

Evidence Against the Reactive Rotamer Explanation of the *Gem*-Dialkyl Effect

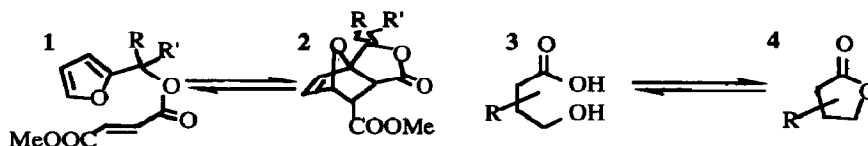
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Abstract: Acceleration of intramolecular reaction rates with increasing substitution has been known for a long time. The most common explanation used for this phenomenon is the 'Reactive Rotamer Effect' which states that "The ring closure reaction proceeds at a greater rate on geminal (or alkyl) substitution because of the resultant decrease in unprofitable rotamer distribution".¹ This research presents evidence against this explanation and suggests an alternate explanation for the cause of the *gem*-dialkyl effect.

The rate of an intramolecular reaction is often increased when alkyl groups are placed on a chain between the two reacting centers.¹⁻⁵ This is known as the *gem*-dialkyl effect, and has been exploited to promote difficult cyclization reactions.⁶ Several explanations for this effect have been proposed, but none have been rigorously proven or universally accepted. The first explanation, proposed in 1915, is the 'Thorpe-Ingold effect', which proposes that the substitution of alkyl groups for hydrogen pushes the reactive centers closer together by compressing the internal angle of the carbon chain, thus facilitating the reaction.⁵ However, at least two studies have been published which demonstrate that this is not a major contributor to the *gem*-dialkyl effect.^{3,4} A second explanation was proposed by Bruice and Pandit and is called the 'Reactive Rotamer Effect'. They stated that "The ring closure reaction proceeds at a greater rate on geminal (or alkyl) substitution because of the resultant decrease in unprofitable rotamer distribution".¹ Their explanation supposes that the rate is dependent on the concentration of the reactive rotamer(s). This explanation has been frequently used in studies of the *gem*-dialkyl effect even though it seems to violate the Curtin-Hammett principle. Recently we have shown how complete conformational search has been extremely useful in studying product distributions in the IMDAF reaction.⁷

The conformational search program, WIZARD,⁸⁻¹⁰ was utilized to study the systems reported by Jung and Gervay³ and by Sebelius¹¹ (Table 1) in greater detail. The ensemble of conformations was analyzed in terms of various conformational parameters. Those conformations which clustered near to the values corresponding to the transition state were chosen as the "reactive rotamers".



Scheme 1. Reactions studied.

Table 1. Relative Rates Observed for the Formation of **2** from **1** and **4** from **3**.

Reaction	R	R'	Rel. Rate
1a -> 2a	H	H	1 ^a
1b -> 2b	H	Me	8.35 ^a
1c -> 2c		-(CH ₂) ₂ -	10.5 ^a
1d -> 2d		-(CH ₂) ₃ -	208 ^a
1e -> 2e	Me	Me	2123 ^a
1f -> 2f	H	t-Bu	8.32 ^a
3a -> 4a	H		1 ^b
3b -> 4b	2-CH ₃		5.3 ^b
3c -> 4c	4-CH ₃		3.53 ^b
3d -> 4d	4,4-(CH ₃) ₂		12.3 ^b

a: Rate relative to 1a -> 1b b: Rate relative to 3a -> 4a

The percentages of the reactive rotamers were determined using a Boltzmann distribution based on the energies determined with MM2(87).¹² If the 'Reactive Rotamer Effect' is the major contributor to the *gem*-dialkyl effect, a plot of rate (or relative rate) versus reactive rotamer population should result in a linear plot. Figure 1 demonstrates that this is not observed.

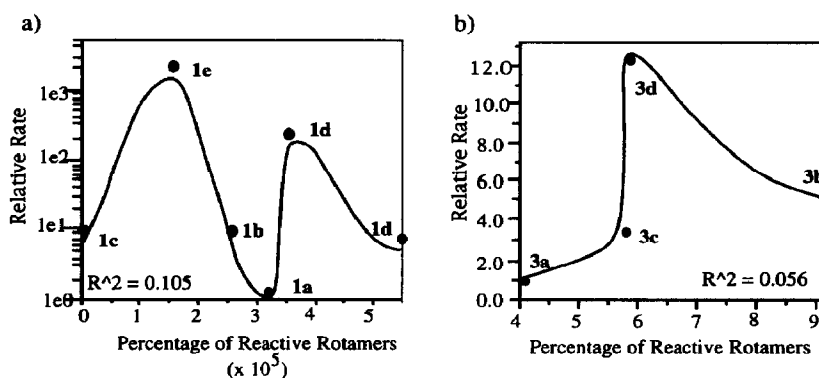


Figure 1. Relative Rate versus Reactive Rotamer Percentage; a) IMDAF System
b) Lactonization System

