extrusion occurs easily.[5] Data in Scheme III (which shows only the concerted path, the one that is probable for ordinary troponoids;[5] the type-b pathway of Scheme I likely occurs for troponoids carrying at the right place substituents that can accept the negative charge[5]) suggest that whether the α or the α' group is expelled depends solely on the stabilization of the developing negative charge on the cyclohexadiene ring by the powerful electron-attracting substituents at C-4 or C-5. In fact, with **4b** the poor nucleofuge MeO^- is lost in preference to the good nucleofuge Br^- because a NO_2 substituent at C-5 can accept the negative charge which develops during breaking of **5** along path a. Conversely, for similar reasons a powerful electron-accepting group like CO_2Me when placed at C-4 can only favor decomposition of **5** along path b.[5] In contrast, the relative stabilities of the two leaving groups X^- and Y^- do not play any role[5] (Scheme III). However, without such powerful electron-attracting substituents, both path a and path b intervene, thus reflecting in part the relative stabilities of Y^- and X^-.[5]

The usefulness of these rearrangements for structural elucidation of troponoids through benzenoids is apparent.

With less mobile, mesomerically strongly electron-donating groups at the troponoidal α carbon, such as with 2-(dialkylamino)tropones, ring contraction is entirely suppressed. Only replacement of the dialkylamino group is observed, albeit at a very low rate.[7b]

Uncommon cases of C-1 extrusion from troponoids by bases are also known, promoted either by an activating, mobile group, such as bromine, at C-4 in combination with other substituents,[8a] or by activating but immobile groups, in which case the final product is a dihydroarene.[8b] When none of the above conditions is fulfilled, such as with tropone itself, its alkyl derivatives, or simple β-halo- or γ-halotropones, resinification in alkali is the rule.[3a]

An important point that begins to emerge here is the division of troponoids into activated and deactivated ones, as far as their behavior toward bases is concerned. Activation is provided by electron-attracting groups, most effectively by those which, like nitro, can accept a full negative charge, but also by chlorine or bromine. Deactivation is imparted by electron-releasing substituents, most effectively by dialkylamino, but also by alkoxy substituents. Activation leads to a variety of ring carbon extrusions, while deactivation renders the seven-membered ring inert, allowing only slow nucleophilic replacement at the α position.[7b]

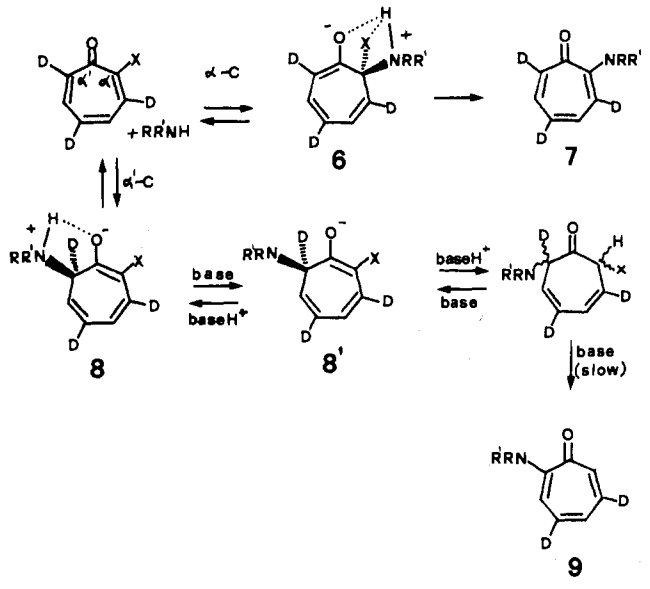
Attack at the α Carbon. Two general cases are known of ipso substitution at the α carbon carrying the mobile group. Evidence for such a pathway is retention in the product of deuterium atoms at positions 3, 5, and 7 of a tropone with halogen, methoxy, or tosyloxy substituents, in the 2-position. Reactions with primary or secondary amines as nucleophiles[9] replace at very much the same rates, independently of the solvent nature, either typically good leaving groups, such as tosyloxy and halogens, or typically poor leaving groups, such as methoxy, according to eq M1, Scheme II. These reactions are kinetically second order. Invariance of the reaction rates results from $\Delta H^{\ddagger} - \Delta S^{\ddagger}$ compensation. Interestingly, fluorine is an exception,[9] being replaced about a thousand times faster than the other nucleofugic groups mentioned. The behavior of fluorine is reminiscent of that in S_NAr reactions of benzene derivatives.[10] It is appealing to imagine that the leveling out of the rates, and therefore the isokinetic relationships, come from intramolecular hydrogen bonding assistance of the type later shown for **6** in Scheme IV.

