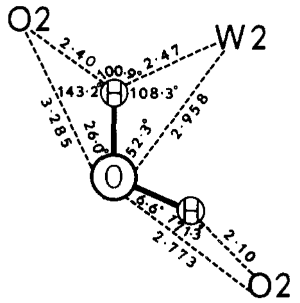

Figure 11. Schematic drawing of water molecule 1 which crystallizes with dimer **4**, showing geometry about bifurcated hydrogen bond. Distances are in angstroms.

dl stereoisomers of **3d** in the photo- and electrochemical preparations of **3d.** Thus, at least in the case of **3d,** the meso form is found not simply because it crystallizes better than the corresponding **dl** form, but rather because it is formed in considerably higher yield.

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Supplementary Material Available: Tables of bond distances and angles involving hydrogen and those in the disordered ethanol molecule which crystallizes with **3d** (3 pages). Ordering information is given on any current masthead page.

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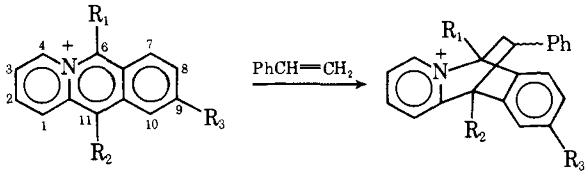
Steric Effects in Some Cycloaddition Reactions[1,2]

C. K. Bradsher,* T. G. Wallis, I. J. Westerman, and N. A. Porter

Contribution from the Paul M. Gross Chemical Laboratories, Duke University, Durham, North Carolina 27706. *Received September 21, 1976*

Abstract: The log of the relative rate constants (k/k_0) for the cycloaddition of six 3-substituted-2-methylisoquinolinium iodides gives a significant correlation with the Hammett substituent constant σ_m, but the rate of cycloaddition of a seventh analogue, 3-*tert*-butyl-2-methylisoquinolinium iodide, is much too high for inclusion in a significant correlation. It is suggested that this acceleration of rate has its origin in the relief of steric strain during cycloaddition. The 13.6-fold increase in the rate of cycloaddition observed when a methyl group is substituted at meso position 11 of the acridizinium (benzo[*b*]quinolizinium) ion must also have its origin in the relief of strain. Further increase of the strain through introduction of a flanking methyl at position 10 (in 7,10,11-trimethylacridizinium ion) results in an over tenfold increase in the reaction rate. From literature data it can be demonstrated that a large part of the acceleration in the rate of cycloaddition observed when methyl groups are introduced into the meso positions of anthracene has its origin in the relief of peri strain. That the rate of cycloaddition of the acridizinium ion, as well as the enthalpy of activation, is lowered by introduction of a methyl group at meso position 6 indicates a larger negative entropy of activation for the 6-methyl derivatives.

In earlier work[3] it was shown that the rate of cycloaddition of the acridizinium ion (**1**) with styrene was influenced by the nature of the substituent at position 9 of the acridizinium (benzo[*b*]quinolizinium) ring. A significant correlation of the log of the relative rate of cycloaddition with Hammett σ_p constants was obtained with the reaction constant ρ positive (1.69). The suggestion[3] that the substituent at position 9 may act by altering the electron deficiency at position 6 has gained support from the demonstration[4] that there is a significant correlation between the log of the relative rate of cycloaddition



1, $R_1 = R_2 = H$
2, $R_1 = Me$; $R_2 = H$
3, $R_1 = H$; $R_2 = Me$

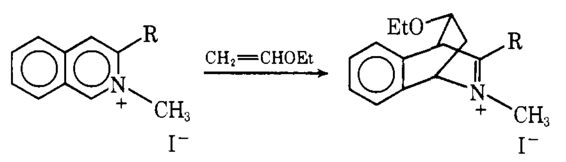
Table I. Rates of Addition of Ethyl Vinyl Ether to 3-Substituted Isoquinolinium Iodides

3-R	$k \times 10^3$, min^{-1}	σ_m[a]	n[b]
H	0.82 ± 0.06	0.00	3
NH_2	0.48 ± 0.01	−0.16	3
t-Bu	3.1 ± 0.2	−0.10	2
CH_3	0.65 ± 0.05	−0.069	4
C_6H_5	2.6 ± 0.2	0.06	3
$NHCOCH_3$	10.6 ± 0.3	0.21	3
Br	25.8 ± 0.9	0.391	2

