Stereopopulation Control: The Apparent Stabilization of a Lactone to Ring Opening

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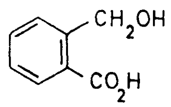
Summary The lactone, 3,3,4,7-tetramethylphthalide, is completely resistant to ring opening by a variety of nucleophiles; since the carbonyl group is subject to ^{18}O exchange, hydride reduction, and Grignard addition, the effect is not due to steric inaccessibility of the carbonyl, but to a rate of recyclization of the acyclic species so great that it escapes isolation.

FOR several years we have been exploring severe van der Waals repulsion as a device for simulation of enzyme-catalysed reactions.[1] Having found that the rate constants for lactonisation of (**2**) are considerably enhanced over those for (**1**) by virtue of the gem-dimethyl groups,[2] and that the 'trialkyl lock' in (**4**) produces a remarkable enhancement of rate relative to (**3**), we examined an even more promising case, the conversion of (**5**) into (**6**). The rate constants for lactonisation of (**5**) were expected to be greater than those for (**4**),† since cyclisation of the former involves formation of a five-membered ring [one less rotational mode than in (**4**)], and since the attacking species in (**5**) is an alcohol rather than the less nucleophilic phenol.

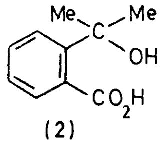
The lactone (**6**) was readily prepared by reaction of 3,6-dimethylphthalic anhydride with MeMgCl (2 equiv.) in THF. Surprisingly, (**6**) was resistant to ring opening by alkali, ammonia, amines, or hydrazine. This is not due to steric inaccessibility of the lactone carbonyl to nucleophiles, or to steric overcrowding in the transition state, since the same lactone readily incorporates ^{18}O into its carbonyl group in aqueous alkali–$H_2{}^{18}O$, reacts with Grignard reagent to form the lactol (**7**), and undergoes hydride reduction to the lactol (**8**). Both these lactols are resistant to further hydride reduction to diols or to further reaction with Grignard, these results being indicative of the overwhelming desire of the lactols to persist as their cyclic tautomers.

We interpret the results as an extreme example of stereopopulation control.[1] Models indicate the tertiary alcohol in (**5**) to be so frozen in place by the adjacent aryl methyl group (the trialkyl lock) that its hydroxy-group would be virtually incapable of escaping a *cisoid* conformation. Simultaneously, the carboxy-group is forced, by steric interaction with the ring *ortho*-substituents, to assume a conformation perpendicular to the aromatic plane, the *p*-orbital of the sp^2 carbon being oriented directly towards a lone pair of the hydroxylic oxygen. Thus, the recyclisation of any acyclic species formed must occur so rapidly that the latter cannot be detected. Alternatively, a tetrahedral intermediate, once formed, may partition very selectively back into lactone; however, the ease of lactol formation from (**6**), and the ease of alkaline ring opening of the lactone corresponding to (**2**), do not support the latter interpretation.

Compound (**5**) has a set of non-bonded repulsions which serve to limit severely the rotational freedom of the participants in the intramolecular process. As the reactant groups are brought into close proximity and are simultaneously restricted in their rotational freedom, there may be a favourable change in the orientations of orbitals destined to overlap;[3] overlap and distortion of these orbitals may have begun in the ground state, there may be desolvation of reactant groups and squeezing out of solvent between the groups, and perhaps other phenomena,[4] but all these factors combine to produce a single result—an increase in the similarity of the ground and transition states and, thus, a decrease in the activation free energy for the reaction.



(1)



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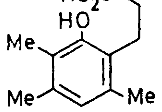

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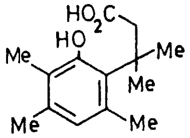

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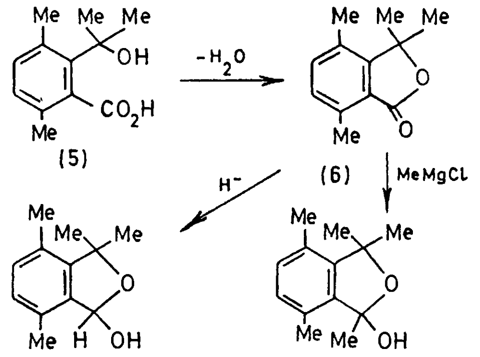

(5) (6) (8) (7)

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† At pH 6 (30°) this compound has a half-life of *ca.* 1 s.

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[2] S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, 1969, **91**, 4585.
[3] D. R. Storm and D. E. Koshland, jun., *Proc. Nat. Acad. Sci. U.S.A.*, 1970, **66**, 445.
[4] *E.g.* L. Eberson and H. Welinder, *J. Amer. Chem. Soc.*, 1971, **93**, 5821.