Regiochemistry of Polar Cycloaddition. Validity of the Electrophilic Addition Model[1]

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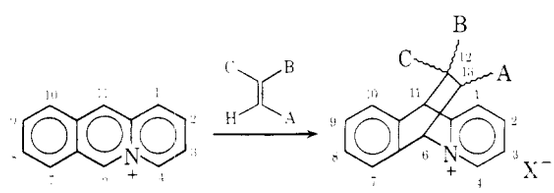
The regiochemistry of the polar cycloaddition of eight unsymmetrical alkenes with the acridizinium (benzo[*b*]-quinolizinium) ion has been examined in the light of an electrophilic addition model. For alkenes having a double bond conjugated with an electron-withdrawing group, prediction of the regiochemistry of addition is complicated by the fact that the preferred reaction site of the highest occupied molecular orbital cannot be selected from a consideration of ground state polarization alone. With ethyl acrylate, *cis*-crotononitrile, and 2-stilbazole, the first examples of nonregiospecific cycloaddition to the acridizinium ion have been found.

In a cycloaddition involving two unsymmetrical reactants more than one regioisomer may result, and although in the classical Diels–Alder reaction there is considerable selectivity,[2] both regioisomers are usually formed. Since selectivity for a given positional isomer also reflects a preferred orientation in the transition state, numerous attempts[2-6] have been made to explain regioselectivity in terms of a given mechanism. However, as recently as 1967 it was stated[7] that "no satisfactory explanation can be given for these orientation phenomena."

The well-known Woodward–Hoffman rules[8] have been unable to account properly for the observed regioselectivity, and much of Firestone's criticism[5] of concerted mechanisms has been directed at the failure of even highly sophisticated molecular orbital calculations to predict the favored regioisomer.

Other theoreticians[3,4] have concluded also that the secondary interactions originally proposed by Woodward are insufficient to determine the regiochemistry and have emphasized the mutual importance of electrostatic effects and frontier orbital interactions. Salem has reported[4] that in the dimerization of acrolein "the major contribution [60–70%] to the favoring of one regioisomer relative to the other arises from electrostatic terms." The relative importance of these electrostatic effects appears to be predictable from frontier orbital considerations.[9-11]

In contrast to the mere regioselectivity of the classical Diels–Alder reaction, polar cycloadditions[12,13] have shown a remarkable regiospecificity. For example, of the 20 unsymmetrical alkenes which had been added to the acridizinium (benzo[*b*]quinolizinium) ion (**1**) at the time of the last review,[13] all had been reported[14] to add regiospecifically (**1** → **2**).



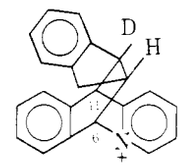
1 **2**

Similar specificity has been found in the addition of unsymmetrical alkenes to isoquinolinium salts[15,16] and as well as to other cations.[12]

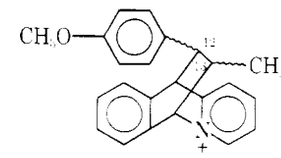
The regiochemistry of polar cycloaddition is understandable in terms of an electrophilic addition model in which the most electron-deficient (electrophilic) carbon atom of the cation becomes bonded to the more negatively polarizable end of the multiple bond (alkene or alkyne) of the donor molecule.[17] Earlier difficulties in applying the model will be discussed further on.

The purpose of the present investigation was to examine the regiochemistry of addition to the acridizinium ion of further unsymmetrical addends which might test the usefulness of the electrophilic addition model. The regiochemistry of the cycloadduct (usually a mixture of stereoisomers) is in most cases conveniently determined by NMR spectroscopy from the multiplicity of the bridgehead protons of the adducts. From observations made on a large number of adducts (**2**) obtained from the acridizinium ion (**1**), Fields et al.[18] have pointed out that the resonance due to the proton at the C-6 bridgehead of the adduct will appear at δ 6.63 ± 0.14 while the resonance arising from the C-11 bridgehead will appear at δ 5.49 ± 0.21.

In the cycloaddition with styrene,[18,19] the electrophilic center of the acridizinium ion becomes bonded to the β carbon of the styrene, as would be predicted from the rules of electrophilic addition. Now it has been found that indene adds regiospecifically to the acridizinium ion (affording **3**). Again the electrophilic center of the cation adds to that carbon atom of the double bond which would lead to the transition state which could better accommodate a developing positive charge. For convenience in analyzing the NMR spectrum, the reaction was carried out with 1,1,3-trideuterioindene.