[a] Reference 11. [b] Number of trials.

and the chemical shift of the proton at position 6. Consistent with these results appeared the observation[5] that the introduction of a methyl group at position 6 (cf. **2**, R_3 = H) lowered the rate of cycloaddition of styrene. If instead, the methyl group was introduced at the other meso position, position 11 (cf. **3**, R_3 = H), the rate of cycloaddition was actually *accelerated* 13.6-fold. Since the steric environment of a methyl group at position 6 is almost identical with one at position 11, the conclusion[5] was reached that the two meso positions must play different roles in the rate-determining process, a conclusion that still appears valid. The additional suggestion[5] that the acceleration caused by the introduction of the methyl group at position 11 may have an electronic basis now appears to be erroneous.

2,3-Dimethylisoquinolinium iodide (**4**, R = Me) undergoes cycloaddition[6,7] with ethyl vinyl ether, yielding an adduct (**5**, R = Me) demonstrated[8] to have the stereochemistry shown. Since other 3-substituted 2-methylisoquinolinium iodides were available an opportunity was afforded to extend further our studies[3,5,9] on the influence of substituents on the rate of polar cycloaddition. The results of the present study are summarized in Table I.



4 **5**

A Hammett plot of the data in Table I (Figure 1) does not give a significant[10] correlation with σ_m,[11] but if the rate constant for the 3-*tert*-butyl compound is omitted from the calculations, a significant correlation with σ_m is obtained (ρ = 3.47 ± 0.36, r = 0.979).[12] It seems most likely that enhancement in the rate of cycloaddition of *tert*-butylisoquinolinium iodide over that which would be predicted by the curve of Figure 1 has its origin in the relief of peri strain encountered when the hydrogen at position 4, hemmed in by the *tert*-butyl group at position 3 (which is in turn buttressed by the methyl at position 2) and the peri hydrogen at position 8, moves out of plane as the ring folds during cycloaddition (see **5**).

Since it seemed probable that the unexplained acceleration of rate observed when 11-methylacridizinium ion undergoes cycloaddition might likewise have a steric origin, it appeared desirable to determine whether the introduction of an additional methyl group at position 10, flanking the methyl group at position 11, might enhance the rate of cycloaddition. Using x-ray analysis, Jameson et al.[13] have shown that the *peri*-methyl groups of 3-bromo-1,8-dimethylnaphthalene are highly strained, and more recently Hart et al.[14] have shown that relief of peri strain is the decisive factor in directing the addition of a proton to 1,4,5,8,9-pentamethylanthracene.

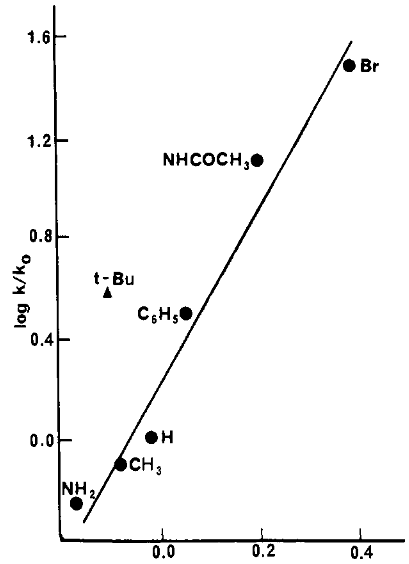
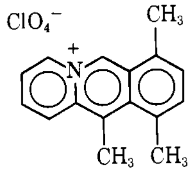


Figure 1. Plot of log k/k_0 for the cycloaddition of 3-substituted-2-methylisoquinolinium iodides with ethyl vinyl ether vs. σ_m. The *tert*-butyl rate constant was not included in the calculation of the fitted line.

Since 10,11-dimethylacridizinium salts would be difficult to prepare, the more readily available 7,10,11-trimethylacridizinium perchlorate[4,14] (**6**) was selected for the rate measurement. The rate found for the trimethyl derivative (**6**) was more than ten times as great as for 11-methylacridizinium perchlorate (**3**) or over 100 times the rate for acridizinium (**1**, R_3 = H) itself. Since the methyl group is electron releasing and when substituted on the acridizinium ion should act electronically to slow rather than to accelerate the cycloaddition, this is very clearly an example of *steric* acceleration and is due to relief of peri strain.