With thiolate ion nucleophiles, chlorine, bromine, and iodine are replaced at nearly the same rate while fluorine is about 30 times more mobile. However, a 2-methoxy group is not replaced at all.[11] The reason, no doubt, is that an arylthio group is a good nucleofuge and a methoxy group a rather poor one, so that the intermediate σ complex in eq M1 reverts to reactants rather than expelling methoxide ion. Raising the temperature leads to demethylation of 2-methoxytropone, tropolonate acting as the leaving group.[12]

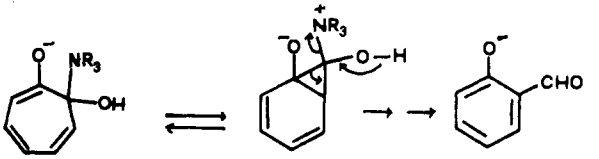
However, as alluded to before, the complexity of these systems, and consequently both their interest and usefulness, are greater than appears here. In fact, in the reactions of amines with tropones α-substituted with a trialkylammonio group, there is a complete shift from ipso substitution at the α carbon to a very rapid, clean telesubstitution at the α' carbon, with loss of the α' deuterium (Scheme IV: X = $^+NR_3$; route to **9**).[7] Telesubstitution at the α' carbon occurs also with 2-chlorotropone in reaction with ammonia or *m*-chloroaniline (Scheme IV, X = Cl; route to **9**), though only in the presence of triethylamine in the latter case. Without Et_3N, *m*-chloroaniline effects ipso substitution

(6) R. G. Pearson, *Surv. Prog. Chem.*, **5**, 1 (1969).
(7) (a) G. Biggi, F. Del Cima, and F. Pietra, *J. Am. Chem. Soc.*, **94**, 4700 (1972); (b) G. Biggi, F. Del Cima, and F. Pietra, *ibid.*, **95**, 7101 (1973).
(8) (a) Y. Kitahara, I. Murata, and T. Muroi, *Bull. Chem. Soc. Jpn.*, **38**, 1195 (1965); (b) K. Kikuchi, *ibid.*, **40**, 355 (1967).
(9) F. Pietra and F. Del Cima, *J. Chem. Soc. B*, 2224 (1971).
(10) J. F. Bunnett, E. W. Garbish, Jr., and K. M. Pruitt, *J. Am. Chem. Soc.*, **79**, 385 (1957).
(11) M. Cavazza, G. Biggi, F. Del Cima, and F. Pietra, *J. Chem. Soc., Perkin Trans. 2*, 1636 (1975).
(12) G. Biggi, F. Del Cima, and F. Pietra, *Tetrahedron Lett.*, 183 (1973).

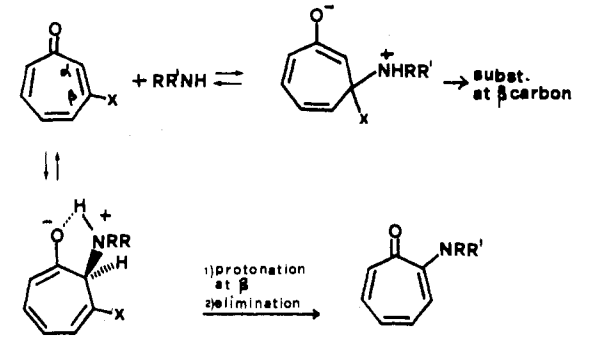
Scheme IV



Scheme V



Scheme VI



at the α carbon.[7b] 2-Chlorotropone is not as efficient as a 2-(trialkylammonio)tropone in these refunctionalization reactions: half of it is lost as benzoic amides via the C-1 extrusion path.[7b]

