Carbanion Additions and Cyclizations Involving Anionic σ Complexes. Meta Bridging Reactions of Aromatics

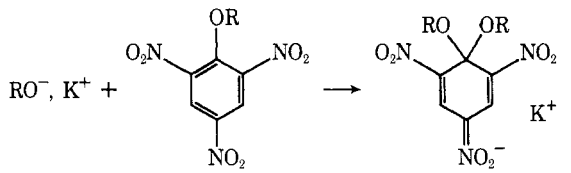
Michael J. Strauss

Department of Chemistry, University of Vermont, Burlington, Vermont 05401

Received January 21, 1974

The intensely colored solutions which result from mixing electron-deficient aromatic compounds with bases have fascinated chemists since the late 1800's. A variety of interactions can occur, but one of the most common is formation of covalently bonded σ complexes.

The first reference to such complexes appeared in 1900 when Jackson and Gazzolo proposed 1 as the colored product resulting from reaction of picryl ethers with potassium alkoxides.[1a] Meisenheimer further substantiated this proposal by isolating the same complex from 2,4,6-trinitrophenetole and potassium methoxide and from 2,4,6-trinitroanisole and potassium ethoxide.[1b]

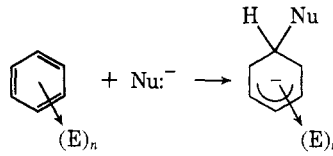


1

Many further reports of such complexes resulting from a variety of bases and electron-deficient aromatics followed the initial report by Jackson and Gazzolo. Many of these were unsubstantiated, the only evidence for σ complexation being development of color on mixing the reactants. Since charge-transfer complexes, radical ions, acid–base reactions, and substitution reactions are all complicating factors, a more definitive method for assigning structures was needed.

In 1964 a major development in the structural characterization of anionic σ complexes occurred with a report of the pmr spectrum of 1 (R = CH_3)[2a] which is fully consistent with the structure originally proposed by Jackson and Gazzolo. After this report, pmr data on numerous σ complexes rapidly accumulated in the literature. Recent crystallographic studies support the pmr data.[2b-d] The general structure of such complexes is now well established.

Formation of the complexes involves delocalization of electron density originally associated with the nucleophile into the electron-deficient aromatic with concomitant formation of a covalent bond to an aromatic ring carbon. The latter becomes tetrahedral in the complex. This process is represented schematically in eq 1 for the simple case of a charged nucleophile reacting with an electron-deficient benzene containing the electron-withdrawing group(s) E.



(1)

The complexes initially studied most intensely were the adducts of nucleophiles with benzenoid and naphthalenoid polynitro aromatics. It is now realized that nitro groups are not necessary for rapid irreversible complexation. Numerous aromatic and heteroaromatic compounds readily form quite stable complexes with many different nucleophiles. The aromatics have included thiophenes,[3] selenophanes,[4] furans,[5] purines,[6] anthracenes,[7] pyridines,[8] diazines,[9] polycyanobenzenes,[10] benzofuroxans,[11] azulenes,[12] and tropones,[13] as well as numerous benzenoid and naphthalenoid polynitroaromatics. The nucleophiles have ranged from simple hydride, sulfite, methoxide, cyanide, hydroxide ions, etc., to carbanions, amines, halomethyl anions, and a variety of organometallic compounds.

The appearance of several reviews of the chemistry of such anionic σ complexes during 1968–1970[14] and extensive experimental work show that such organic anions are of much interest to physical organic chemists. Detailed study of the factors which influence the formation and decomposition of anionic σ

Michael J. Strauss was born in San Francisco in 1940. He received his B.S. degree from California State College at San Jose, the Ph.D. from University of California, Davis, and then spent a postdoctoral year at the University of Dundee as I.C.I. Fellow. He is now Associate Professor of Chemistry at the University of Vermont. His research interests include structural and mechanistic investigations of the reactions of electron-deficient aromatics. Professor Strauss has recently been awarded an NIH Research Career Development Award (1974–1979).

(1) (a) C. J. Jackson and F. H. Gazzolo, *Amer. J. Chem.*, **23**, 376 (1900); (b) J. Meisenheimer, *Justus Liebigs Ann. Chem.*, **323**, 205 (1902).

(2) (a) M. R. Crampton and V. Gold, *J. Chem. Soc.*, 3293 (1964); (b) R. Destro, C. Gramaccioli, and M. Simonetta, *Acta Crystallogr.*, **24**, 1369 (1968); (c) G. G. Messmer and G. J. Palenik, *Chem. Commun.*, 470 (1969); (d) H. Veda, N. Sakabe, J. Tanaka, and A. Furusaki, *Bull. Chem Soc. Jap.*, **41**, 2866 (1968).

(3) D. Spinelli, *J. Heterocycl. Chem.*, **7**, 1441 (1970).

(4) C. Paulmier, M. Simonnin, A. Chatrousse, and F. Terrier, *Tetrahedron Lett.*, 1123 (1973).

(5) T. Severin and H. Kullmer, *Chem. Ber.*, **106**, 1688 (1973).

(6) (a) C. L. Liotta and A. Abidaud, *J. Amer. Chem. Soc.*, **94**, 7927 (1972); (b) R. P. Taylor and J. B. Vatz, *ibid.*, **95**, 5819 (1973).

(7) R. Foster, C. A. Fyfe, P. H. Emslie, and M. I. Forman, *Tetrahedron*, **23**, 227 (1967).

(8) M. Biffin and J. Miller, *Aust. J. Chem.*, **23**, 957 (1970).

(9) J. A. Zoltewicz and L. S. Helmick, *J. Amer. Chem. Soc.*, **94**, 682 (1972).

(10) J. Kuthon, *Chem. Commun.*, **6**, 250 (1971).

(11) A. J. Boulton and D. P. Clifford, *J. Chem. Soc.*, 5414 (1965).

(12) C. M. Lok, M. Den Boer, and J. Cornelisse, *Recl. Trav. Chim. Pays-Bas*, **92**, 340 (1973).

(13) T. Abe and T. Asao, *Tetrahedron Lett.*, 1327 (1973).

