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Enthalpy and Entropy in Ring Closure Reactions

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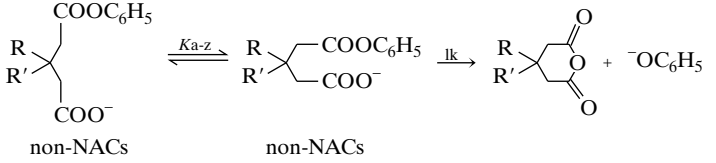
The strain and entropy effects of the lactone formation from ω-bromoalkane-carboxylate ions in ring sizes 3 to 23 is reevaluated. We find that $\Delta H^{\ddagger}$ is the largest contributor to the observed rates ($\Delta G^{\ddagger}$) for ring sizes 3 to 6, while $-T\,\Delta S^{\ddagger}$ has little influence, $-T\,\Delta S^{\ddagger}$ has more effect on the observed rates for ring sizes 8 and larger.

Historically, a large amount of experimental and theoretical data have been amassed toward the understanding of macrocyclization and intramolecular reactions. Some may consider the field well understood. However, the exact source of rate or equilibrium enhancements is unknown and under discussion. Recently, we used computational methods (*1*, *2*) to examine the intramolecular reactions of a family of monophenyl esters, listed in Table 1 (*3*, *4*). Because these esters have comparably large rate enhancements as enzymes do, the theories proposed to understand these esters have had a profound influence on the perceptions of enzyme catalysis. Like enzymes these esters bring the nucleophile and electrophile in close proximity of each other. If the reactants are positioned in a reactive conformation where the transition state is easily entered (near attack conformation, NAC), then the rate constants for the reaction are large. Our approach in investigating these esters was to use molecular mechanics to study the ground state conformations (*1*) and to use *ab initio* methods to study the transition states (*2*).

In the molecular mechanics study of the ground state, we established that an NAC would be achieved prior to entering the transition state (TS) as expressed in Eq. [1] (*1*). First the geometry of the NAC was defined, where the nucleophile and the electrophile



[1]

were within ~3 Å of each other and in a cone of 30°. Most importantly, the NAC is a minima state where the sp^2 carbon of the ester remains planar—the process

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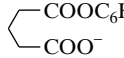
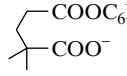
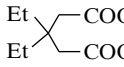
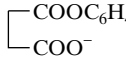
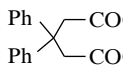
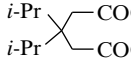
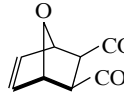
TABLE 1
List of the Monophenyl Esters Studied and Their Relative Rate Constants

		k_{rel}
	$CH_2COO^- + CH_3COOC_6H_5Br(p)$	1.0
I		1×10^3 M
II		$\sim 3.6 \times 10^3$ M
III		1.8×10^5 M
IV		2.3×10^5 M
V		2.7×10^5 M
VI		1.3×10^6 M
VII		$\sim 8 \times 10^7$ M

of bond making and breaking have not started. Once the NAC had been defined, a conformational search (*5*, *6*) was performed for each ester, and the energy of each conformation was calculated using MM3(92) (*7*). We showed that the mole fraction of NACs for each ester was directly correlated to the experimental relative rate enhancements. We have also shown that change in enthalpy, not the change in entropy, is the dominant driving force of the reaction since ΔH° is directly correlated to the mole fraction of NACs and the experimental relative rate enhancements.

In the *ab initio* study of the transition states and the reaction coordinates, three of the monophenyl esters, glutarate (**I**), succinate (**IV**), and 3,6-endoxo-Δ^4-tetrahydrophthalate (**VII**), were chosen as representatives of the family of esters (*2*). At a reasonably high level of theory, RHF/6-31 + G(d) (*8*), the transition state geometries for the rate-determining step of these three monophenyl esters were found to be essentially identical. Using intrinsic reaction coordinate (IRC) (*9*, *10*) calculations in the gas phase, the nearest local minima on the reactant and product sides of the TS were determined. For the reactant side, the intramolecular reaction of an anion (CO_2^-) with a neutral substrate ($-CO_2-Ph$) provides an intramolecular ion-molecule complex (IIMC) for the reactions of glutarate and succinate monoester and a