To delineate the picture further, with 2-methoxy-, 2-(dialkylamino)-, or 2-fluorotropone, only ipso substitution at the α carbon occurs (Scheme IV: X = OMe, NR_2, or F; route to **7**).[7b] These reactions are fast for 2-fluorotropone but very slow in the other two cases.[7b]

Why should a nucleophile effect telesubstitution at α' rather than ipso substitution at the α position? Presuming that ipso attack will normally be followed by departure of a suitably nucleofugal group, we conclude that telesubstitution must involve faster initial attack of the nucleophile at the α' (to form σ complex **8**) than at the α position (to form **6**). In this connection, we note that nucleophiles often attach to benzene derivatives carrying a nucleofugal substituent preferentially at a hydrogen position; thus, 2,4,6-trinitroanisole combines with methoxide ion most rapidly at the 3 position, although the ipso σ complex is thermodynamically favored.[13] No doubt steric hindrance to ipso attack by a large troponoid α substituent such as a trialkylammonio group would reinforce other factors favoring α' attack.

Once a nucleophile has arrived at the α' position, what can it do? Inasmuch as nucleophiles are also nucleofugal, in most cases detachment to regenerate the substrate is the only option available. However, the α' σ complex derived from a primary or secondary amine nucleophile can yield an N–H proton to a base, which might be another molecule of the amine or an added amine such as Et_3N, and thereby form conjugate base σ-complex **8′**. In **8′**, the amino group is rather secure because a dialkylamino group is a poor nucleofuge—it would have to be expelled as a high energy dialkylamide ion. If **8′** is protonated at nitrogen, it will revert to **8** and perhaps thence to the substrate, but protonation at the α position forms a ketone from which α,ζ elimination can occur to form telesubstitution product **9**.

This rationalization is supported by the fact that with strong electron-attracting X groups, such as the trialkylammonio group, species of type **8′** can be spectroscopically detected. These either lie in a cul de sac if no protons are available, as in the case of thiolate ion nucleophiles in dimethyl sulfoxide,[11] or are found along the reaction path to **9** in reactions with amines.[7]

The synthetic usefulness of the reactions of tropones with nucleophiles is increased by the observation of de novo functionalization at the α carbon. Thus, amines in benzene are known to replace the α hydrogen, formally as hydride, in regiospecific reactions.[14]

Going to benzenoid contractions, extrusion of the α carbon is rare. So far it has been encountered only when 2-quinuclidinio-3,5,7-trideuteriotropone iodide is treated with very concentrated (8 M) sodium hydroxide to give a mixture of α,3,5-trideuterio-2-hydroxybenzaldehyde (via C-3 extrusion) and 3,5-dideuterio-2-hydroxybenzaldehyde (via C-2 extrusion).[15] It seems plausible that ipso attack results preferentially in extrusion of C-2 rather than in ipso substitution because the norcaradiene intermediate can collapse to the aldehyde by proton loss (Scheme V).[11] This mechanism is not available to nonprotic nucleophiles such as a thiolate or an alkoxide ion.

Attack at the β Carbon. Both substitution at and extrusion of the troponoidal β carbon are known. The first process (Scheme II, eq M2) needs the presence of a good leaving group at the β carbon while the second process only occurs with certain tropones carrying an electron-attracting, displaceable group at the α carbon.