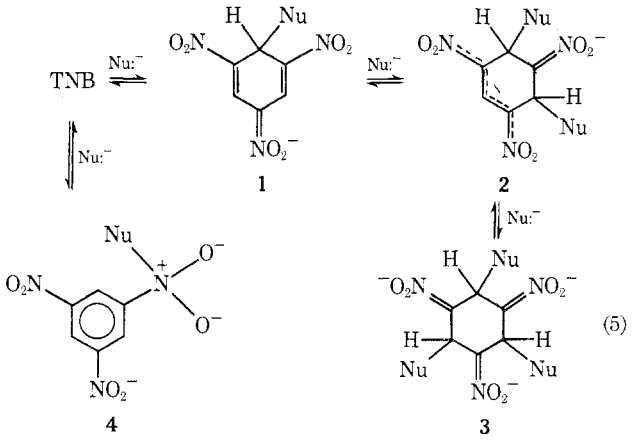
(14) (a) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev. Chem. Soc.*, **22**, 123 (1968); (b) P. Buck, *Angew. Chem., Int. Ed. Engl.*, **8**, 120 (1969); (c) M. R. Crampton, *Advan. Phys. Org. Chem.*, **7**, 211 (1969); (d) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).

complexes provides valuable information about the structure and general behavior of organic anions in solution. Moreover, formation of such complexes is a useful tool for studying nucleophilic reactivity and mechanisms of base catalysis,[15-17] as well as mechanisms of enzyme and micellar catalysis.[6,18]

Anionic σ complexes result from reaction of sodium cellulosate membranes and fabrics[19] with 2,4,6-trinitrostyrene and related aromatics and are also considered to arise from addition of cellular thiol and amino groups to appropriately structured electron-deficient drugs, resulting in inhibition of nucleic acid synthesis and potential antileukemic activity.[20] Moreover, they have for many years been important in a variety of pharmaceutical color tests.[21] Very recently they have been proposed as biophysical probes in immunological studies because of their fluorescent properties.[22]

The complexity of the simple addition process, eq 1, is increased if there is more than one site on the aromatic which can be attacked or if the nucleophile is ambident or tautomeric, *i.e.*, eq 2-4.[23-26] The factors which govern the possible modes of isomeric addition have been studied intensively. In the case of methoxide addition to 2,4,6-trinitroanisole, rapid addition at C-3 yields the kinetically favored product which slowly rearranges to the thermodynamically favored C-1 complex, **1** (R = CH_3).[27] Similar behavior is observed for related systems as in eq 4.[26] Quantitative studies of kinetics and equilibria in complexation of this type have been made by many workers.

Even in symmetrical systems where isomeric additions, *i.e.*, (2)-(4), are precluded, simple nucleophiles can give several adducts. The interaction of hydroxide with *sym*-trinitrobenzene (TNB) is illustrative (eq 5, Nu =OH).[28,29] Although there is substantial



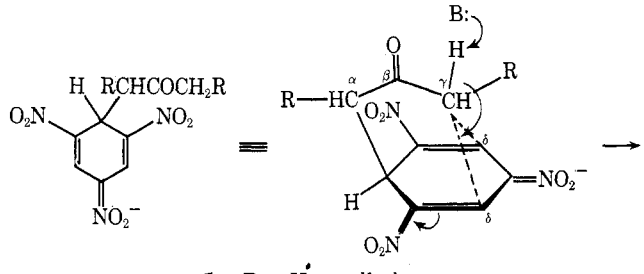
evidence in certain cases for nucleophilic amine attack on a ring substituent (*i.e.*, NO_2) to yield structures like **4**[30,31] (Nu = NR_2), such structures are not as commonly observed as those arising from nucleophilic attack on the ring.[32-37]

Few chemical reactions of anionic σ complexes other than simple oxidation or reduction have been investigated in much detail. The most common "reaction" is merely departure of the aromatic substituent bonded to the carbon which suffered nucleophilic attack in complexation, *i.e.*, consummation of S_NAr displacement for which the complex is an unstable intermediate. If this substituent is hydrogen, the poor nucleofugicity of hydride ion usually results in a relatively stable complex.

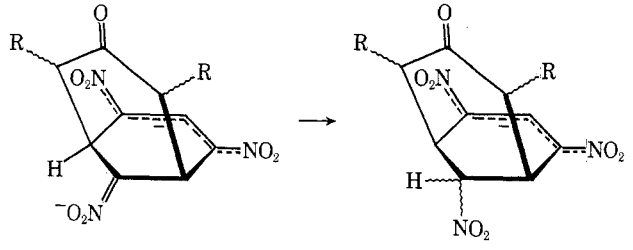
We and workers in Japan have observed in several cases[38-49] an intramolecular analog of the multiple

(15) K. T. Leffek and P. H. Tremaine, *Can. J. Chem.*, **51**, 1659 (1973).
(16) J. A. Orvik and J. F. Bunnett, *J. Amer. Chem. Soc.*, **92**, 2417 (1970).
(17) C. F. Bernasconi, *J. Amer. Chem. Soc.*, **92**, 129 (1970).
(18) J. H. Fendler, E. J. Fendler, and S. A. Chang, *J. Amer. Chem. Soc.*, **95**, 3273 (1973).
(19) Y. Avny, R. Rahman, and A. Zilkha, *J. Macromol. Sci. Chem.*, **6**, 177 (1972).
(20) P. B. Ghosh, B. Ternai, and M. Whitehouse, *J. Med. Chem.*, **15**, 255 (1973).
(21) K. A. Kovar, *Pharm. Unserer Zeit*, **1**, 17 (1972).
(22) R. Taylor, personal communication.
(23) R. Foster and C. A. Fyfe, *J. Chem. Soc. B*, 53 (1966).
(24) E. Buncel, personal communication.
(25) S. M. Shein, *Zh. Org. Khim.*, **8**, 323 (1972).
(26) F. Millot and F. Terrier, *Bull Soc. Chim. Fr.*, 2692 (1969).
(27) C. Bernasconi, *J. Amer. Chem. Soc.*, **93**, 6975 (1971), and references therein.
(28) C. A. Fyfe, M. I. Foreman, and R. Foster, *Tetrahedron Lett.*, 1521 (1969).
(29) (a) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966); (b) F. Cuita and J. Pisecky, *Collect. Czech. Chem. Commun.*, **23**, 628 (1958).
(30) C. F. Bernasconi, *J. Amer. Chem. Soc.*, **92**, 129 (1970).
(31) M. J. Strauss, S. P. B. Taylor, and A. Reznick, *J. Org. Chem.*, **37**, 3076 (1972).
(32) T. Abe, *Bull. Chem. Soc. Jap.*, **37**, 508 (1964).
(33) K. L. Servis, *J. Amer. Chem. Soc.*, **89**, 1508 (1967).
(34) T. Abe, *Bull. Chem. Soc. Jap.*, **32**, 339 (1959).
(35) C. F. Bernasconi and R. Bergstrom, *J. Amer. Chem. Soc.*, **95**, 3603 (1973).
(36) M. J. Strauss and S. P. B. Taylor, *J. Amer. Chem. Soc.*, **95**, 3813 (1973).
(37) M. R. Crampton and V. Gold, *J. Chem. Soc. B*, 893 (1966).
(38) M. J. Strauss and H. Schran, *J. Amer. Chem. Soc.*, **91**, 3974 (1969).