3 (plus geometrical isomer)



4 picrate

Additional evidence for the controlling effect of the aryl function was obtained in the cycloaddition of anethole, *trans*-1-(4-methoxyphenyl)-1-propene, to acridizinium picrate. The reaction was determined to be regiospecific with the 4-methoxyphenyl group located exclusively at C-12 as depicted for adduct **4**. Since anethole is a substituted β-methylstyrene, these results indicate that a β-alkyl group does not alter the regiochemistry previously observed for styrenes in cycloadditions to aromatic cations.

However, if a phenyl group must compete with a β-alkoxy substituent, the aryl group is no longer "regio-controlling." This was demonstrated when *cis*-β-methoxystyrene was added to acridizinium fluoborate. The reaction was again stereospecific but with the aryl group now located at C-13. This regiochemistry was deduced from decoupling experiments which revealed that of the two bridge hydrogens the C-12 proton appeared further downfield. This observation is only consistent with the regioisomer **5**. The structural assignment for **5** is in agreement with the orientation assigned by Fields et al.[18] for the analogous adduct of β-dimethylaminostyrene with the acridizinium ion. Again these results are consistent with predictions based upon an electrophilic model;

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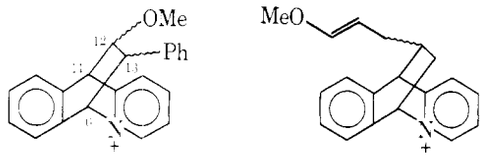

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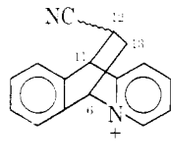
6



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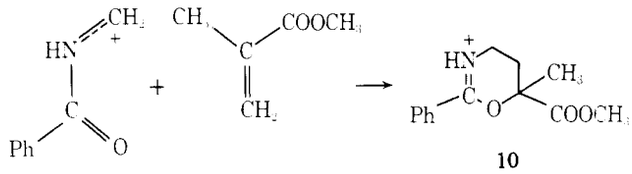
the orientation is such that the more cation-stabilizing group is located at C-12.

In the addition of 1-methoxy-1,3-butadiene to the acridizinium ion, theoretically any of the four carbon atoms of the diene chain could become bonded to C-6 in the adduct, but only a single regioisomer was isolated. The assignment of this isomer as adduct **6** follows from its facile acid hydrolysis to an aldehyde and the observed bridgehead multiplicities. If all possible resonance forms are drawn for 1-methoxybutadiene, the observed addition to C-4 is that which would be predicted from the electrophilic model; but on the other hand, the low isolated yield makes it impossible to exclude the possibility that regioisomers are formed.

Of more interest are the less nucleophilic unsymmetrical alkenes which on polar cycloaddition give products of regiochemistry opposite to that predicted from ground state polarization alone. With the acridizinium ion the single known example of such an addition was that of acrylonitrile, which was shown[18] to afford a single regioisomer (**7**) in which the nitrile group is at position 12. In a polar cycloaddition involving the benzoylamidomethylenium ion (**8**), Schmidt[20]



8 9 10

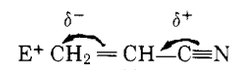
found that methyl methacrylate (**9**) gave a cycloadduct (**10**) in which the electrophilic center of the cation becomes attached to the β-carbon atom of the ethylenic system. Again the regiochemistry is opposite that predicted from the ground state polarization of the conjugated ethylenic system. These "anomalous" orientations caused Fields et al. and Schmidt (independently) to reject the electrophilic model, a decision reflecting the widely held belief that it is possible to predict the regiochemistry of the addition of a cation or cationoid to a conjugated double bond solely on the basis of the ground state polarization of the bond. So firmly entrenched is this belief that the addition of a nonanionic species to the β-carbon atom of such a conjugated species has been almost universally regarded as evidence that the addend must be radical in character.[21,22]

Cause for skepticism[17] concerning the validity of arguments that orientations observed in polar cycloaddition did not always have a polar origin was afforded by the apparent lack of regioisomers in the "anomalous" polar cycloadditions as well as by the lack of rationale for the observed stereoselectivity.