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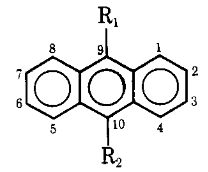

7, $R_1 = R_2$ = H
8, $R_1 = R_2$ = Me
9, $R_1 = R_2$ = MeO
10, R_1 = F; R_2 = Me
11, R_1 = F; R_2 = MeO

From the results described here it would be logical to assume that the 218-fold increase in reactivity toward maleic anhydride caused by the introduction of methyl groups into the 9 and 10 positions of anthracene (**7** → **8**)[15] could in large measure also have its origin in relief of peri strain. A simple test of this hypothesis is afforded by a previously published[15] comparison of the rate of cycloaddition when both of the methyl groups are replaced by the more electron releasing, but much less sterically demanding methoxyl groups (cf. **9**). The difference in rate is remarkable; in fact 9,10-dimethoxyanthracene is *less* reactive than anthracene itself toward maleic anhydride. Sauer et al.[15] were aware of this inconsistency, and suggested that "the increase in rate produced by methoxy groups is smaller than that of alkyl groups because of the impaired coplanarity (*peri*-hydrogens)." A similar steric inhibition of resonance argument was introduced by Klanderman et al.[16] to explain the relative rates of cycloaddition of *meso*-methyl- and *meso*-methoxyanthracenes with benzyne. The literature reveals that the relative electron release of a methyl and a methoxyl group at the meso position of anthracene has

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Table II. Pseudo-First-Order Reaction Rates, Arrhenius Activation Energies, and Entropies of Activation for the Acridizinium Ion and Its *meso*-Methyl Derivatives

R	Rate, $k \times 10^3$, min^{-1} (±5%), at temp (±0.5 °C)					E_A, kcal/mol	$\Delta S^{\ddagger}$,[a] eu
	65 °C	77 °C	87.5 °C	100.0 °C	110.6 °C		
H	5.0	11.0	22.0	51.0	74.0	15.7 ± 0.6	−33.1
11-Me	68.0	130.0	260.0	460.0	690	13.4 ± 0.5	−34.7
6-Me	2.5	4.9	8.7	19.0	32.0	14.6 ± 0.4	−37.6

[a] Since the entropies of activation were calculated from pseudo-first-order rather than from absolute rates, they are subject to some absolute error, but are useful in making comparisons within the table.

been answered beyond question, but the importance of the data to the cycloaddition problem was not pointed out. Anderson et al.[17] measured the ^{19}F chemical shift of a series of 9-fluoro-10-substituted anthracenes and showed that the methoxy derivative (**11**) had a larger positive chemical shift (4.03 ppm) than the methyl counterpart (**10**) (2.44 ppm). This amounts to a demonstration that even within the constraints offered by the *peri*-hydrogens the methoxyl group is more electron releasing than the methyl group. It follows that a large part of the enhancement of reactivity caused by introduction of methyl groups into the meso position of anthracene must have a steric origin, the relief of peri strain.

While the relief of peri strain explanation makes it clear why a methyl group of position 9 of anthracene or at position 11 of the acridizinium cation might cause an enhancement in the rate of cycloaddition, the unanswered question, which was not addressed in our original communication,[4] is why a similar rate enhancement is not seen when a methyl group is introduced at the other meso position of the acridizinium ion, the 6-position (see **2**, R_3 = H). A methyl group at position 6 should cause peri strain that is at least qualitatively similar to that caused by introduction of a methyl group at the other meso position, position 11. Electronically the two meso positions are very different, the carbon at position 6 being the most electron deficient in the molecule, while that at position 11 bears no positive charge in any of the canonical forms contributing to the ground state of the cation. A possible explanation is that a methyl group at position 6 might cause an entropy effect large enough to overwhelm any steric acceleration which might be expected from relief of peri strain.

Arrhenius parameters for the cycloaddition of styrene to the acridizinium ion and its 6- and 11-methyl homologues were determined by measuring pseudo-first-order reaction rates of each at five different temperatures. The results are summarized in Table II.