Scheme I



5a, R = H or alkyl
b, R = C_6H_5, CO_2CH_3, or any electron-withdrawing group



6a, R = H or alkyl
b, R = C_6H_5, CO_2CH_3, or any electron-withdrawing group

7a, R = H or alkyl
b, R = C_6H_5, CO_2CH_3, or any electron-withdrawing group

addition leading to **2**. This reaction (Scheme I) readily occurs under appropriate conditions for complexes containing a potential nucleophilic site γ to the tetrahedral ring carbon. The ease with which it takes place can be rationalized by looking at the geometry of a typical complex, **5**, of a ketone with TNB. The distance between C_γ and C_δ in the conformation of **5** favorable for cyclization (measured from Dreiding models) is quite appropriate for bonding. In the presence of a weak or strong base, direct base attack at C_δ to yield structures like **2** cannot compete with proton abstraction at C_γ followed by intramolecular attack to yield **6**. In view of the large number of different types of easily prepared σ complexes containing potentially nucleophilic side chains, this reaction has promise for the preparation of new bicyclic and heterobicyclic systems if methods for modifying the nitronate functions can be found.

The mechanisms by which these bicyclic structures form, including the directive effects of aromatic substituents and the effects of side-chain structure on the ease of intramolecular cyclization, are of interest to us. Much of our initial work has been done with carbanions and enamines, but it appears that urethanes, guanidines, amidines, and other related structures will also yield bicyclic anions similar to **6** and **7** when they are condensed with electron-deficient aromatics (*vide infra*).

Addition of excess tertiary amine to a saturated solution of TNB in acetone results in the rapid formation of the trialkylammonium salt of the complex **5a** which precipitates from solution as purple crystals after a short time. Formation of **5a** in this instance occurs by irreversible attack of small equilibrium quantities of acetonate produced from reaction of the amine with acetone.[26,45,50] *No further reactions of the trialkylammonium salts of* **5a** *have been observed to occur in such solutions.*

Surprisingly different results are observed when (1) stronger bases than tertiary amines or (2) more acidic ketones than acetone are employed in preparation of the complex, or (3) when complexes like **5a** containing nonacidic ketones are prepared with secondary rather than tertiary amines. These changes modify the reaction sufficiently so that intramolecular cyclizations leading to **6** and **7** can occur.

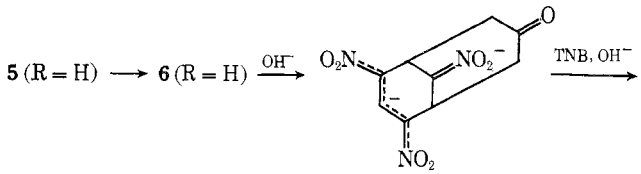
Although this behavior was puzzling at first, it can be understood when the detailed mechanisms for the formation of **6** and **7** are considered.[40,45] Ions like **6a** and **6b** as well as **7a** and **7b** can form similarly. Base abstraction of H_γ in **5** followed by intramolecular attack at C_δ yields **6a** or **6b**. The abstraction in **5a** is facilitated by strong base (*i.e.*, sodium hydroxide[49]), whereas in **5b** it is facilitated by the presence of the electron-withdrawing groups R.[39,45] The unreactivity of the trialkylammonium salt of **5a** in solutions of tertiary amine is thus understandable since in the presence of weak base the nonacidic H_γ is not readily removed. If the conjugate acid of the base used to form **6** is sufficiently strong, protonation of the unconjugated nitronate function in **6** leads to **7**. With sodium hydroxide **6a** is isolated as the disodium salt, whereas with trialkylamines **7** is isolated as the trialkylammonium salt. In strong base, and with simple ketones like acetone, even further addition and cyclization can occur to yield tetracyclic salts like **8**.[47]

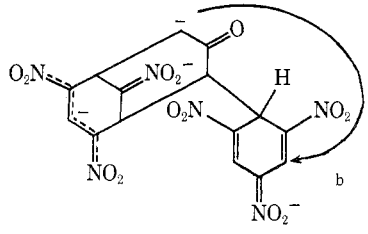
Since the secondary amines used to form the dialkylammonium salts of **7a** are not significantly more basic than the tertiary amines (*i.e.*, triethylamine) which lead only to the stable and unreactive trialkylammonium salt of **5a**, an alternate mechanism must be operative in the case of cyclizations effected in these instances. We have shown that in the case of secondary amines the enamine intermediates **9** and **10** are precursors to the diethylammonium salt of **7a** (R = CH_3).[40]

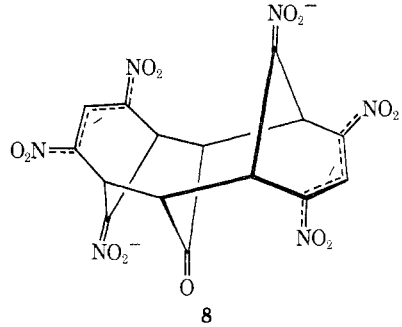
Addition of previously prepared and purified enamines (like **11**) to TNB results in formation of an isolable immonium zwitterion **12**, which upon hydrolysis yields **7a** (R = CH_3).

The bicyclic ions **7** are amazingly stable crystalline salts which melt in many instances without decomposition at temperatures ranging from 100 to 200°. It is most surprising that simple *monocyclic* bis adducts like **2** which are analogous to **6** and **7** cannot be readily isolated. There have been only two reports of isolated bis adducts (Nu = SO_3^- – and CH_3COCH_2–).[51a,b]

