

**STUDIES ON THE EFFECTS OF SUBSTITUENTS ON RATE ENHANCEMENTS
IN INTRAMOLECULAR DIELS-ALDER REACTIONS:
REASONS FOR THE GEM-DIMETHYL EFFECT**

MICHAEL E. JUNG*¹ and JACQUELYN GERVAY

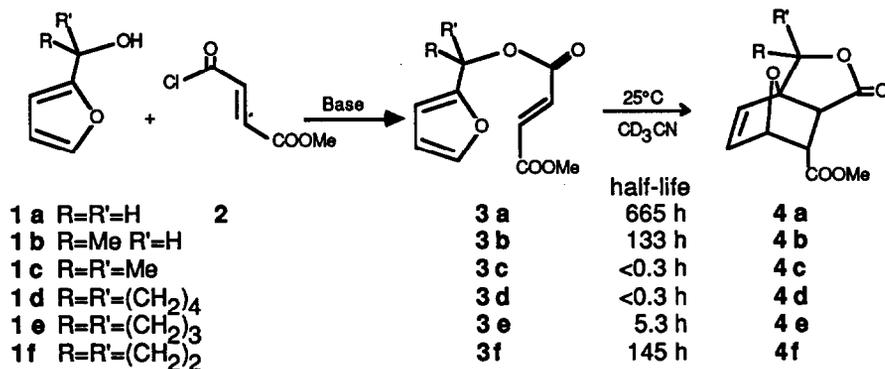
Department of Chemistry and Biochemistry, University of California, Los Angeles, California, 90024

Abstract: Comparison of the rates of cyclization of a series of 2-furfuryl methyl fumarates leads to the conclusion that the *gem*-dimethyl effect is due primarily to higher population of reactive rotamers.

Our recent observation of significant rate acceleration of the intramolecular Diels-Alder reaction of *N*-furfuryl acrylamides due to alkyl substituents on the connecting chain² has prompted us to investigate more closely the reasons for this rate enhancement, the so-called *gem*-dimethyl effect.³ The acceleration of cyclizations of acyclic precursors by alkyl substituents was noted as early as 1915.⁴ The first hypothesis to explain the reasons behind this effect was put forward by Thorpe⁴ and Ingold⁵. They suggested that substitution decreases the internal bond angle which effectively places the reacting centers in closer proximity, thus causing the rate acceleration.⁶ This explanation is commonly referred to as the "Thorpe-Ingold effect." Often this term and the "*gem*-dimethyl effect" are used interchangeably, but more correctly the "Thorpe-Ingold effect" refers specifically to the angle change on substitution, while the "*gem*-dimethyl effect" refers to the overall acceleration. In 1961, Schleyer published an excellent study of intramolecular hydrogen bonding in 2-substituted 1,3-propanediols, which provided strong experimental evidence for the Thorpe-Ingold effect but concluded that it probably accounted for only a small portion of the *gem*-dimethyl effect.⁷ An alternative explanation for the rate increase on substitution is that there is a higher population of reactive syn rotamers due to alkyl substituents on the chain connecting the reaction centers.⁸ The effect of alkyl substituents on the entropy and enthalpy of cyclizations has been discussed.⁹ We now report results of the cyclization of a series of furfuryl methyl fumarates 3a-f, which allow one to determine the relative importance of these two factors.

The choice of substituents α to the furyl ring is critical since they must clearly distinguish the two possibilities of "reactive rotamer" and "decreased angle." Our a priori hypothesis was that both effects would be important but that the "reactive rotamer" effect would outweigh that of the "decreased angle." Our results bear this out. We prepared six furyl

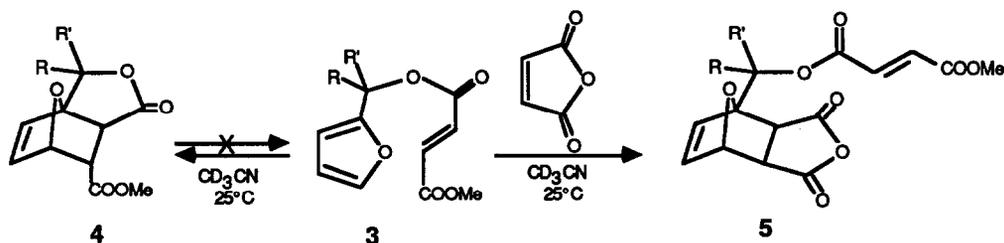
carbinols **1a-f** from 2-furyllithium or the corresponding Grignard reagent and the corresponding ketones.¹⁰ Acylation of these alcohols with E-2-(carbomethoxy)acryloyl chloride **2** produced the furfuryl methyl fumarates **3a-f**,^{11,12} the desired substrates for the cyclization studies. These mixed esters were allowed to stir at 25°C in CD₃CN with regular