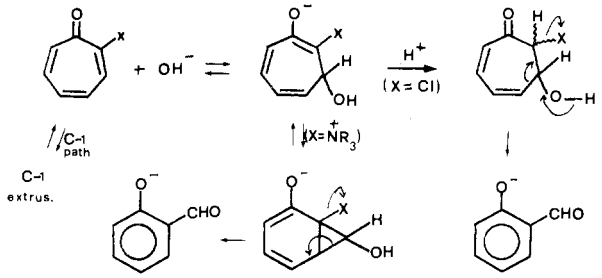
Beginning with the substitution process, we note that anionic nucleophiles show a different behavior from protic amine nucleophiles. With amine nucleophiles, cine substitution at C-2 competes with substitution at C-3 (Scheme VI). Thus, simple substitutions at C-3 were found to occur in reactions of 3-chloro- and 3-tosyloxytropone with sodium methanethiolate in ethanol and of 3-tosyloxytropone with alkoxide or phenoxide ions in ethanol,[16a] leading to a general synthesis

(13) M. R. Crampton and V. Gold, *J. Chem. Soc. B*, 893 (1966); K. L. Servis, *J. Am. Chem. Soc.*, **89**, 1508 (1967).

(14) (a) B. Ricciarelli, R. Cabrino, F. Del Cima, C. A. Veracini, and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 723 (1974); (b) M. Cavazza, R. Cabrino, F. Del Cima, and F. Pietra, *J. Chem. Soc., Perkin Trans. 1*, 609 (1978).

(15) G. Biggi, F. Del Cima, and F. Pietra, *Tetrahedron Lett.*, 3537 (1974).

Scheme VII



of β-tropolone ethers.[16b] In contrast, in reactions of primary and secondary amines with both 3-chloro- and 3-tosyloxytropone, substitution at C-3 competes with substitution at C-2, the former being favored by polar solvents, such as dimethyl sulfoxide. Nonpolar solvents, like benzene, induce instead predominating substitution at C-2, except that with 3-tosyloxytropone at very high amine concentrations a substantial proportion of substitution at C-3 occurs.[16c]

All these observations can be interpreted in line with ideas developed above. Substitution at the α carbon is proposed to proceed in nonpolar solvents because of a specific stabilization of the transition state for attack at C-2 by intramolecular hydrogen bonding (Scheme VI). However in polar solvents, or with great excess of the amine (which is equivalent from the point of view of the polarity of the medium), transition states are so well solvated by the surrounding medium that intramolecular assistance is no longer required, and substitution of the good leaving group X is preferred.

With regard to ring contractions, extrusion of the β carbon was found to compete with extrusion of the β' carbon, the relative proportions of the two processes depending on the nature both of the attacking base and of the mobile substituent at C-2. Clean extrusion of the β carbon, evidenced by deuterium labeling of the troponoidal ring, has been observed in alkali with both 2-chloro-[17] and 2-quinuclidiniotropone,[18] but by different mechanisms.

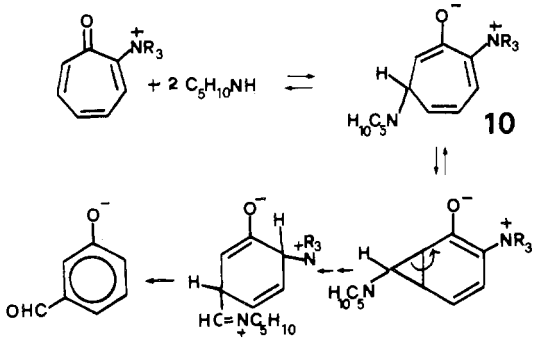
Curiously, the balance between C-3 extrusion to give salicylaldehyde and C-1 extrusion to give benzoic acid is shifted toward the aldehyde either by decreasing the alkali concentration in the case of 2-chlorotropone[17] or by increasing the alkali concentration in the case of 2-quinuclidiniotropone.[18] This can be rationalized in terms of a pathway to the aldehyde (Scheme VII) requiring protonation (and thus being the less likely the more the alkali is concentrated) for reaction of 2-chlorotropone. Protonation assists the reaction because displacement of a nucleofugal group X^- occurs more easily from an sp^3 carbon (as in the protonated form, which, moreover, can easily assume a favorable conformation with trans-coplanar migrating bonds[17]) than from an sp^2 carbon (as in the nonprotonated form). That protonation is not needed in the case of the trialkylammonio salt is attributed to the great activation by this positively charged group which leads to loss of

(16) (a) M. Cavazza, M. P. Colombini, M. Martinelli, L. Nucci, L. Pardi, F. Pietra, and S. Santucci, *J. Am. Chem. Soc.*, **99**, 5997 (1977); (b) M. Cavazza, R. Cabrino, and F. Pietra, *Synthesis*, 298 (1977); (c) B. Ricciarelli, G. Biggi, R. Cabrino, and F. Pietra, *ibid.*, 189 (1975).

