Rate Accelerations by Alteration in the Orientation of Reacting Atoms. Comparison of Lactonizations in Bicyclo[2,2,2] and Bicyclo[2,2,1] Ring Structures

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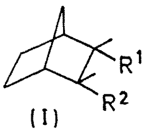
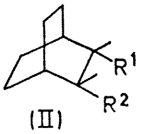
Summary The effects of slight changes in structure on reactivity was tested by comparing rates of ring closures of identical rings attached to bicyclo-[2,2,1] and -[2,2,2] supporting ring structures; the rates of the γ-lactonizations and γ-thiolactonizations were found to be 21 and 52 fold greater for the bicyclo[2,2,2] compounds compared to their bicyclo[2,2,1] analogues.

ALTHOUGH it is known that atomic orbitals have a directional preference,[1] the precise sensitivity of reaction velocity to small changes in the angle of approach of the reacting atom is unknown. It was desirable to evaluate this orientation factor since it has been suggested[2] that a higher sensitivity than commonly supposed could explain the velocity of some intramolecular reactions and might be a source of some of the unusual catalytic power of enzymes. The effect of small changes in the orientation of the reacting atoms was tested by comparing the rates of formation of five-membered lactones attached to bicyclo-[2,2,2] and -[2,2,1] structures.



(I)



(II)

R^1 R^2
a; CO_2H CH_2OH
b; CO_2H CH_2SH

The γ-lactones corresponding to *endo*-3-carboxy-2-hydroxymethylbicyclo[2,2,1]heptane (Ia) and 3-carboxy-2-hydroxymethylbicyclo[2,2,2]octane (IIa) were prepared by the method of Vaughan *et al.*[3] and the analogous γ-thiolactones corresponding to the thio-acids [(Ib) and (IIb)] were prepared by the method described for the synthesis of 2-thiophthalide.[4] Sodium salts of the γ-substituted acids were obtained by hydrolysis of the γ-lactones and γ-thiolactones. The rates of lactonization and thiolactonization were followed by monitoring the absorbance changes at 233 and 240 nm, respectively. The second-order acid-catalysed rate coefficients were calculated from the measured first-order rate constants studied at various acid concentrations.

The results of the rate studies and the comparisons of the angles are shown in the Table. The bicyclo[2,2,2]-γ-hydroxy-acid reacts 20 times more readily than the [2,2,1] analogue, and the corresponding bicyclo[2,2,2]-γ-mercapto-compound reacts 50 times faster than its [2,2,1] analogue. Because of rotation around the CCH_2–OH and C–CO_2H bonds, these compounds can in principle adopt many conformational positions. The systematic differences in

Comparison of the rates of lactonizations and thiolactonizations in the bicyclic [2,2,1] *and* [2,2,2] *ring systems*

Compound	$k(H^+)^a$ (M^{-1} min^{-1})	Orientation parameter, δ^b	Rate ratio [2,2,2]/[2,2,1]
(Ia)	7·23	20°	
			21
(IIa)	152	8°	
(Ib)	$2{\cdot}88 \times 10^{-4}$	28°	
			52
(IIb)	$1{\cdot}50 \times 10^{-2}$	13°	

[a] Second-order caid catalysed rate constants; lactonizations followed in 30% ethanol and thiolactonizations in water; all kinetics were followed at 25°; [b] δ represents the angle of deviation from the perpendicular approach with bonds aligned to place the alcoholic O or mercaptide S in position of closest approach to the carboxyl carbon.

orientation, however, can be illustrated by comparing the angle of the reacting atoms† in analogous positions.

The degree of conformational restriction is the same in both pairs of γ-substituted acids. The effect of solvation should be minor since the acid-catalysed esterifications are relatively insensitive to solvation effects. For example,the rate of hydrolysis of ethyl acetate varies less than four fold on going from pure water to 60% acetone.[5] Moreover, significant differences in the ground state solvation of the γ-substituted acids should be reflected in the ionization constants of the carboxylic acids. The pK_a's for (Ia), (IIa), (Ib), and (IIb) are 5·09, 5·18, 5·42, and 5·44, respectively. The similarity of these values makes it unlikely that solvation differences account for the observed rate differences. In addition, the similarity between the ionisation constants for both pairs of γ-substituted acids indicates the hydrogen bonding between the hydroxy- or mercapto-group is not selectively stabilizing one of the γ-substituted acids. The generation of torsional strain with ring closure should also be the same with both pairs of reactants. Compression effects, *i.e.*, release of ground state van der Waals repulsions,[6] are difficult to analyse but the distance between reacting atoms in analogous conformations is in each case closer in the [2,2,1] system. Nevertheless, the [2,2,2] compounds react more rapidly.

There is a systematic difference in the angles of approach, with the bicyclic [2,2,2] system being nearer the perpendicular approach in each analogous case. Bender has suggested that approach of the attacking nucleophile perpendicular to the π electron system of the carboxy-group is the optimal orientation for esterifications.[7] Our results do not prove his thesis but are consistent with it. The magnitudes of the rate ratios are significant for such small angle changes, since all other factors have been held constant as far as possible. They indicate that orientation factors in reaction rates should be quite large since (i) the ratios measured represent rates averaged over many rotamers and (ii) only if the compounds chosen were fortuitously probing the steepest part of the reactivity *versus* angle curve would the rate ratios be maximal. It would appear, therefore, that the results support the thesis that large accelerations in rates could be achieved by orientation of reacting atoms in intramolecular and enzymatic reactions.

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† It is of interest that two atoms, each having a reactive zone with a 10° angle of rotation, would react in an oriented collision 10 times as fast as in a random collision. "Orbital steering" does not require a simplistic linear relationship between reactivity and solid angle. It merely suggests that the reactivity will increase greatly when the orientation is within a defined angle.

[1] L. Pauling, *J. Amer. Chem. Soc.*, 1931, **53**, 3225; R. S. Mulliken, *Phys. Rev.*, 1932, **40**, 55; 1932, **41**, 751; A. Streitwieser, jun., "Molecular Orbital Theory," 1st edn., John Wiley and Sons, New York, 1966, p. 7; C. J. Ballhausen and H. B. Gray, "Molecular Orbital Theory," Benjamin, New York, 1964.
[2] D. R. Storm and D. E. Koshland, jun., *Proc. Nat. Acad. Sci. U.S.A.*, 1970, **66**, 445.
[3] W. R. Vaughan, C. T. Goetschel, M. H. Goodrow, and C. L. Warren, *J. Amer. Chem. Soc.*, 1963, **85**, 2282.
[4] M. Protiva, M. Rajsmer, E. Adlerova, V. Seidlova, and Z. J. Vejdelek, *Coll. Czech. Chem., Comm.*, 1964, **29**, 2161.
[5] D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, 1951, **49**, 1.
[6] C. K. Ingold, *Quart. Rev.*, 1957, **11**, 1.
[7] M. L. Bender, *Chem. Rev.*, 1960, **60**, 53; *J. Amer. Chem. Soc.*, 1957, **79**, 1258.