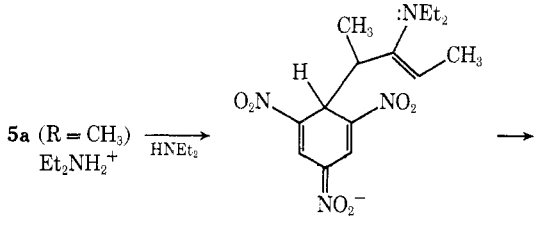
(39) M. J. Strauss, T. C. Jensen, H. Schran, and K. O'Conner, *J. Org. Chem.*, **35**, 383 (1970).
(40) H. Schran and M. J. Strauss, *J. Org. Chem.*, **36**, 856 (1971).
(41) M. J. Strauss and H. Schran, *Tetrahedron Lett.*, **25**, 2349 (1971).
(42) M. J. Strauss, S. P. B. Taylor, and H. Shindo, *J. Org. Chem.*, **37**, 3658 (1972).
(43) M. J. Strauss and S. P. B. Taylor, *J. Org. Chem.*, **38**, 856 (1973).
(44) M. J. Strauss and S. P. B. Taylor, *J. Org. Chem.*, **38**, 1330 (1973).
(45) M. J. Strauss, H. F. Schran, and R. R. Bard, *J. Org. Chem.*, **38**, 3394 (1973).
(46) K. Kohashi, Y. Ohkura, and T. Momose, *Chem. Pharm. Bull.*, **18**, 2151 (1970).
(47) K. Kohashi, Y. Ohkura, and T. Momose, *Chem. Pharm. Bull.*, **19**, 213 (1971).
(48) T. Kabeya, K. Kohashi, Y. Ohkura, and T. Momose, *Chem. Pharm. Bull.*, **19**, 645 (1971).
(49) T. Momose, Y. Ohkura, and K. Kohashi, *Chem. Pharm. Bull.*, **17**, 858 (1969).
(50) R. M. Murphy, C. A. Wulff, and M. J. Strauss, *J. Amer. Chem. Soc.*, **96**, 2678 (1974).



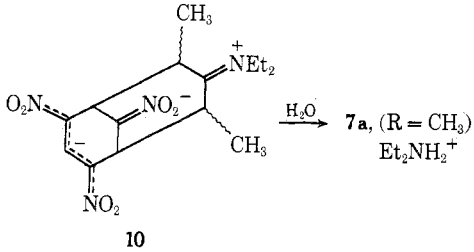




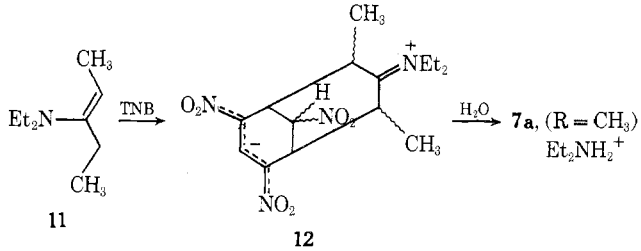
8



9



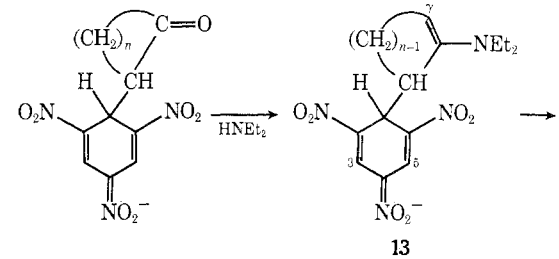
10



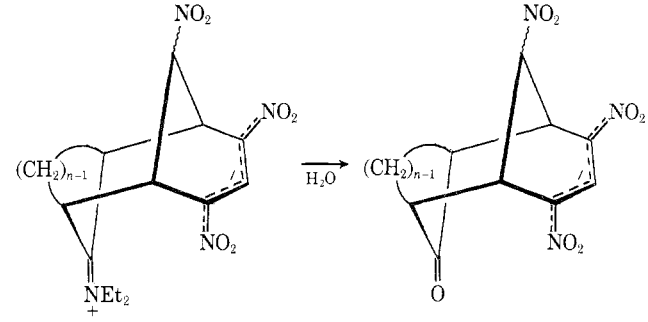
11 12

Several types of electron-deficient aromatics and ketones have been condensed in an effort to determine the scope of the reaction and to understand the structural factors favoring cyclization. Using the symmetrical aromatic TNB, we can study the effects of varying the ketone component. Variation of the aromatic reactant clarifies the directional effects of aromatic substituents on the cyclization. These points are now considered.

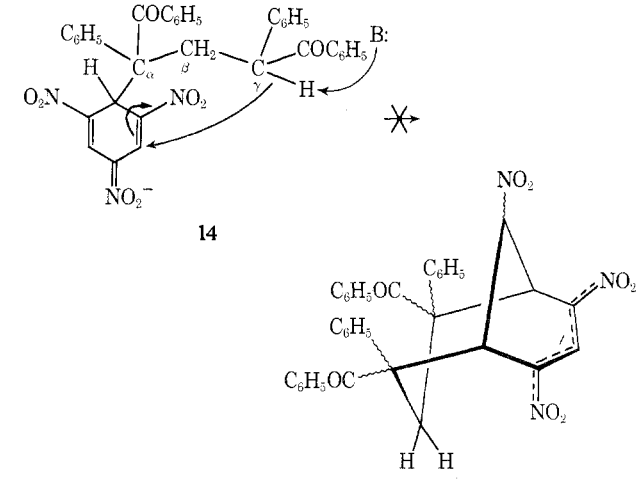
The steric requirement for reasonably close proximity of the nucleophilic site on the side chain and the electrophilic nitro olefin moiety of the ring is demonstrated when TNB is bridged with simple cyclic ketones, presumably through enamine intermediates like **13**, analogous to **9**.[42] When $n = 4$ or 5 cyclization readily occurs, but with $n = 3$, no bicyclic product can be obtained. In this latter instance reaction terminates at the σ complex stage. Dreiding models of **13** show that the distance between C-3 (C-5) and C_γ in **13** ($n = 3$) is almost 50% greater than in **13** ($n = 4$ or 5) in the most favorable conformations for intramolecular cyclization.



13



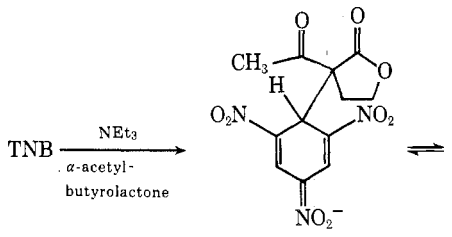
Since the σ complex precursors to bicyclic products always have an sp^2 center adjacent to the nucleophilic site in the side chain and β to the ring, it was of interest to determine whether or not this trigonal center favorably influenced the geometry of the complex for intramolecular cyclization. Examination of the favorable conformation for cyclization (*i.e.*, **5a**) led us to believe that this would be the case since the internal nucleophilic site is brought in close proximity to the nitro olefin portion of the ring by this trigonal geometry. Interestingly, attempts at cyclization of **14** which has a potentially nucleophilic side chain similar to that in **5a** (R = C_6H_5), but which has a *tetrahedral* center β to the ring, fail-