(17) E. J. Forbes, D. C. Warrell, and W. J. Fry, *J. Chem. Soc. C*, 1693 (1967).

(18) (a) G. Biggi, F. Del Cima, and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 1627 (1971); (b) G. Biggi, A. J. de Hoog, F. Del Cima, and F. Pietra, *J. Am. Chem. Soc.*, **95**, 7108 (1973).

Scheme VIII



the starting troponoid by conjugate attack of OH^- at sufficiently high concentration of OH^- (Scheme VII).[18b]

Smooth extrusion of the β' carbon was observed with 2-quinuclidiniotropone upon changing from hydroxide to piperidine in water as the attacking nucleophile.[18] A plausible mechanism is proposed in Scheme VIII. The intermediacy of the iminium salt accounts for the observation that primary amines are much less effective than secondary amines in promoting extrusion of C-6, presumably because of less effective stabilization of the iminium salt by a single alkyl group.[18] The mechanism of Scheme VIII for the reaction in water is consistent with that of Scheme IV for the same system in dimethyl sulfoxide. In fact, for the sake of simplicity Scheme IV was drawn without indication that in dimethyl sulfoxide observation of intermediate 8′ is preceded by that of a closely related species which is believed to be **10**.[7a] Clearly, efficient protonation in water drives **10** toward the aldehyde. However, why species **10** is formed faster than 8′ remains open to speculation.[18b]

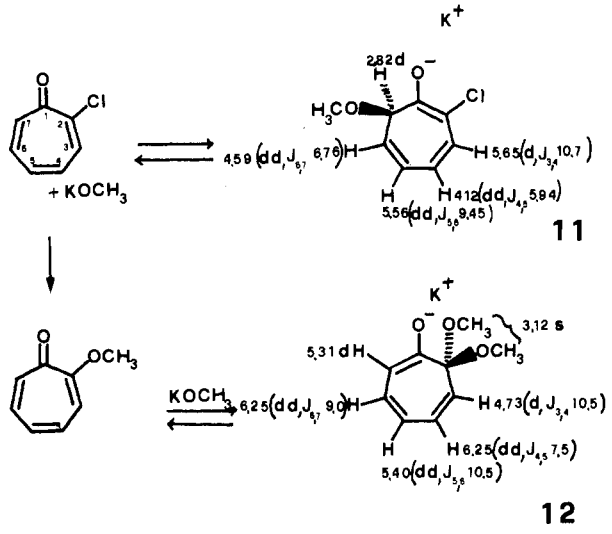
Attack at the γ Carbon. Substitution of mobile groups at the troponoidal γ carbon by both neutral and anionic nucleophiles, according to eq M3, Scheme II, has been found in a number of cases. These include second-order substitutions of both chlorine and the tosyloxy group by sodium methanethiolate in ethanol as well as substitution of chlorine, bromine, iodine, and the tosyloxy group by dimethylamine in dimethyl sulfoxide.[16a]

Investigation of these processes generated a number of interesting observations, although their rationalization is still uncertain. The first striking observation concerns the reactivity order at the various troponoidal carbons carrying a mobile group according to eq M1–M3, Scheme II. Thus, the decreasing reactivity order C-3 > C-2 ≈ C-4 was observed for all the reactions above.[16a] The second, surprising observation regards the leaving-group mobility at C-4. Dimethylamine in dimethyl sulfoxide was found to replace iodine and bromine much faster than the tosyloxy group from C-4.[19] The reverse order of nucleofugal aptitudes is commonly observed.