The energies of activation fall within the range of values which have been observed for typical Diels-Alder reactions[18,19] as well as for a Diels-Alder with inverse electron demand.[20] Since the acridizinium ion has a known affinity for electron-rich dienes,[21,22] the energy of activation for its cycloaddition with styrene (15.7 kcal/mol) is understandably lower than that reported[20] for the reaction of 9,10-dimethylanthracene with styrene (17.9 kcal/mol). For hexachlorocyclopentadiene, which is not a cation, but does undergo the Diels-Alder with inverse electron demand, the energy of activation for the reaction with styrene[20] (15.2 kcal/mol) is almost the same as that for the acridizinium ion (Table II).

Of the *meso*-methylacridizinium ions the 11-methyl is the more straightforward, for in keeping with its 13.6-fold increase in reaction rate over that of the acridizinium ion, the energy of activation is significantly lower (by 2.3 kcal/mol). As would be predicted from the discussion of the importance of peri strain in promoting the cycloaddition reaction, the energy of activation for the formation of the styrene cycloadduct from 6-methylacridizinium ion is actually lower (by 1.1 kcal/mol) than that for the similar reactions of the acridizinium ion. That the rate of cycloaddition of the 6-methyl derivative is actually *slower* than that for the parent acridizinium ion points to a larger negative entropy of activation (−37.6 eu) when a methyl group is introduced at position 6, in comparison with a less important entropy factor (−34.7 eu) when a methyl group is introduced at the other meso position, position 11. This observation supports earlier evidence[3] concerning the importance of position 6 in the rate-determining step of the cycloaddition of acridizinium salts.

It seems probable that the decrease in the rate of cycloaddition of maleic anhydride with anthracene reported[15] to occur when methoxyl groups are substituted at the meso positions also must be due to an important negative entropy of activation. The methoxyl groups when so substituted *are* electron releasing, but the molecular vibrations of these flexible groups reduce the number of pathways by which a maleic anhydride molecule can make a fruitful approach for cycloaddition.

Table III. Preparation of 3-Substituted Isoquinolinium Methiodides

3-Substituent	Yield,[a] %	Mp, °C Obsd	Mp, °C Lit.	Ref.[b]
H		159-160.5	158-161	23
NH_2	84	218-219		24
t-Bu	21	222 dec		25
Me		223-224	221-222	26
Ph	95	172-173		25
$NHCOCH_3$	82	169-169.5 dec		27
Br	72	188-189		28

[a] Yields have not been given for methiodides found in the literature. The Editor has been supplied with acceptable analysis for all new methiodides. [b] References are to the methiodide, if previously prepared, otherwise to the literature preparation of the base actually used.

Experimental Section

3-Substituted-2-methylisoquinolinium Iodides for Cycloaddition Studies. The name iodides were prepared by reaction of the appropriate base with methyl iodide. Yields and melting points of the acetonitrile-recrystallized products are summarized in Table III.

Rates of Cycloaddition to Isoquinolinium Iodides. The isoquinolinium iodides were all of analytical purity. All solvents were freshly distilled before use. A small quantity of hydroquinone was added to the stock solution of ethyl vinyl ether to inhibit polymerization.

The rates of addition of ethyl vinyl ether were determined as follows: 1 mL (0.05 mmol) of 0.05 M 3-substituted isoquinolinium iodide in dimethyl sulfoxide and 1 mL (1.00 mmol) of 1.00 M ethyl vinyl ether in dimethyl sulfoxide were mixed at 25 ± 1 °C (silicone oil bath). The disappearance of the long wavelength absorption in the UV spectrum of the isoquinolinium ion was used to follow the progress of the reaction. UV samples were prepared by dilution with 95% ethanol of 100 μL of the reaction mixture to a volume of 25 mL. The rate for each trial was obtained by a nonweighted least-squares fit of $-\log A$ vs. time. The reported rates are the average of two to four trials and are reported in Table I.