After a demonstration[17] that changes in electrophilicity of the acridizinium ion (**1**) produced by substituents at the 9 position affect the rate of cycloaddition to acrylonitrile qualitatively in the same way as was observed[23] with styrene, hence the nitrile was acting as the *nucleophilic* component, it was concluded "that the regiospecificity or regioselectivity observed in polar cycloaddition always has a polar origin and is not only understandable in terms of ground state polarization and polarizability, but also provides a new tool for the study of the electrophilic addition of large cations."

Following the lead of Houk,[10] Fleming[24] recently has used frontier orbital theory to rationalize the orientation of the addition of acrylonitrile to the acridizinium ion, pointing out that in this reaction the largest[25] HOMO coefficient of the acrylonitrile (donor) is at the β-carbon atom, the atom which should become linked to the 6 position, site of the largest LUMO coefficient of the acridizinium ion (acceptor).

In classical terms, acrylonitrile is polarizable and in the presence of a cation its double bond has a charge distribution (**11**) opposite to that predicted from a simplistic application of ground state polarization alone. From this it follows that if an ethylene having a single electron-withdrawing but very poorly polarizable group could be made to react with the acridizinium ion, the chief cycloadduct should be the one with the substituent at position 13, i.e., the regiochemistry which would be predicted from ground state polarization alone. While polarization and polarizability are important in the regiochemistry of electrophilic addition of cationic and cationoid reagents to conjugated systems such as methacrylate esters or acrylonitrile, the actual regiochemistry observed is undoubtedly influenced by the variable tendency of the unshared electrons of the electron-withdrawing group to enter into complexes with the cationoid reagents as well as by the size (or activity) of the cation, factors invoked by Traynham[26] to explain the "abnormal" addition of hypochlorous acids to certain methylene cycloalkanes. It is interesting that methacrylate esters have been found to react with several electrophilic reagents to give products having the orientation to be expected if the cationic and cationoid species had added to the β-carbon atom of the ethylenic bond. The reagents include hypochlorous acid,[27] nitrosyl chloride,[28] and nitryl chloride.[29]



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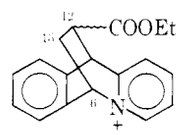
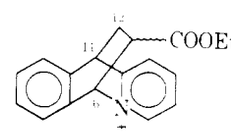
Although the possibility seems less likely in terms of everything known about polar cycloaddition, one could explain the "anomalous" regiochemistry of addition of acrylonitrile to the acridizinium ion in terms of diradical or more exactly diradical cation addition. There is a consensus that a radical would attack the β carbon of a monosubstituted ethylene regardless of the polarity of the substituent. Indeed Firestone[5] has proposed a diradical mechanism to account for the unidirectional addition of both electron-rich and electron-deficient monosubstituted dipolarophiles to many 1,3 dipoles. It appeared that the attractiveness of such a mechanism for polar cycloaddition would certainly be diminished if it were possible to find a monosubstituted ethylene which underwent polar cycloaddition to yield a mixture of regioisomers. Such an alkene has now been found in ethyl acrylate.

The ethyl acrylate adducts consist of a regioisomeric mixture in which the chief product (80%) is the 12-ethoxycarbonyl derivative **12**, in which the electron-withdrawing group oc-



12 (80%)



13 (20%)

cupies the position (12) that it does in the acrylonitrile adduct. Of more interest is the minor product **13**, the one which would

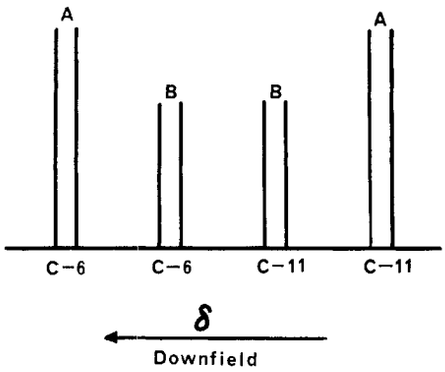
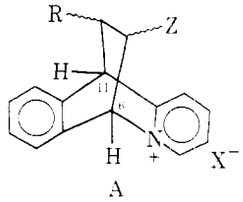


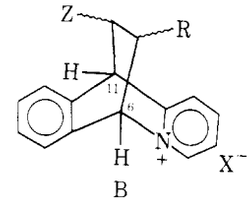
Figure 1. An idealized representation of the NMR signals expected from an unequal mixture of regioisomeric adducts A and B where R is an electron-releasing substituent and Z is an electron-attracting substituent.

be predicted if only ground state polarization of the ethyl acrylate was important.