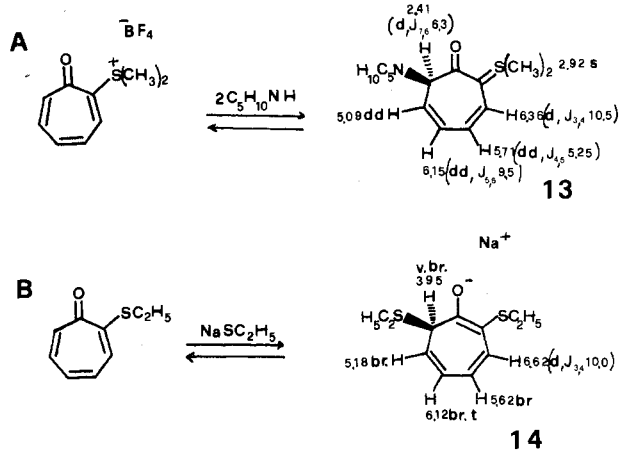
We are unable to go much beyond appreciating the pragmatic value of the above observations for synthesis. However, it is peculiar that in all these cases the faster reactions behave so by escaping from the isokinetic correlation for the other reactions.[16a,19] Our inability to translate these observations into clearly stated mechanisms reflects, in our opinion, our current insufficient knowledge about isokinetic relationships,[20] the

(19) M. Cavazza and F. Pietra, *J. Chem. Soc., Perkin Trans. 2*, in press.

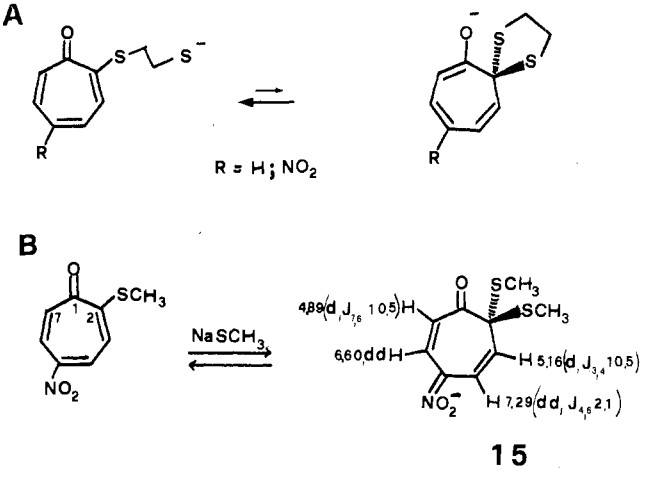
Scheme IX



Scheme X



Scheme XI



study of which seems to have been abandoned before attainment of real understanding.

Extrusion of the γ carbon by bases seems to be confined to strongly activated troponoids, such as 2-chloro-5,7-dinitrotropone. This is so labile that, on simple dissolution in dilute aqueous acetic acid, it undergoes C-4 extrusion to give 2-chloro-3-hydroxy-4,6-dinitrobenzaldehyde.[21]

σ Adducts. In the preceding sections we have stressed the views, gained from either kinetic or product studies, that the chemistry of troponoids in basic media is dictated primarily by the formation of a host of intermediates by attack of the base on the troponoid and that these intermediates are reversibly interconnected through the troponoid itself. A typical example is shown in Scheme IV. Such indirect evidence for the formation of these species is, however, directly supported by ultraviolet and NMR spectral detection of these species. For example, in the case of 2-chlorotropone, the σ intermediate **11** has been characterized by Fourier transform ^{1}H NMR spectroscopy even though this ephemeral intermediate is ultimately trapped as the geminal σ adduct **12** (Scheme IX).[22]