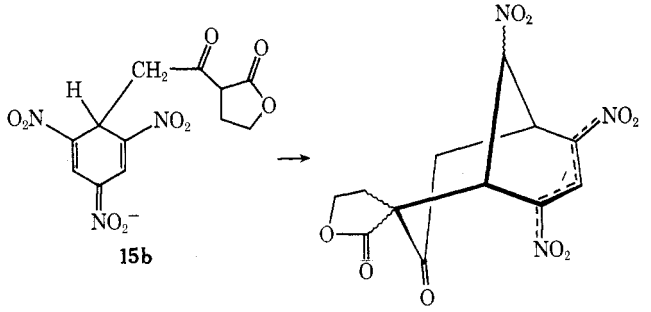
14

(51) (a) R. A. Henry, *J. Org. Chem.*, **27**, 1637 (1962); (b) I. M. Sosonkin, S. S. Gitis, and A. Y. Kaminski, *J. Org. Chem. USSR*, **7**, 2322 (1971); (c) H. Schran, S. P. B. Taylor, and M. J. Strauss, unpublished results.

ed.[51c] Although it might be concluded that this failure results from the hybridizational change of trigonal to tetrahedral at C_β, the steric problem introduced by the *two* bulky groups C_6H_5 and COC_6H_5 at C_γ cannot be overlooked. In fact, σ complexes prepared from TNB and 1,1-di- as well as 1,1,3,3-tetraphenylacetone which might be expected to cyclize as readily as **5a** (R = C_6H_5) do so only *very* slowly.[51c] Tertiary carbanionic sites on the exocyclic side chain can attack intramolecularly, however, as **15** readily cyclizes to **16.** The steric problems in this latter case should be much less than in **14.**



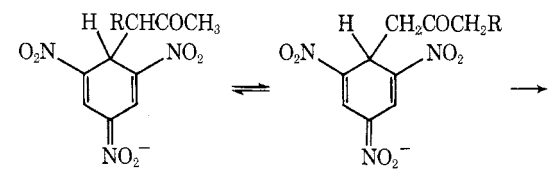
15a



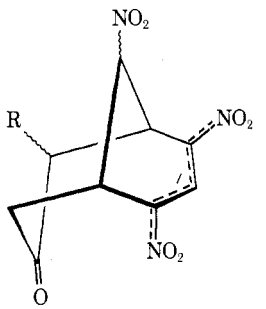
15b **16**

Formation of **16** might not be expected to result from cyclization of **15a** since **5a** does not cyclize in the presence of tertiary amine. However, **15a** should form readily in solutions of tertiary amine, acetylbutyrolactone, and TNB. The fact that **16** is the final product of this reaction deserves some comment.

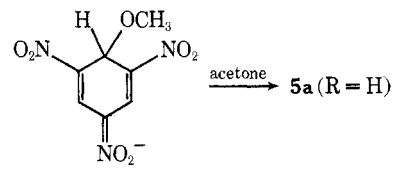
Although **5a** (R = H) will not cyclize in the presence of weak tertiary amine bases, σ complexes prepared from TNB and acetylacetone or ethyl acetoacetate, **17** (R = CH_3CO or $C_2H_5O_2C$), cyclize rapidly under such conditions.[39] The initial complex which might be expected to result from addition of tertiary amine to a solution of TNB and ethyl acetoacetate or acetylacetone might be **17a,** which by analogy to the behavior of **5a** (R = H) would not be expected to cyclize. Rapid equilibration of **17a** and **17b** would allow a pathway for cyclization through **17b,** however, and this is presumably what occurs. Similar equilibration of **15a** and **15b** must provide a route to **16.**



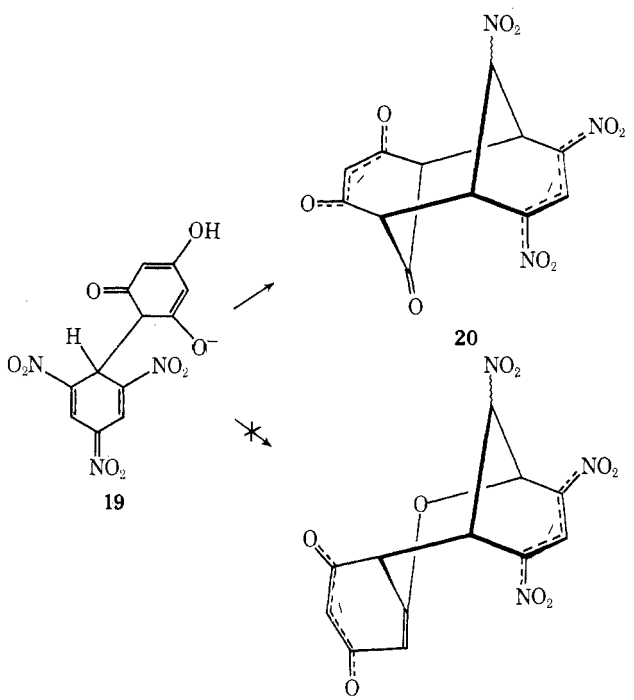
17a **17b**



In the systems we have studied, intramolecular oxygen attack by the enolate side chain is never observed. This might seem surprising in view of the wide variety of σ complexes prepared with oxygen bases. It appears that the nucleophilicity of enolate carbon toward electron-deficient aromatic carbon is considerably greater than that of enolate oxygen. This supposition is confirmed by recent thermodynamic measurements.[50] In fact, solvolysis of the methoxide complex of TNB, **18,** in acetone rapidly yields **5a** (R = H).[52] It is, therefore, not surprising that even the complex **19,** prepared from phloroglucinol and TNB in the presence of tertiary amine, cyclized to **20,** not **21.**[42]



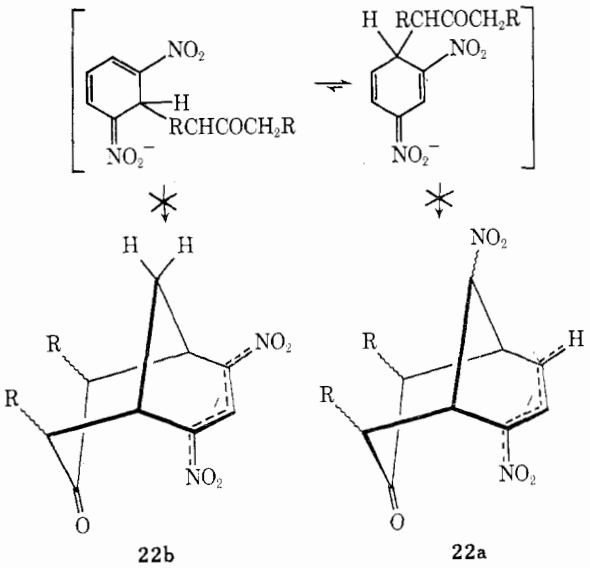
18



19 **20** **21**

Aromatic substituents also affect the pattern of cyclization. The simplest change from symmetrical TNB is replacement of one nitro group to yield a 1-X-3,5-dinitrobenzene. When X = H, cyclization fails to occur.[51c] This is not surprising since the propene nitronate product **22a** should be much less stable than the nitropropene nitronate product **7** resulting from cyclization of **5.** Formation of **22b** does not occur for reasons to be discussed shortly.