Evidence for the occurence of regioisomers in cycloadditions involving the acridizinium ion is afforded by the appearance of two signals for each of the bridgehead protons (C-6 and C-11) in the ^{1}H NMR spectrum. The observed signals are fairly easily distinguished from the resonances which arise from the diastereoisomers involved. The analytical procedure can probably be best illustrated by considering the general example shown in Figure 1 in which the relative chemical shifts of the bridgehead protons in regioisomers A and B will be predicted. In this example Z is an electron-withdrawing group and R is hydrogen or an electron-releasing substituent. For adduct A the deshielding effect of the quaternary nitrogen on the C-6 proton is reinforced by the proximity of the electron-withdrawing substituent Z at C-13. Consequently, the C-6 proton in adduct A would be expected to appear further downfield than any of the other bridgehead resonances. Since the electron-releasing group (or hydrogen in the case of ethyl acrylate) is located at the adjacent 12 position, the C-11 signal would be expected to appear furthest upfield of all those arising from bridgehead protons.



A

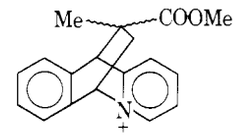


B

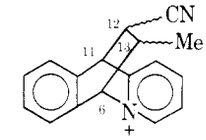
In adduct B the substituents are located so as to compress the normal separation of the bridgehead resonances. The electron-releasing R group at C-13 will shift the C-6 signal upfield by opposing the deshielding effect of the adjacent azonia group, while the electron-withdrawing Z group at C-12 will send the signal from C-11 downfield by reducing the electron density. Consequently, the signals for C-6 and C-11 in adduct 13 would be predicted to occur in the middle, bracketed by the extremes represented in adduct A. Finally, and most importantly, the relative intensities of the resonances must correspond to the pairing assignments.

Consistent with the theorized spectrum for a regioisomeric mixture, the adduct from the reaction of ethyl acrylate with the acridizinium ion possessed four bridgehead resonances: the strong signals of δ 6.43 and 5.50 representing the bridgehead resonances for the major isomer **12** and the weak signals at δ 6.72 and 5.15 corresponding to the minor isomer **13.** Integration of the bridgehead resonances showed that the adduct **12** constituted 80 ± 3% of the mixture.

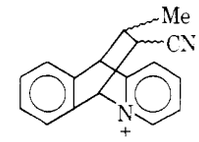
As might have been predicted from its reaction with the benzoylamidomethylenium ion (**8**),[20] methyl methacrylate (**9**) undergoes cycloaddition with the acridizinium ion regiospecifically to yield **14.** Here again polarizability must be a more important factor than the ground state polarization.



14



15 (85%)

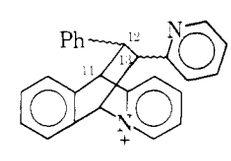


16 (15%)

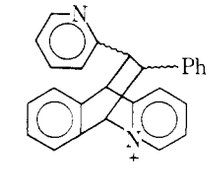
With *cis*-crotononitrile a mixture of regioisomers is obtained, the predominant one (**15**) having the nitrile group at position 12, as in the acrylonitrile adduct **7.** For polar cycloaddition, this is the first example of the occurrence of regioisomers with an ethylenic derivative having groups of significantly different polarity[30] in positions 1 and 2.

Since in the acridizinium series nonregiospecificity has been observed only with poorly nucleophilic alkenes which react slowly, even under forcing conditions, the question naturally arises as to whether regiospecificity is directly related to reactivity. Consequently, the relative rates were determined for several weakly nucelophilic alkenes of differing regiochemical behavior. Intended only for comparisons within in the series, each rate represents a single trial at 130 °C using a 50:1 ratio of alkene to acridizinium ion. The relative reactivities are as follows: ethyl acrylate, 110; methyl methacrylate, 93; acrylonitrile, 11; and *cis*-crotononitrile, 1. Whereas only the first and last members of this series are nonregiospecific, it is apparent that rate and orientation are not directly related. Instead, the regiochemistry must depend upon the nature and location of the substituents on the alkene.

The relatively unreactive 2-stilbazole was likewise found to give regioisomers on addition to acridizinium tetrafluoroborate. Although the steric demands of the two aryl substituents on the ethylene are nearly identical, a 2:1 preference is shown for the formation of the adduct **17** with the phenyl group at position 12 over that of the regioisomer **18.** Again the



17



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selectivity is explicable in terms of an electrophilic model, a benzylic carbon being superior to a 2-picolyl group in ability to stabilize a positive charge.