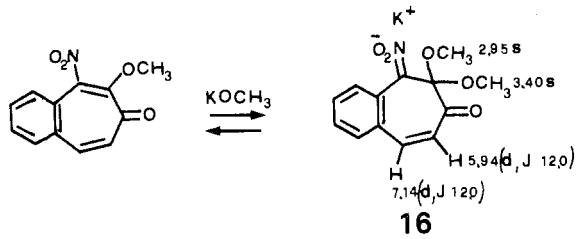
The behavior shown in Scheme IX substantiates beautifully our view, repeatedly set forth in this Account, that electron-attracting substituents such as chlorine activate the tropone ring toward attack by nucleophiles, whereas electron-releasing substituents such as methoxy deactivate the ring. In fact, **11** is formed much faster than **12** from their respective immediate precursors.[22,23] This point is further strengthened by the similar behavior of both the sulfonium salt in Scheme X (A)[24] and of the sulfide in Scheme X (B)[25] to give, respectively, **13** and **14**. Moreover, 3-(ethylthio)tropone and 4-(methylthio)-tropone add sodium methanethiolate in $(CD_3)_2SO$ at, respectively, C-2 and C-7.[26] In all cases, negative charge acceptance by the sulfur substituent dictates the position of attack on the troponoidal ring by the thiolate.[24-26]

The high stability of **12** and our inability to observe *gem*-dithioalkyl analogues under corresponding conditions were reminiscent of a similar situation in the benzenoid series and presented the challenging problem of preparing *gem*-dialkylthio σ adducts in the troponoidal series. The obvious spiroannelation route[27] failed, due to unexpectedly high repulsions in the dithiane ring (Scheme XI, A),[28] but species **15** was finally obtained.[28] Clearly, in the case of **15** attack at C-2 benefits from charge acceptance by the nitro group, whereas attack at C-7 could not do so.

Further interesting structural information about species **11**–**15** is revealed by the selective upfield shift of the protons at ring positions to which the negative charge can be delocalized.[22-28] This suggests a flattening of the seven-membered ring[23] in spite of the strain due to the sp^3 ring carbon, which causes ring puckering in cycloheptatriene. This interpretation is supported by PCILO calculations on both **12** and cycloheptatriene; these showed the energy minimum to be obtained for, respectively, the planar ring and a puckered ring structure.[29]

(20) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, 1963.
(21) E. J. Forbes, M. J. Gregory, and D. C. Warrell, *J. Chem. Soc. C*, 1969 (1968).
(22) F. Pietra, *J. Chem. Soc., Chem. Commun.*, 544 (1974).
(23) G. Biggi, C. A. Veracini, and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 523 (1973).
(24) M. Cavazza, C. A. Veracini, and F. Pietra, *Tetrahedron Lett.*, 2085 (1975).
(25) C. A. Veracini and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 623 (1974).
(26) M. Cavazza, C. A. Veracini, G. Morganti, and F. Pietra, *Tetrahedron Lett.*, 2593 (1978).
(27) E. Farina, C. A. Veracini, and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 672 (1974).
(28) M. Cavazza, C. A. Veracini, G. Morganti, and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 167 (1978).

Scheme XII

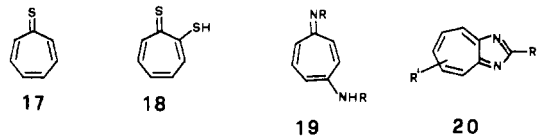


16

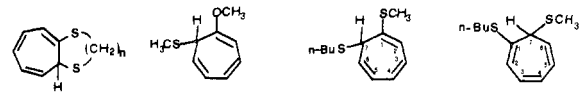
From this discussion it is clear that the equivalence of the methoxy groups of **12** is a consequence of the planarity of the ring. In retrospect, the classical equivalence of the *gem*-dialkoxy groups of Meisenheimer–Jackson complexes[30] has a similar origin in the planarity of the cyclohexadiene ring. We found it exciting to apply these ideas to generate the first σ adduct with nonequivalent but identical *gem*-dialkoxy groups. The reasoning was that if we succeed in inhibiting charge dispersal in **12**, the strain due to the sp^3 carbon should induce ring puckering. This goal was obtained by double bond fixation by an annelated benzene ring, as evidenced by the diastereotopic relationship of the two methoxyl groups in σ adduct **16** (Scheme XII).[31]