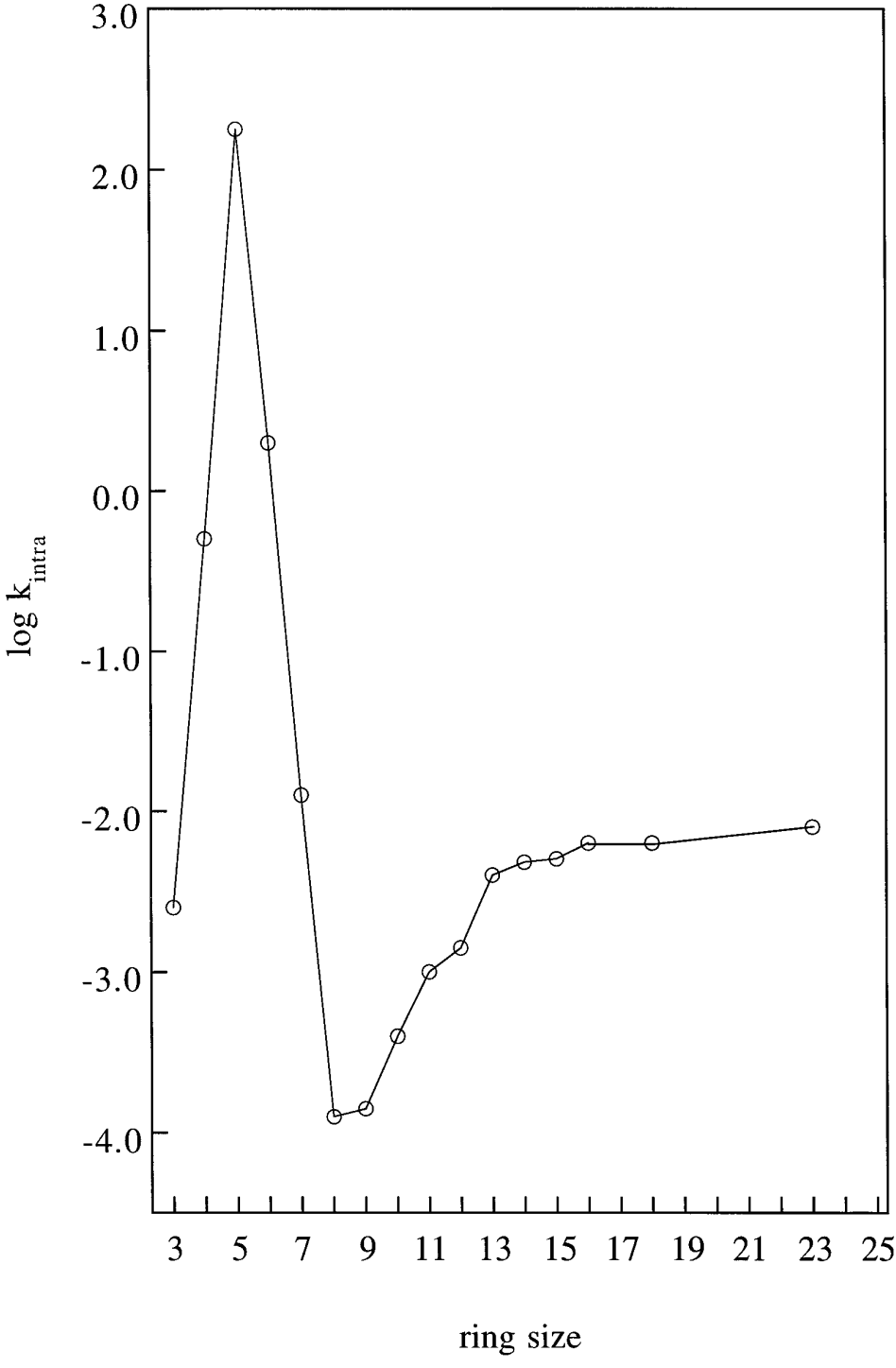


FIG. 1. Reactivity profile for lactone formation. Reproduced from Ref. (*11*).