The electrophilic addition model appears to rationalize the regioselectivity of all polar cycloadditions. Difficulty in using the model is apparently confined to addends which have an electron-withdrawing but polarizable group conjugated with the double (or triple) bond. Since in these cases ground state polarization and polarizability lead to opposite orientations, prediction of the regiochemistry can best be made by determining which atom has the largest HOMO coefficient of the system in reactions involving a cation.

From the success of the electrophilic model in explaining regiochemistry in polar cycloaddition, it must not be concluded, as was done earlier,[30] that two discrete steps are in-

volved with a carbonium ion as an intermediate. The present thought[31] is that two *stages* are involved, the first being the usual interaction of the HOMO of the donor (alkene or alkyne) with the LUMO of the acceptor (cation), with the initial interaction being in the nature of a charge-transfer complex formation. The transition state must resemble the adduct but have considerable charge-transfer character. The new bond which has the greater σ bond character will be that formed by the initial HOMO–LUMO interaction. Undoubtedly the great regioselectivity which distinguishes cationic polar cycloaddition from other types of cycloaddition with inverse electron demand has its orgin in the fact that cations have a very strong tendency toward the formation of charge-transfer complexes.[32]

Experimental Section

General. The elemental analysis on all adducts was determined by M-H-W Laboratories, Garden City, Mich. Proton magnetic spectra were determined using either a Varian A-60 or T-60 spectrometer with tetramethylsilane as an internal standard. Melting points were taken in capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. The terms syn and anti are with regard to the benzenoid ring of the adduct.

General Procedure for Cycloaddition Reactions. Cycloaddition reactions were usually carried out by refluxing a 10 molar ratio of the alkene with the acridizinium salt in acetonitrile to which a small quantity of hydroquinone had been added. The adducts were isolated by evaporation of the solvent under reduced pressure and trituration of the residue with ethyl acetate or anhydrous ethyl ether to remove any polymer which might have been formed.

Adduct (3) of Acridizinium Tetrafluoroborate[33] with Indene. The usual procedure was followed except that only a twofold excess of freshly distilled indene was used in the 6-h reflux. From the trituration a 96% yield of the adduct **3**, mp 172–178 °C, was obtained.

Decoupling experiments indicated that the reaction was regiospecific with the phenyl group attached to C-12. This was confirmed by repeating the cycloaddition using 1,1,3-trideuterioindene. The appearance of the C-4 proton as a pair of overlapping doublets revealed that the product was a mixture of two stereoisomers, and a partial separation was achieved by fractional crystallization from ethanol: mp 142–148 and 194–195 °C; ^{1}H NMR (CF_3COOH) high-melting isomer, δ 2.51–3.74 (m, 2, C-14), 3.93–4.31 (m, 1, C-13), 5.27 (d, 1, J = 3.5 Hz, C-11), 6.25 (d, 1, J = 2.5 Hz, C-6), 6.67–8.71 (m, 11), and 8.93 (m, 1, C-14).

Anal. Calcd for $C_{22}H_{18}BF_4N$: C, 68.95; H, 4.73; N, 3.66. Found: C, 68.82; H, 4.78; N, 3.47.

12-(4-Methoxyphenyl)-13-methyl-6,11-dihydro-6,11-ethanoacridizinium Picrate (4). Only a fourfold excess of anethole was used in the reaction with acridizinium picrate (48 h). The NMR spectrum of the crude adduct (92% yield) gave no evidence of the presence of a regioisomer. Recrystallization from ethyl acetate gave a bright yellow powder: mp 193–197 °C; ^{1}H NMR (Me_2SO-d_6) δ 0.92 (m, 3, C-13 Me), 2.37–2.93 (m, 2, C-12, C-13), 3.71 (s, 3, OMe), 5.10 (broad s, 1, C-11), 6.40–6.93 (m, 5, C-6, shielded aromatics), 7.22–7.94 (m, 4), 8.00–8.82 (m, 5, C-1, C-2, C-3, and picrate protons), and 9.47 (d, 1, J = 6 Hz, C-4).

Anal. Calcd for $C_{29}H_{24}N_4O_8$: C, 62.59; H, 4.35; N, 10.07. Found: C, 62.73; H, 4.26; N, 10.12.