Rate of Styrene Addition to 7,10,11-Trimethylacridizinium Perchlorate. Subsequent to the appearance of our communication of steric acceleration[4] a communication by Hart et al.[14] described in some detail the preparation of the above named salt by essentially the method which we used. Our perchlorate, mp 269–270 °C dec (lit.[14] mp > 265 °C), reacted with styrene too fast to give reproducible rate constants at 65 °C using the previously described procedure,[3] although an estimate of the rate constant ($\times 10^3$, min^{-1}) was 700 vs. 5.0 previously observed for the unsubstituted acridizinium ion. At 25 ± 1 °C using the same procedure the observed rate constant was 63×10^{-3} vs. 0.22×10^{-3} min^{-1} estimated for the unsubstituted compound by extrapolation of available $\ln k/T$ vs. $1/T$ plots. A similar estimate of the expected rate of addition of 11-methylacridizinium perchlorate to styrene at 25 °C was 4.9×10^{-3} (min^{-1}).

Rate Studies of Cycloaddition of the Acridizinium Ion and Its 6-Methyl and 11-Methyl Derivatives at Temperatures in the Range 65–110.6 °C. The acridizinium perchlorates were prepared according to previously published[29,30] directions and melting points agreed closely with those reported. The procedures employed in the rate determinations have been discussed in detail.[3] Pseudo-first-order conditions were maintained by using a 10:1 ratio of alkene to acridizinium salt. The rate at the given temperature was followed by loss of the long wavelength absorbance in the visible spectrum of the acridizinium salt. All spectra were measured in a Beckman DB-G UV-visible spectrometer. Temperature controls were maintained by use of vapor baths. Since corrections were not made for fluctuations of atmospheric pressure the temperatures are correct only to ±0.5 °C. In view of the range of reactivities involved the temperature range 65–110.6 °C was near the maximum for convenience, employing this method. The linear correlations and resultant parameters were calculated by means of a nonweighted least-squares program. The statistical treatments and evaluation standards were those recommended by Jaffé.[10] The listed uncertainties in values include two-thirds of all possible deviations.

References and Notes

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Ring-Closure Reactions. 7.[1] Kinetics and Activation Parameters of Lactone Formation in the Range of 3- to 23-Membered Rings[2]

Carlo Galli, Gabriello Illuminati,* Luigi Mandolini, and Pasquale Tamborra

Contribution from the Centro di Studio sui Meccanismi di Reazione del Consiglio Nazionale delle Ricerche, Istituto di Chimica Organica dell'Università, 00185 Rome, Italy.

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Abstract: The ring size (n) range for the quantitative investigation of the lactonization of ω-bromoalkanoic acids with strong bases in 99% aqueous Me_2SO has been considerably extended by the determination of the rate constants for several large rings (n = 13–16, 18, and 23) and for n = 3. Also activation parameters have been determined for all the compounds studied so far in the range between 7 and 23 and for n = 3. The three-membered ring lactone is a reactive intermediate rather than a final product and is assumed to form in a slow, kinetically detectable step. Extremely high rates are found for the formation of the four-, five-, and six-membered ring lactones and have required the use of an ethyldiisopropylamine–ethyldiisopropylammonium p-toluenesulfonate buffer system in Me_2SO solution and of an appropriate kinetics analysis. The reactivities span six powers of ten, the most reactive compound being the one for n = 5 and the least reactive for n = 8. They tend to level off in the large ring region and vary within a factor of 2 between n = 13 and n = 23. The reaction is characterized by a very low k_3/k_5 ratio. The $\Delta H^{\ddagger}$ vs. n profile provides a measure of the strain energy accompanying ring closure. In particular, the highest strains are experienced for n = 3 and 8. The entropies of activation provide another clean-cut physical organic demonstration of Ruzicka's hypothesis by undergoing a general and substantial drop as the length of the bifunctional chain increases.

The lactonization of ω-bromo acids is a reaction suitable for quantitative work in the field of ring-closure reactivity. Our previous work[3] has dealt with the kinetics of this reaction in the ring size range n = 7–12, at 50 °C, in 99% Me_2SO solution (eq 1, n = ring size) and with the appropriate intermolecular reference reaction[1] (eq 2) for use in the calculation of the related effective molarities. In order to obtain a deeper understanding of the factors involved in ring closure, in this paper we wish to report rate data which considerably extend the above ring size range by including terms with n = 3, 4, 5, 6, 13,

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