Intramolecular Diels-Alder Reactions with Furan:
The Gem-Dialkyl Effect Revisited

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Abstract: Remote substituents that influence ground state state rotamer populations were found
            to be important controlling factors in the intramolecular Diels-Alder reaction with
            furan.

The effect of substituents on cyclization rates[1] and stereochemistry has taken on greater

importance recently, partly because of the widespread utilization of intramolecular reactions,

most notably the intramolecular Diels-Alder (IMDA) reaction.[2] During the course of our work on

the intramolecular Diels-Alder reaction with furan as a diene, we noticed that the success of

this reaction depended on the substituent pattern of the bridging alkyl chain.[3] Others[4] have

noticed similar effects on heteroatom containing bridging chains as well as a few cases where

the chain was composed of carbons only.[5] Since we are interested in the synthetic utility of

this reaction and because of the relevance of the factors that govern this cyclization to other

processes, we undertook a systematic study of substituent effects on the rates and equilibria of

the IMDA reaction with furan as a diene (eq. 1). These results combined with crystallographic

data for one reactant-product pair[6] have allowed us to reach some conclusions about subtle

substituent effects in this cyclization.

The reaction we examined is depicted in eq. 1. All reactions were conducted in benzene-d_6

at 80°C in sealed nmr tubes. Mixtures of epimeric exo products were obtained in each case. The

rates were monitored by nmr and reflect a disappearance of starting furan and the appearance of

the mixture of epimers (no attempt was made to determine the rate of formation of each epimer).

When R=H no product could be observed (see Table I). When R=CH_3 less than 5% of products was

observed after prolonged heating (no rate data are available for this reaction). It is striking

that changing CH_3 to $CH_2CH_2CH_3$ resulted in a ca. 10 fold increase in the yield of cyclization

products. Notice also that when comparing cyclic versus acyclic geminal substitution (entries C

and D; E and F) the acyclic precursors cyclize somewhat faster and to a greater extent. It is

also of interest that heteroatom substitution directly on the bridging chain (entries E,F,G)

facilitates this reaction more than carbon substitution.

It is interesting to note that with the exception of entry F, the increase in rates

parallels the increase in equilibrium constants. This is consistent with the assumption that

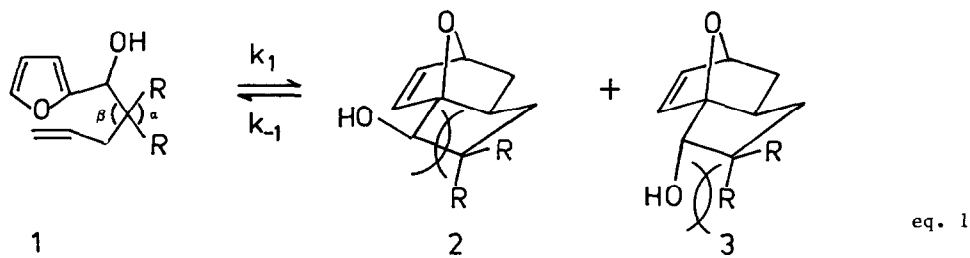the different substituents at the carbon predominantly affect the ground state energy of the

eq. 1

1   **2**   **3**

Table I. Substituent Effects on Rates and Equilibria of Intramolecular Diels-Alder Reactions

	R	$k_1 \times 10^6 s^{-1}$ [a]	rel. rate	$K_{eq.}^b$	$t_{1/2}(h)$	%yield
A	H	--	--	no reaction	--	
B	$-CH_3$	--	--	<0.05	--	<5
C	$-CH_2CH_2$ CH_2 $-CH_2CH_2$	1.46	1	0.9	131	47
D	$-CH_2-CH_2CH_3$	2.73	1.8	1.4	71	58
E	$-SCH_2$ CH_2 $-SCH_2$	5.95	4.1	3.2	32	76
F	$-SCH_2CH_3$	6.94	4.8	5.7	28	85
G	$-OCH_2CH_3$	14.3	9.8	4.7	13	82

a.) The reaction was monitored by ^1H NMR following the disappearance of the furan protons and the appearance of the new olefin protons. b.) The equilibrium constants were determined when no significant change in starting material concentration could be observed after a 3 day period.

IMDA precursors without a concommitant effect on the transition states or ground states of the products.

Several explanations of the rate enhancements for cyclization due to geminal substitution have been cited. Crystallographic studies of 1E and 2E have allowed examination of some of these for this system in the solid state (Figure 1). The Thorpe-Ingold effect ascribes the aforementioned enhancement to an increase in angle α, caused by the mutual repulsion of the geminal substituents (eq. 1), which causes a decrease in angle β and thereby makes cyclization more favorable. While this explanation may be operative when small rings (3-4 atoms) are being formed, it is not likely to be important for larger rings. Indeed, in the solid state, 1E