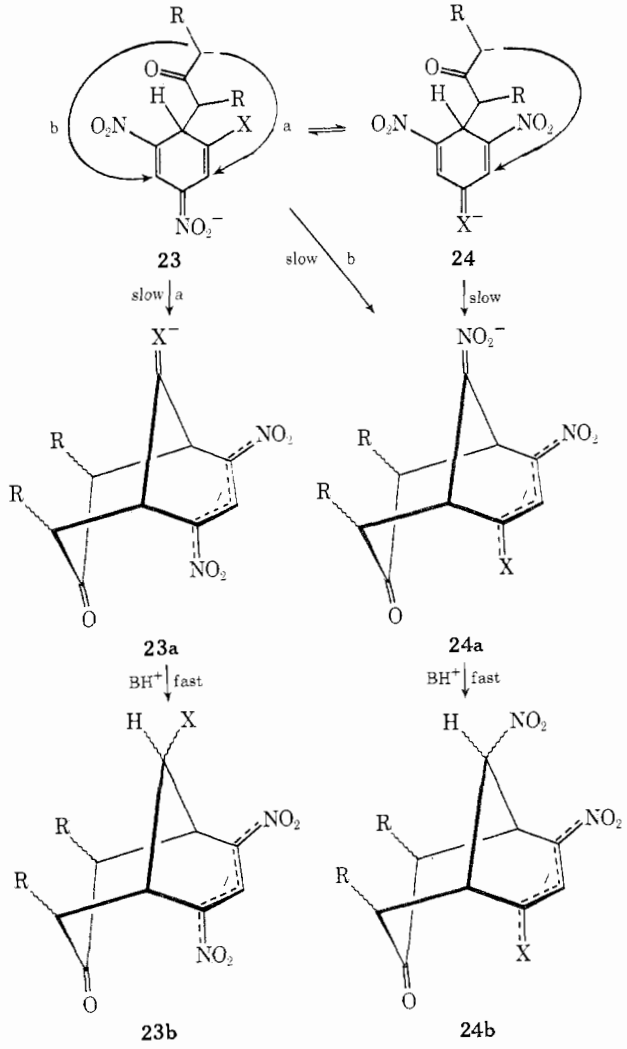
(52) R. Foster and C. A. Fyfe, *Tetrahedron,* **21,** 3363 (1965).



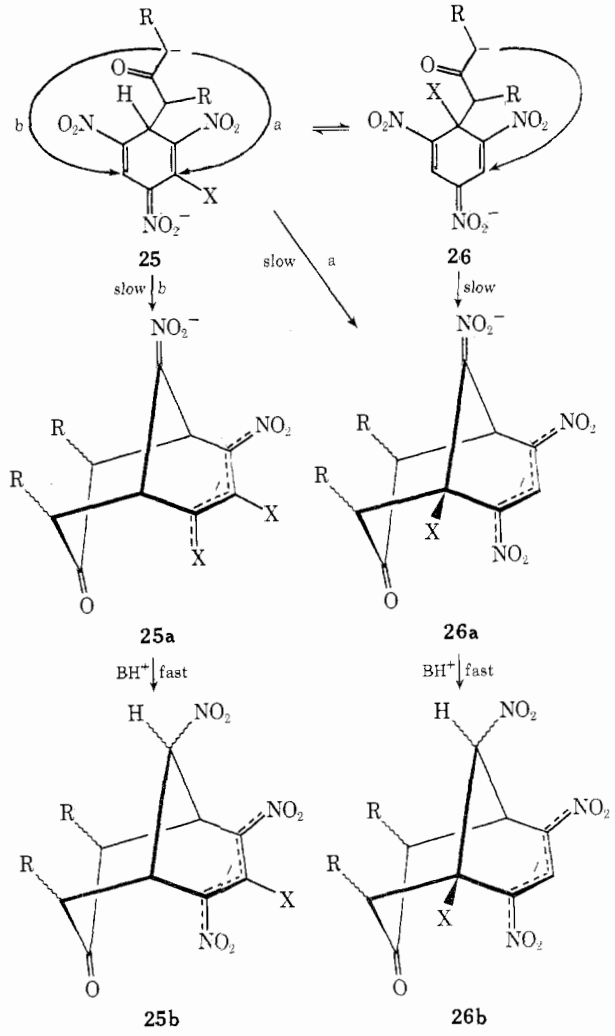
22b 22a

When X is some electron-withdrawing substituent other than NO_2, two isomeric σ complexes, **23** and **24,** can form, and each of these could presumably cyclize to two different products, **23b** and **24b,** through the bicyclic dianion intermediates **23a** and **24a.** The only product observed for several different X substituents (X = CN, CO_2R, COR) is **24b,** and this result can be rationalized in two different ways.[44] The activated complex for the slow step in the cyclization process resembles **23a** or **24a** as charge is developing on X or NO_2 ortho to the side chain.[45] Since **24a** should be much more stable than **23a,** cyclization occurs solely through the former to **24b** regardless of which σ complex is formed initially. Alternately, it is possible that the only σ complex precursor to product is **24,** which may be kinetically favored over **23.** This latter possibility is supported by recent work which provides evidence for kinetically favored σ complexes formed by nucleophilic acetonate attack para to the X substituent.[53] Such an explanation would require that cyclization of **24** be much more rapid than its reversion to **23,** however.

Adding a fourth substituent to a symmetrically substituted trinitro aromatic ring provides for the possibility of bridgehead- or anion-substituted bicyclic products, and the factors which influence product distribution in these instances are more subtle.[44] If the σ complex **26** forms, only the bridgehead product **26b** can result from cyclization. If **25** is formed, **25b** or **26b** could result from cyclization. When X is electron donating (*i.e.*, CH_3), nucleophiles always attack meta to yield σ complexes analogous to **25.**[54,55]



23b 24b



25a 26a 25b 26b

(53) M. R. Crampton and H. A. Khan, *J. Chem. Soc., Perkin Trans. 2,* 733 (1972).