12-Methoxy-13-phenyl-6,11-dihydro-6,11-ethanoacridizinium Tetrafluoroborate (5). The general procedure was followed except that only an 8-fold excess of *cis*-β-methoxystyrene was used in the 5.5-day reflux. The product obtained from the trituration with ether was finely ground and purified by suspension in ethyl acetate. This material (99% yield) was then recrystallized from ethanol–ethyl acetate as a colorless powder: mp 220–221 °C; ^{1}H NMR (CF_3CO_2H) δ 3.15 (s, 3, OMe), 4.08 (m, 1, C-13), 4.55 (m, 1, $J_{12,13}$ = 7 Hz, C-12), 5.59 (d, 1, J = 4 Hz, C-11), 6.33 (d, 1, J = 2 Hz, C-6), 6.86 (m, 2, ortho phenyl protons), 7.09–8.73 (m, 10), and 9.08 (d, 1, J = 6 Hz, C-4).

Anal. Calcd for $C_{22}H_{20}BF_4NO$: C, 63.03; H, 5.29; N, 3.34. Found: C, 62.80; H, 4.98; N, 3.08.

The product (**5**) was confirmed to be a single regioisomer by decoupling experiments on the ^{1}H NMR spectrometer.

12-(β-Methoxyvinyl)-6,11-dihydro-6,11-ethanoacridizinium (6). A solution containing 5.9 g (22.7 mmol) of acridizinium bromide and 2.3 g (27.3 mmol) of 1-methoxy-1,3-butadiene in a mixture of 150 mL of ethanol and 20 mL of tetrahydrothiophene 1,1-dioxide was allowed to react at room temperature for 2 days. The crude product (3.4 g) isolated in the usual way was recrystallized from methanol–ether to afford 2.0 g (27%) of a colorless adduct, mp 105–115 °C. An analytical sample was recrystallized from 95% ethanol, providing a colorless adduct: mp 136–141 °C; ^{1}H NMR (CD_3CN) δ 1.43–1.77 (m, 1 syn C-13), 2.60–3.07 (m, 1, anti C-13), 3.37 (s, 1, C-11), 6.40 (s, 1, vinyl), 6.60 (s, 1, vinyl), 6.92 (m, 1, C-6), 7.40–8.73 (m, 7), and 9.57 (d, 1, J = 6 Hz, C-4).

Anal. Calcd for $C_{18}H_{18}BrNO$: C, 62.80; 5.27; N, 4.07. Found: C, 62.68; H, 5.44; N, 4.16.

Transformation of 6 by Hot Perchloric Acid. To a hot solution of 0.3 g of the adduct **6** in water was added 35% perchloric acid, precipitating 0.2 g (65%) of a hydrolysis product as a hygroscopic perchlorate salt: mp 165–170 °C; IR (NaCl) 1720 (C=O, aldehyde) and 1095 (ClO_4^-) cm^{-1}; ^{1}H NMR (CF_3CO_2H) δ 1.62–1.92 (m, 1, syn C-13), 2.52–3.18 (m, 3, anti C-12, C-13, C-14), 5.13 (broad s, 1, C-11), 6.48 (broad s, 1, C-6), 7.52–8.82 (m, 7), 9.20 (d, 1, J = 6 Hz, C-4), and 9.85 (broad s, 1, CHO).

Mixture of Regioisomers (12 and 13) Obtained by Reaction of Acridizinium Tetrafluoroborate with Ethyl Acrylate. Cycloaddition by the standard procedure (12-h reflux) afforded an 89% yield of adduct, mp 129–154 °C. The ^{1}H NMR spectrum indicated that both regioisomers (**12** and **13**) were present, and from the integration of the distinctive bridgehead absorbances 80% of the mixture had the ester group at C-12 (cf. **12**).

Recrystallization of the crude isomer from 95% ethanol provided a mixture of regioisomers which was used as an analytical sample: mp 186–188 °C; IR (KBr) 1740 (C=O, ester) and 1070 (BF_4^-) cm^{-1}; ^{1}H NMR (CF_3CO_2H) δ 1.30 (t, 3, ester Me), 2.43–2.93 (m, 2, bridge, CH_2), 3.36–3.68 (m, 1, bridge CH), 4.25 (q, 2, ester CH_2), 5.15 (m, 0.2, C-11 of **13**), 5.50 (d, 0.8, J = 2 Hz, C-11 of **12**), 6.43 (m, 0.8, C-6 of **12**), 6.74 (d, 0.2, J = 2 Hz, C-6 of **13**), 7.28–8.78 (m, 7), and 9.17 (d, 1, J = 6 Hz, C-4).