Synthetic Use

Recently, refunctionalization of cycloheptatrienones has provided a variety of interesting analogues such as tropothione (**17**),[32a] dithiotropolone (**18**),[32b] and 4-aminocycloheptatrienylidenamines (**19**).[32c]



17 18 19 20



21 22 23 24

In a similar fashion, regiospecifically functionalized 1,3-diazaazulenes (**20**) have been obtained by condensation of tropones with amidines.[14b,33] The direction of the condensation closely follows the reactivity trend discussed in the previous sections for simple nucleophilic substitutions, including "hydride" replacement.[14b,33] Such processes are under exploitation for natural product synthesis.

Another interesting point concerns the serendipitous discovery of **21**, n = 2 or 3, during attempted dithioketalization of tropone.[34] This inspired the synthesis of **22**, **23**, **24**, and close analogues by reaction, at low temperature, respectively, of methoxytropenylium with methanethiolate, methylthiotropenylium with butanethiolate, and butylthiotropenylium with methanethiolate ion.[35] Interestingly, **23** and **24** in chloroform solution undergo interconversion of the alkylthio groups at C-1 and C-7. At room temperature the equilibrium composition at 44% **23** and 56% **24** was reached in ~6 h.[35] These results can be rationalized in terms of a rapid [1,7] sigmatropic shift of alkylthio groups. This implies the intermediacy of the long sought tropone dithioketals. In accordance with this view, double bond fixation in the tropone ring, as with 4,5-benzotropone, leads smoothly to tropone dithioketals.[36]

These processes constitute the first simple regiospecific entry into difunctionalized cycloheptatrienes from tropone. It is easy to conceive extension of this method to, we hope, the regiospecific polyfunctionalization of the cycloheptatriene skeleton. Such compounds are so far unavailable.

Finally we want to mention the use of bicyclo[3.2.0]heptadienones, photochemically generated from troponoids, for the synthesis of prostanoids. This involved opening of the four-membered ring by ozone.[37]

Concluding Remarks

I have attempted to present in a coherent way how cycloheptatrienones react with bases by undergoing refunctionalization, de novo functionalization via "hydride" replacement, modification at a side chain or, finally, ring contraction to benzenoids. The interconnection among all these pathways is now rather well understood. We have identified, with a large degree of confidence, the factors which cause the system to behave in any desired fashion.

I wish to express my deep gratitude to my students and colleagues who have made our work possible. Their names appear in the references. I also wish to thank Professor J. F. Bunnett for constructive, penetrating criticism during the writing of this Account. Financial support by C.N.R., Rome, of the work described here is gratefully acknowledged.

(29) G. Salvatore, M. Morandi Cecchi, and F. Pietra, unpublished.
(30) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry", Benjamin, New York, 1965, p 846.
(31) V. Farina, M. Cavazza, R. Cabrino, C. A. Veracini, and F. Pietra, *Tetrahedron Lett.*, 1319 (1976).
(32) (a) R. Cabrino, G. Biggi, and F. Pietra, *Synthesis*, 276 (1974); (b) C. E. Forbes and R. H. Holm, *J. Am. Chem. Soc.*, **92**, 2297 (1970); (c) M. Cavazza and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 413 (1976).
(33) R. Cabrino, B. Ricciarelli, and F. Pietra, *Tetrahedron Lett.*, 3069 (1974); F. Del Cima, M. Cavazza, C. A. Veracini, and F. Pietra, *ibid.*, 4267 (1975).
(34) M. Cavazza, G. Morganti, and F. Pietra, *Tetrahedron Lett.*, 2137 (1978).
(35) M. Cavazza, G. Morganti, and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 710, 945 (1978).
(36) M. Cavazza, G. Morganti, and F. Pietra, *Recl. Trav. Chim. Pays-Bas*, in press.
(37) A. Green and P. Crabbé, *Tetrahedron Lett.*, 2215 (1975).