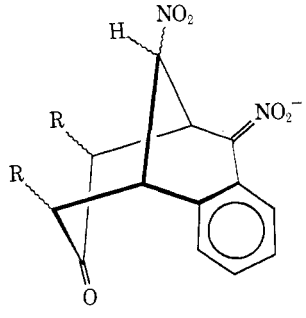
(54) E. Buncel, A. R. Norris, and W. Proudlock, *Can. J. Chem.,* **46,** 2759 (1968).

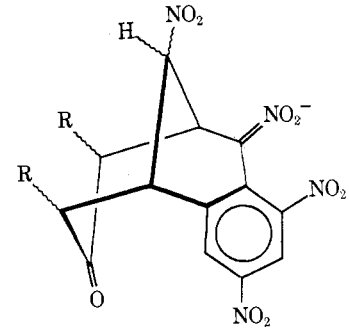
(55) E. Buncel, A. R. Norris, K. E. Russell, and R. Tucker, *J. Amer. Chem. Soc.,* **94,** 1646 (1972).

In the case of 2,4,6-trinitrotoluene, the only bridged product which can be detected and isolated from reaction with ketones is **25b** (X = CH_3). Formation of **26** or **26a** (X = CH_3) on the reaction coordinate leading to product is thus not occurring in this instance. In fact the product **25b** (X = CH_3) may well be thermodynamically more stable than **26b.**[44] It is likely, however, that the reaction pathway is not controlled by the thermodynamic stability of the products in any case, but is kinetically controlled by the relative stability of the precursor intermediate **25** relative to **26** and the energies of activated complexes leading to the bicyclic intermediates for the alternate routes of cyclization. If **25** is always the precursor to cyclized product even when X is electron withdrawing, the preference for cyclization *via* path b remains, although to a lesser extent. The electronic effect of X does not cause a profound change in the course of the reaction. When X = CO_2CH_3, both **25b** and **26b** are isolated in a ratio of ~80:20. When X = N-(2-$O_2NC_6H_5$) only **25b** is obtained. If cyclization always occurs through **25** regardless of the electron-withdrawing power of X, the preference for cyclization *via* path b could be partly steric in origin, resulting from noncoplanarity of the ring and NO_2 group ortho to both X and the side chain in **25.** Such noncoplanarity would favor attack by path b where the NO_2 group developing additional charge during cyclization is well conjugated with the site of anionic attack. When X is electron withdrawing, this effect may be partially moderated by increased electrophilicity at the carbon bonded to X, allowing part of the product to arise *via* path a. Alternately, the equilibrium between **25** and **26** may shift toward the latter when X is electron withdrawing, which can only cyclize to **26b.**

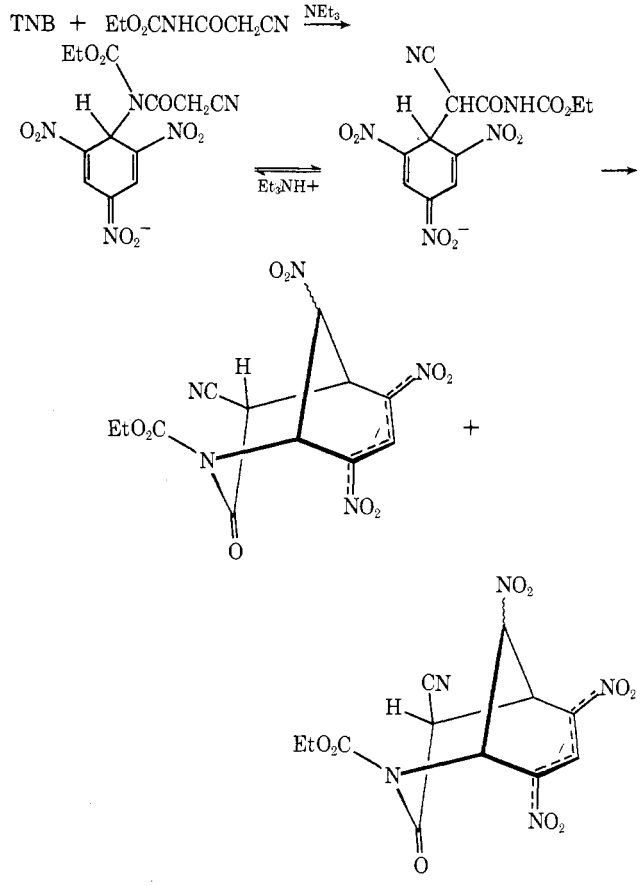
In summary, for both 1-X-3,5-dinitroaromatics and 1-X-2,4,6-trinitroaromatics, it appears that the charge-stabilizing ability of the ring substituent developing charge in cyclization of the σ complex precursor to product is a major directing influence in intramolecular cyclizations of anionic σ complexes.

It is not surprising that electron-deficient naphthalenes are bridged by ketones to yield benzobicyclic adducts, since naphthalenoid σ complexes readily form and have been studied extensively by Fendler, Terrier, and others.[56,57] Both 1,3-di- and 1,3,6,8-tetranitronaphthalene rapidly yield the corresponding bridged adducts when mixed with relatively acidic ketones and tertiary amines.[43,58]





The potential utility of meta bridging reactions will become apparent when they are considered in light of further general extensions with other types of nucleophiles and when methods for modifying the nitronate functionality of the bicyclic products can be devised. These latter areas are now under investigation in our laboratories and a complete summary is not yet available. The initial results are quite intriguing, however. Cyanoacetylurethane readily bridges TNB to yield a mixture of two bicyclic ions containing the 2-azabicyclononane skeleton.[59] Acet-

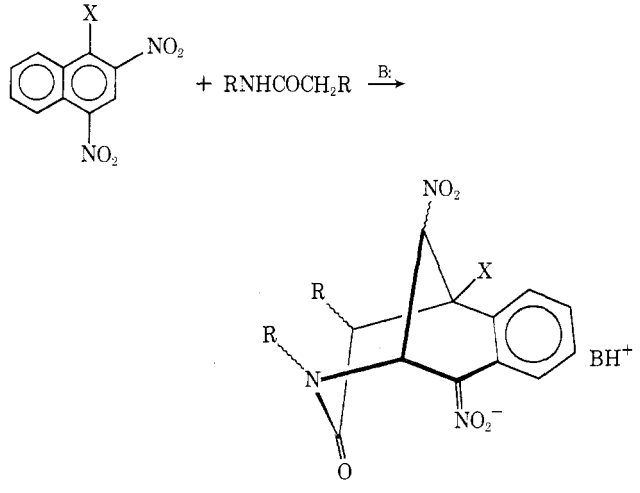


amidine bridges TNB to yield what appears to be tetracyclic ions similar to **8,** whereas *N,N*-dimethylphenylacetamidine yields a stable zwitterion analogous to **10.**[60] The observation that electron-deficient

(56) F. Millot and F. Terrier, *Bull. Soc. Chim. Fr.*, **11**, 3897 (1971).
(57) E. J. Fendler and J. H. Fendler, *J. Chem. Soc., Perkin Trans. 2*, 1403 (1972).