Anal. Calcd for $C_{18}H_{18}BF_4NO_2$: C, 58.88; H, 4.94; N, 3.81. Found: C, 58.74; H, 5.15; N, 4.06.

12-Carbomethoxy-12-methyl-6,11-dihydro-6,11-ethanoacridizinium Tetrafluoroborate (14). Prepared by the general procedure (12-h reflux), the crude adduct, mp 94–130 °C (87% yield), had a ^{1}H NMR spectrum consistent with the presence of only a single regioisomer. Recrystallization from 1-butanol indicated the presence of both C-12 stereoisomers, but only a partial separation was made and structural assignments were not attempted. The more soluble isomer was the major product, about 67% of the mixture: mp 107–110 °C; ^{1}H NMR (CF_3CO_2H) δ 1.27 (s, 3, C-12 Me), 2.02 (d, 1, J = 14 Hz, syn C-13), 2.97–3.33 (m, 1, anti C-13), 3.82 (s, 3, ester Me), 5.22 (s, 1, C-11), 6.46 (broad s, 1, J = 3 Hz, C-6), 7.18–8.72 (m, 7), and 9.12 (d, 1, J = 6 Hz, C-4).

An analytical sample was provided by recrystallization of the less soluble isomer from ethanol: mp 165–168 °C; IR (KBr) 1735 (C=O, ester) and 1060 (BF_4^-) cm^{-1}; ^{1}H NMR (CF_3CO_2H) δ 1.40 (s, 3, C-12 Me), 2.03–2,37 (m, 1, syn C-13), 3.23 (d, 1, J = 14 Hz, anti C-13), 3.80 (s, 3, ester Me), 5.32 (s, 1, C-11), 6.48 (broad s, 1, J = 3 Hz, C-6), 7.18–8.72 (m, 7), and 9.15 (d, 1, J = 6 Hz, C-4).

Anal. Calcd for $C_{18}H_{18}BF_4NO_2$: C, 58.88; H, 4.94; N, 3.81. Found: C, 58.98; H, 5.17; N, 3.62.

Adducts (15 and 16) Obtained by Reaction of *cis*-Crotononitrile with Acridizinium Tetrafluoroborate. The *cis*-crotononitrile, bp 106–107 °C, obtained by fractionation of commercial crotononitrile in a spinning band column was allowed to react with acridizinium tetrafluoroborate in the usual way except that only a sixfold excess of the nitrile was used and the solvent was refluxing 1-butanol (4.5 days).

The ^{1}H NMR spectrum of the crude adduct showed that both regioisomers (**15** and **16**) were present, with **15** predominant (85%). Although separation and isolation of the regioisomers was not accomplished, the syn and anti forms of **15** showed distinct solubility differences. The more soluble of these had mp 228–231 °C; ^{1}H NMR (CF_3CO_2H) δ 1.28 (d, 3, J = 7 Hz, C-13 Me), 2.80–3.21 (m, 1, C-14), 3.71–3.95 (m, 1, J = 10 Hz, C-12), 5.52 (d, 1, J = 2 Hz, C-11), 6.28 (d, 1, J = 1 Hz, C-6), 7.40–8.73 (m, 7), and 9.11 (d, 1, J = 6 Hz, C-4).

Recrystallization of the less soluble portion of the mixture from ethanol provided an analytical sample as colorless needles: mp 286–287 °C dec; IR (KBr) 2245 (CN) and 1060 (BF_4^-) cm^{-1}; ^{1}H NMR (CF_3CO_2H) δ 1.20 (d, 3, J = 7 Hz, C-13 Me), 2.85–3.22 (m, 1, C-13), 3.76–4.06 (m, 1, C-12), 5.39 (d, 1, J = 3 Hz, C-11), 6.20 (d, 1, J = 2 Hz, C-6), 7.42–8.75 (m, 7), and 9.07 (d, 1, J = 6 Hz, C-4).

Anal. Calcd for $C_{17}H_{15}BF_4N_2$: C, 61.11; H, 4.53; N, 8.38. Found: C, 61.20; H, 4.42; N, 8.47.