monitoring of the extent of reaction by proton NMR, in order to determine the half-life of each cyclization. The unsubstituted **3a** and monosubstituted **3b** cases are quite slow, requiring many days to produce any cyclization. The disubstituted compounds with a compressed C–C–O angle, **3cd**, which should experience both of the above mentioned effects, are completely cyclized to **4cd** during the acylation of **1cd** with **2** (2h at 25°C) and thus the half-life can only be estimated. The cyclobutyl system **3e**, which should have the "reactive rotamer" but not the "decreased angle" effect,¹³ cyclizes much faster than the un- and monosubstituted cases but much slower than **3cd**. Likewise, the cyclopropyl compound **3f**, which is a "disubstituted" system but suffers even worse from angle broadening than the cyclobutyl system,¹³ is also intermediate in its cyclization rate (faster than **3a** and comparable to **3b** but also slower than the other "disubstituted" cases **3cde**). Therefore it appears that the "reactive rotamer" effect is more important than the "decreased angle" effect since disubstitution accelerates the cyclization even when the angle is forced to be wider than the mono- or unsubstituted cases due to the presence of a small ring. However, the effect of the bond angles of the connecting chain are not negligible as the results with the cyclopropyl system **3f** indicate.

One further characteristic of these reactions had to be determined, namely whether the reaction was under thermodynamic or kinetic control. All of our arguments concerning the *gem*-dimethyl effect require that the reaction be kinetically controlled since other effects could determine the position of the equilibrium in a thermodynamically controlled process. Since retro Diels-Alder reactions of furyl systems are well-documented (generally at higher temperatures), we had to eliminate the possibility that such retro-cyclizations were occurring here. We have done so as follows. The purified adducts were allowed to react with an excess of maleic anhydride in CD₃CN at 25°C for several

hours. In no instance was the cycloadduct resulting from a retro Diels-Alder reaction to give **3** followed by an intermolecular cyclization with maleic anhydride, namely compound **5**, observed. In addition, the two diastereomers of the monomethyl cycloadduct **4b**, separated by careful chromatography, did not equilibrate under the reaction conditions, namely in CD_3CN solution at 25°C , thereby indicating that no equilibrium with **3b** was established under these conditions. Thus the acceleration is a kinetic phenomenon. Interestingly, the formation of the cycloadduct **5b** was observed when the reaction with maleic anhydride was carried out in normal CDCl_3 but not if the deuteriochloroform was first filtered through basic alumina. Therefore it appears that the retro Diels-Alder reaction of **4b** is catalyzed by trace amounts of HCl in CDCl_3 at 25°C .



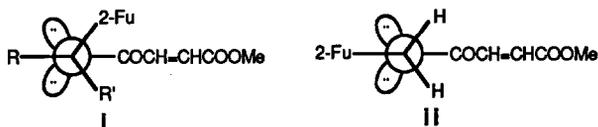
In summary, our studies indicate that the higher population of reactive rotamers due to alkyl substitution on the connecting chain (effectively reducing the entropy of the molecule relative to the transition state and thereby facilitating reaction) is a more important component of the *gem*-dimethyl effect than the decrease in the angle at the substituted carbon of the connecting chain (Thorpe-Ingold effect).

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References and Notes

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4. R. M. Beesley, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.*, **107**, 1080 (1915).
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6. For example, the CCC angle in propane is 112.4° while that of isobutane is 111.15° and that of isopentane 109.5° . Thus replacing one of the two central hydrogens with a methyl group decreases the internal angle by 1.25° while replacing both causes a 2.5° decrease. For a discussion, see reference 7.
7. P. von R. Schleyer, *J. Am. Chem. Soc.*, **83**, 1368 (1961).
8. In the case of compounds **3a-f**, this corresponds to a higher population of syn-clinal conformations about the $\text{CR}_2\text{-O}$ bond, e.g., **i**, which can cycloadd, as opposed to the most stable anti conformation about the $\text{CH}_2\text{-O}$ bond in the unsubstituted case, **ii**, which cannot cyclize. For similar arguments for a different cyclization process,



see: M. Harfenist and E. Thom, *J. Org. Chem.*, **37**, 841 (1972).

9. a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, pp 196-202. b) N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).
10. For the preparation of **1f**, the ethyl hemiacetal of cyclopropanone was used with two equivalents of the furyl organometallic reagent.
11. All new compounds exhibited spectroscopic data (high field ^1H and ^{13}C NMR, IR, MS or analysis) in full accord with their assigned structure.
12. For **3a-d** (53-68%): 1 eq of alcohol **1** was reacted with 1.5 eq NaH in THF at 25°C for 30 min., the THF replaced with toluene, 0.5 eq pyridine and 2 eq of **2** added at -10°C , then brought to 25°C for 2h. For **3e** (68%): the bromomagnesium salt of **1e** (prepared from furylmagnesium bromide and cyclobutanone) was used instead of the sodium salt. For **3f** (78%): 1 eq of the alcohol **1f** and 2 eq of **2** were reacted in pyridine for 12 h at 25°C .
13. Although the reported values for the HCH angle in cyclobutane and cyclopropane differ over a fairly wide range, it is generally conceded that the HCH angle is larger than 109.5° in both, with reasonable numbers being 114° (cyclobutane) and 116° (cyclopropane). For leading references, see: E. Goldish, *J. Chem. Ed.*, **36**, 408 (1959).

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