(58) Although the bicyclic products shown here are ketonic structures, in many instances an appreciable part of the product when dissolved in polar solvents is enolic. Representing the structures as enolic necessitates making a distinction between enolization syn or anti to the benzo fusion, a distinction which we have not yet been able to make.
(59) D. Palmer and M. J. Strauss, unpublished results.
(60) R. Bard and M. J. Strauss, unpublished results.

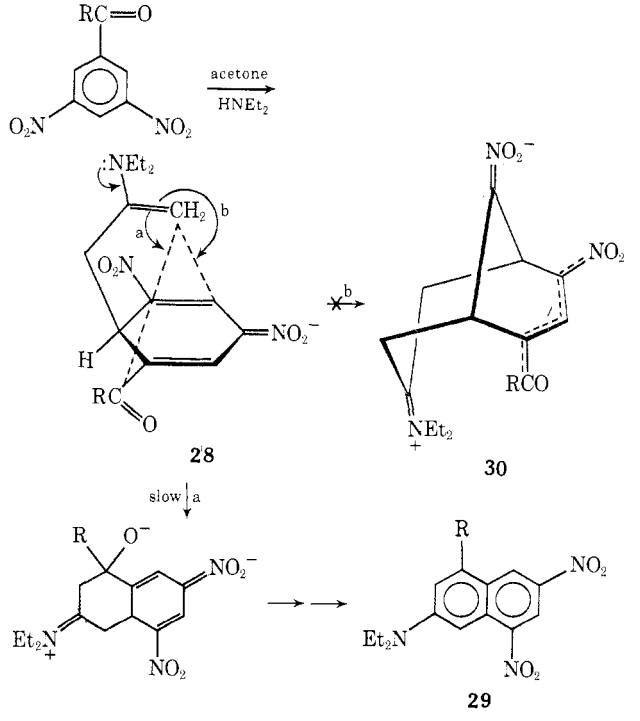
naphthalenes are readily bridged and that urethanes as well as amidines are effective bridging nucleophiles may provide an interesting synthetic route to the benzomorphan skeleton, **27**. Such a simple one-step synthesis could, of course, be of considerable value in preparing a series of potential opiate antagonists, and we are pursuing such research at this time.



27

In order to make such bridging reactions valuable synthetically, methods for modifying nitronate functionality in the products must be found. We and other researchers have begun to investigate propene-nitronate reactivity in a variety of systems, including that in the precursor σ complexes. Bicyclic propene-nitronates are readily converted to α,β-unsaturated oximes, anhydrides, or ketones, and these functions are readily amenable to further modification.[59]

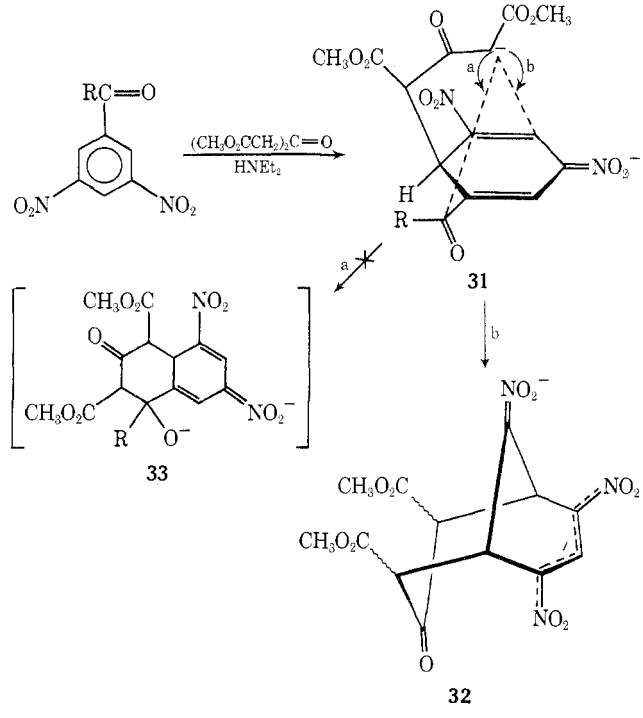
It has been shown in certain cases that σ-complex cyclizations can lead to products other than those arising from meta bridging.[61] When a carbonyl-containing substituent is ortho to the tetrahedral ring carbon bearing an enamine moiety in the complex, attack occurs on the ortho substituent rather than on the meta ring carbon[61,62] and the product is the naphthalene **29**, not the bicyclic ion **30**.



28 **30**

29

It is interesting to note that the same aromatic substrates which yield **28** and **29** (R = C_6H_5) with acetone and diethylamine react quite differently with more acidic ketones. 1,3-Dicarbomethoxyacetone and diethylamine react with 3,5-dinitrobenzophenone to yield **31** which cyclizes to **32**, not **33**.[58,62]



32

Finally, it should be pointed out that since formation of anionic σ complexes from simple nucleophiles and many different kinds of aromatic and heteroaromatic compounds occurs readily, all of these aromatic substrates should be susceptible to meta bridging reactions with carbanions (and possibly amidines, guanidines, and urethanes). The interesting and useful bicyclic and heterobicyclic compounds which might be prepared in this way could make meta bridging reactions quite useful to the organic chemist. Work in this area is just beginning. When more fully developed, and in conjunction with synthetic methods recently reviewed by Preston and Tennant[63] involving ortho-substituted nitroaromatic derivatives, the value of electron-deficient aromatics in organic synthesis should be enhanced.

I wish to thank the Special Action Office for Drug Abuse Prevention (NIMH), the Army Research Office at Durham, the Research Corporation, and the Petroleum Research Fund, administered by the American Chemical Society, for support of work which originated from our laboratories. Thanks are also due to my students, Horst Schran, Stephan Taylor, Ray Bard, and David Palmer. Valuable advice from Professor Martin Kuehne is also much appreciated.

(61) S. R. Alpha, *J. Org. Chem.*, **38**, 3136 (1973).

(62) The published report considers the reaction of **28** (R = CH_3 or H). We have found that when R = C_6H_5 the same reaction occurs. With more acidic ketones bicyclic products are obtained.

(63) P. N. Preston and G. Tennant, *Chem. Rev.*, **72**, 627 (1972).