Determination of Relative Reaction Rates. The rate determinations were carried out at 130 °C in sulfolane using a 50:1 molar ratio of the alkene to acridizinium ion. Progress of the cycloaddition was

monitored by measurement of the UV absorption at 399 nm. The technique was essentially that reported earlier,[23] except that each rate was the result of only a single trial.

Adducts (17 and 18) of Acridizinium Tetrafluoroborate with 2-Stilbazole. The standard procedure was followed except that only a 3:1 ratio of stilbazole to acridizinium salt was used (46-h reflux) and most of the adduct crystallized from the reaction mixture (overall yield 96%). The ^1H NMR spectrum of the crude product showed that the major regioisomer (**17**; ~66%) had the phenyl group at position 12 and indicated that the minor isomer (**18**) consisted of almost equal parts of the two possible geometrical isomers.

Recrystallization from acetronitrile afforded a colorless powder which was analyzed as an isomeric mixture: mp 247–255 °C; ^1H NMR ($(CD_3)_2SO$) δ 3.89–4.72 (m, 2, C-12, C-13), 5.43 (m, 0.6, C-11 of **17**), 5.55 (d, 0.2, J = 2 Hz, C-11 of **18**), 5.79 (d, 0.2, J = 2 Hz, C-11 of **18**), 6.70–9.27 (m, 17), and 9.53 (m, 1, C-4); ^1H NMR (CF_3CO_2H) δ 3.91–4.93 (m, 2, C-12, C-13), 5.36 (m, 0.7, C-11 of **17**), 5.70 (m, 0.3, C-11 of **18**), 6.52 (m, 0.3, C-6 of **18**), 6.56–9.01 (m, 17), and 9.30 (m, 1, C-4).

Anal. Calcd for $C_{26}H_{21}BF_4N_2$: C, 69.66; H, 4.72; N, 6.25. Found: C, 69.70; H, 4.95; N, 6.07.

Registry No.—1 BF_4, 32865-43-3; 1 picrate, 66357-78-6; 1 Br, 7547-88-8; 3 (isomer 1), 66357-80-0; 3 (isomer 2), 66511-02-2; **4**, 66357-82-2; **5**, 66357-84-4; 6 Br (isomer 1), 66357-85-5; 6 Br (isomer 2), 66511-03-3; 6 ClO_4 (isomer 1), 66511-05-5; 6 ClO_4 (isomer 2), 66537-15-3; **9**, 80-62-6; **12** (isomer 1), 66357-87-7; **12** (isomer 2), 66511-07-7; **13** (isomer 1), 66357-89-9; **13** (isomer 2), 66511-09-9; **14** (isomer 1), 66357-91-3; **14** (isomer 2), 66511-11-3; **15**, 66357-93-5; **16**, 66357-95-7; **17**, 66357-97-9; **18**, 66357-99-1; indene, 95-13-6; anethole, 104-46-1; *cis*-β-methoxystyrene, 14371-19-8; 1-methoxy-1,3-butadiene, 3036-66-6; ethyl acrylate, 140-88-5; *cis*-crotononitrile, 1190-76-7; 2-stilbazole, 714-08-9.

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Selectivity in Cycloadditions. 6. Cycloadditions of Nitrile Oxides to Benzofuran. Regiochemistry[1]

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Cycloaddition of benzonitrile oxide and mesitonitrile oxide to benzofuran yields the two regioisomeric cycloadducts **1** and **2** in a 70:30 and 26:74 ratio, respectively. Frontier orbital considerations, using ab initio STO-3G calculations, and a comparison with the regioselectivities observed with indene and styrene allow elucidation of the inversion of regiochemistry of the cycloadditions of the two nitrile oxides to benzofuran.

Although much is known about the physical properties of heteroaromatic compounds and the reactivities of these molecules in electrophilic substitution reactions,[3] the study of the dipolarophilic reactivities of these molecules toward 1,3 dipoles is by far less developed. The reluctance of heteroaromatics to undergo addition reactions is well known and usually rationalized in terms of loss of aromaticity in the addition step.

The study of cycloaddition reactions of heteroaromatics is of interest for mechanistic reasons, since the concerted cycloaddition is expected to be slowed down, so that diradical and zwitterionic pathways, which are normally of no importance in 1,3-dipolar cycloadditions,[4] may become competitive.

The previous paper of this series dealt with the cycloadditions of nitrile oxides to cyclopentadiene,[5] indene,[5] and furan.[1b] In the case of furan a competition between the concerted pathway and a minor two-step pathway was described.

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