Fig. 1

1E   **2E**
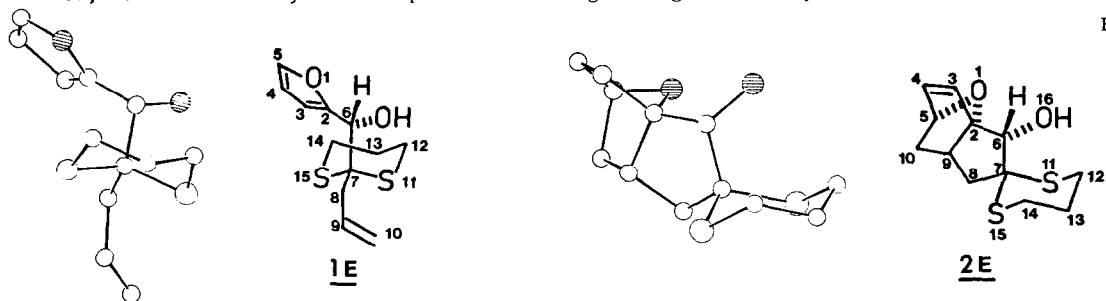
adopts larger than tetrahedral angles for both α and β, 111.7(3) and 111.7(4), respectively. Another explanation, proposed by Allinger, states that ease of cyclization (both rates and equilibria) is related to the number of new <u>gauche</u> interactions produced during cyclization. This explanation works well for 6-membered rings, where the products are easily analyzed in terms of <u>gauche</u> interactions, but is not adequate when considering the formation of 5-membered rings. In fact, recourse to the solid state conformations shows that the <u>gauche</u> interaction involving the hydroxyl group and the axial sulfur in 1E becomes eclipsing in 2E.

Our results are best explained by considering the effect of the substituents on rotamer populations in the ground state of the starting materials. Boeckman[9] has used a similar explanation for the rate enhancements observed in cyclization of geminal dimethyl substituted intramolecular Diels-Alder precursor. The interactions due to the R-groups probably most affect rotamer population with respect to the bonds indicated in Fig. 2. Interactions that disfavor conformer <u>A</u> (or other conformations of energy lower than <u>B</u>) with respect to <u>B</u> will favor cyclization.

Fig. 2.
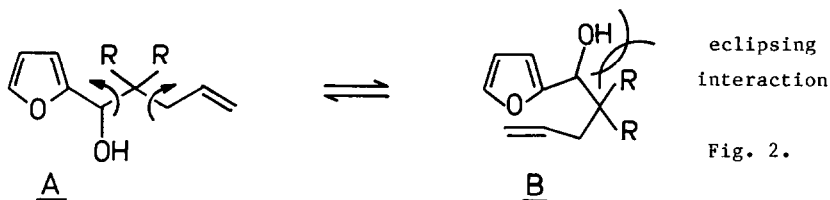
Analysis of the data in Table I reveal two hitherto unrealized factors that contribute to the ease of cyclization. First, while geminal methyl substituents are known[9] to facilitate intramolecular Diels-Alder reactions, the effect is small for furan Diels-Alder reaction in contrast to the effect of geminal propyl substitution (entry 4), which leads to a 58% yield of products. Thus it seems that propyl has a larger effect on rotamer populations than methyl, without a concomitant increase in the reaction-retarding eclipsing interaction. These remote effects on rotamer populations can be depicted as shown in Fig. 3 where the methyl group interacts with groups six atoms removed. Indeed this phenomenon is reminiscent of Newman's

Fig. 3
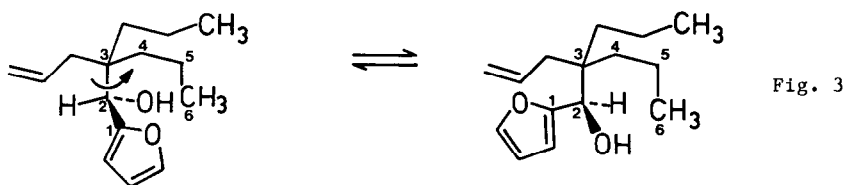
Rule of Six.[10] Newman noticed that the rate of ester hydrolysis is dramatically influenced by the number of atoms situated six atoms from the carbonyl oxygen. While this is an empirical rule its origins are probably due to steric interactions.[10b]

The second factor that is important for this cyclization is the presence of heteratom substitution directly on the tethering chain (entries 5, 6, and 7). A heteroatom at this position can conceivably minimize the developing eclipsing interaction while remote effects on

rotamer populations are still operative. In addition, when sulfur is the heteroatom, the incipient eclipsing interaction is further reduced because of the increased C-S bond length in 1E (1.82 $\overset{\circ}{A}$) versus a C-C bond.[6] Also the van der Waals radius is smaller for sulfur than for CH_3 (1.85 vs. 2.0 $\overset{\circ}{A}$).

In summary, evidence has been presented that points to some subtle ramifications of the gem-dialkyl effect on cyclizations that form 5-membered carbocyclic rings. Namely, factors that disfavor unreactive rotamers without increasing incipient eclipsing interactions are of paramount importance. With a better understanding of these factors in hand, we hope to extend the synthetic utility of the intramolecular Diels-Alder with furan as the diene.

References and Notes

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6. 1E: $C_{12}H_{16}O_2S_2$, M = 250.3, Orthorhombic, a = 9.340(2), b = 8.340(1), c = 16.342(3)$\overset{\circ}{A}$, U = 1273.0 $\overset{\circ}{A}{}^3$, z = 4, space group $P2_12_12_1$. 2E: $C_{12}H_{16}O_2S_2$, M = 250.3, Orthorhombic, a = 13.475(2), b = 18.687(2), c = 9.634(1)$\overset{\circ}{A}$, U = 2426.0 $\overset{\circ}{A}{}^3$, z = 8, space group P bca. Both data sets were collected with Cu-K_α radiation (λ = 1.5418 $\overset{\circ}{A}$). The final R values, over reflections with I>2σ(I), are 0.055 for 1E and 0.050 for 2E. Supplementary crystallographic information defining the structures has been deposited with the Cambridge Crystallographic Data Centre.

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