Next the rate dependence on ΔG^\ddagger was examined. Recently, WIZARD has been augmented with the ability to perform conformational search on transition states.^{13,14} The values of ΔH^\ddagger were found by utilizing WIZARD to perform a conformational search on both ground states and transition states followed by energy calculation using MOPAC.¹⁵ The value of ΔH^\ddagger was determined by calculating the enthalpy difference between the lowest energy transition state and the lowest energy ground state. The Curtin Hammett principle justifies the choice of these two endpoints even though the lowest energy transition state might arise from a different ground state conformer. The value of ΔS^\ddagger would also be required to calculate ΔG^\ddagger . The value of ΔS^\ddagger is related to the difference in the number of conformations between the ground and transition states for each reaction. Calculation of this difference for multiple reactions was feasible because WIZARD performs an

exhaustive search for all conformations in short CPU times. This difference was found to be linearly related to the values of ΔS^\ddagger found by Jung and Gervay. However, the variation in ΔS^\ddagger is small compared to the variation in ΔH^\ddagger , and so the rates should correspond well with ΔH^\ddagger . Figure 2 demonstrates that there is a good correlation between ΔH^\ddagger and the rate for both the Diels Alder reactions studied by Jung and Gervay and the formation of five-membered lactones studied by Sebelius.

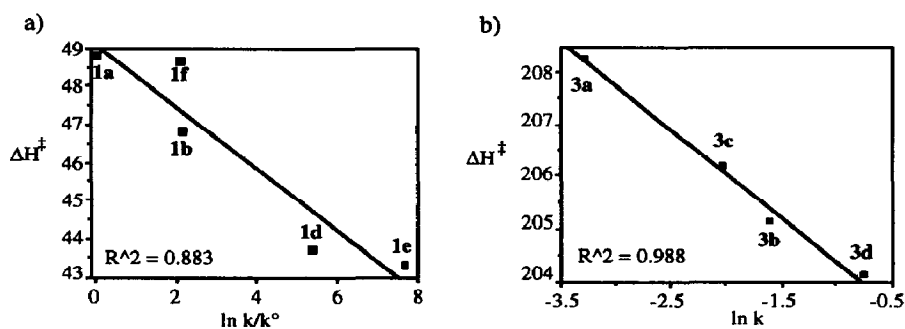


Figure 2. Activation Enthalpy Versus Rate a) IMDAF System b) Lactone System

This study shows that rate enhancements depend on reductions of overall ΔH^\ddagger and not upon the relative concentrations of "reactive rotamers". A physical explanation for this effect arises from the fact that the transition states are more eclipsed than the ground states. Thus any change that lowers the barrier of rotation from the staggered ground state to the eclipsed transition state will lower the overall ΔH^\ddagger . NMR studies have shown that increasing substitution can lower rotational barriers. For example, the rotational barrier for the *tert*-butyl group in 2,2,3-trimethylbutane is 6.9 kcal/mol, but the barrier for the equivalent bond in the more sterically hindered 2,2,3,4-tetramethylpentane is only 6.0 kcal/mol.¹⁶ This is thought to occur since the staggered conformations are more destabilized than the eclipsed conformations.

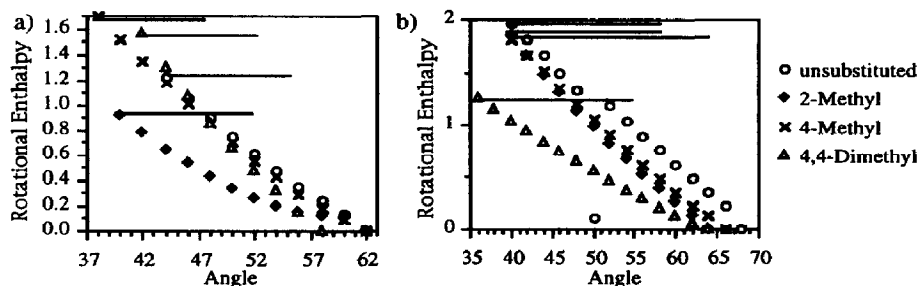


Figure 3. Rotational studies of the lactonization system a) Rotation around the bond between carbons 2 and 3. b) Rotation around the bond between carbons 3 and 4.

Figure 3 shows rotational data generated using the torsion angle driving option in MM2(87) for compounds **3a-3d**. The angles shown represent rotation from a staggered ground state in a reactive

conformation to an angle approximating the transition state. Figure 3a shows the effect of substitution on the rotation of the bond between atoms C2 and C3. Substitution on C2 lowers the rotational barrier. Figure 3b shows the effect of substitution on the rotation of the bond between atoms C3 and C4. Substitution at C4 facilitates rotation around the C3-C4 bond, as demonstrated by the large decrease in the rotational barrier for the 4,4-disubstituted compound. Although 4,4-disubstitution raises the barrier to rotation around the C2-C3 bond, the barrier of rotation around the C3-C4 bond is decreased by more than twice as much. The summation over all rotatable bonds leads to an overall reduction in the rotational barrier between the ground state conformations and the transition states due to the introduction of gauche interactions in the ground state. This means that the *gem*-dialkyl effect is not due to a change in concentrations of reactive rotamers, but due to an overall reduction in the ΔG^\ddagger due to a facilitation of achieving of the transition state from the ground state. We call this effect the 'Facilitated Transition Hypothesis' and further work is being done in this area.

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