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CONFORMATIONAL ANALYSIS USING ULTRASONIC RELAXATION STUDIES - A COMMENT ON THE SCOPE AND LIMITATIONS

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The potential of the ultrasonic relaxation technique to study conformational analysis was realized several years ago;[1] however the scope and limitations of the method are still the subject of current investigation. In some cases, if the limitations of the technique are not taken into account, misunderstandings may arise. The conclusion of a recent note[2] comparing some of our earlier ultrasonic work[3] with new n.m.r. data has prompted us to make a statement, here, on the scope and limitations of the ultrasonic method and also offer a more reasonable alternative explanation for the complimentary ultrasonic and n.m.r. data reported in this note.

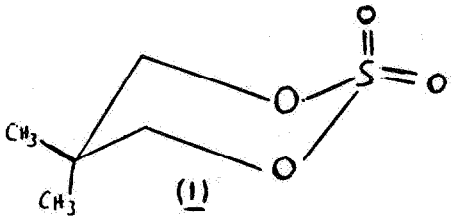
(I) Method The passage of a sound wave through a liquid causes periodic pressure and temperature changes in a given volume of the liquid. A two state conformational equilibrium $A \rightleftharpoons B$, can be perturbed by the sound wave provided there is an enthalpy ($\Delta H°$) or volume ($\Delta V°$) difference between A and B, since

$$d \ln K = \frac{\Delta H°}{RT^2} dT - \frac{\Delta V°}{RT} dP$$

where K is the equilibrium constant at temperature T (°K). When the populations of A and B are unable to follow the temperature or pressure changes accompanying the sound wave, an ultrasonic relaxation will occur at a certain characteristic relaxation frequency, f_c. In theory[1] this relaxation frequency is related to the rates of conformational charges and the amplitude of the relaxation process or "relaxation strength" is related to the thermodynamic equilibrium parameters $\Delta H°$, $\Delta V°$ and K. Whereas the relationship between f_c and the rate constants is unequivocal, there are several approximations used in relating the relaxation strength to $\Delta V°$, $\Delta H°$ and K.[4] At the present time our experience in ultrasonic relaxation studies of conformational analysis has shown that the only reliable data available from experiment are the energies and entropies of activation for the less stable to more

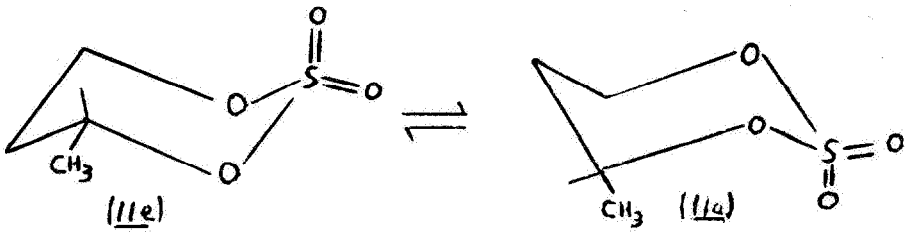
stable conformational change and found from the temperature dependence of the relaxation time. This conclusion is the result of several experiments carried out by comparing ultrasonic and complimentary infrared and n.m.r. data on many different conformational systems. Most of the published values of ΔH° and K from ultrasonic measurements are probably erroneous and at best can only be regarded as qualitative estimates. The technique however has the great advantage that barriers to conformational charges from less stable to more stable isomers can be derived directly from experimental data for very one-sided (anancomeric) equilibria. An exact figure for the population of the less stable form cannot be given; it is certainly less than 0.1%.[5] An ultrasonic relaxation is detected experimentally by a change in the bulk property of sound absorption with frequency. Thus in order to make detailed comments on the experiment, a priori knowledge of the exact form of the conformational equilibrium is required. In the majority of cases this can be done convincingly using complimentary ultrasonic measurements and also by reference to data from spectroscopic techniques. Finally, in ultrasonic conformational studies it is advisable to study two-state conformational equilibria because they are characterised by a single relaxation time.

(II) Comments on a recent note[2] In a recent communication Wood et al.[2] determined the Free Energy of activation ($\Delta G^{\ddagger}$) for the isodynamic chair to chair inversion in 5,5-dimethyltrimethylene sulphate (I) to be 8.1 kcal/mole at -107°C. The only other report of barriers to ring inversion in sulphates is in an ultrasonic paper[3] in which the relaxation



(I)

observed in 4-methyltrimethylene sulphate (II) was attributed to a perturbation of the axial-equatorial chair equilibrium 11e ⇌ 11a.



(11e) (11a)

The assignment of this ultrasonic relaxation seems convincing[3,6] and n.m.r. studies indicated that the above equilibrium was very biased towards the equatorial isomer 11e. The conformational energies quoted from the ultrasonic data were

$$\Delta H^{\ddagger}_{ae} = 4.6 \text{ kcal/mole} \quad \Delta S^{\ddagger}_{ae} = -6.3 \text{ cal/mole/°C}$$

$$\Delta G°(a\text{-}e) = 1.6 \text{ kcal/mole} \quad \Delta S°(a\text{-}e) = -0.5 \text{ cal/mole/°C}$$

In comparing barriers to ring inversion for similar molecules it is preferable to compare those found from an isodynamic equilibrium with the more stable to less stable barrier in an anancomeric equilibrium. Thus Wood et al.,[2] by neglecting entropy terms,[7] compared their free energy barrier $\Delta G^{\ddagger}$ at -107°C for (I) of 8.1 kcal/mole with the more stable to less stable enthalpy barrier, $\Delta H^{\ddagger}_{ea}$ ($= \Delta H^{\ddagger}_{ae} + \Delta H°$), of 6.2 kcal/mole from the ultrasonic work.[3] They concluded that since this difference was so large an alternative assignment was necessary for the ultrasonic relaxation in terms of a chair - non chair equilibrium. In view of the comments already made about the limitations of the ultrasonic method, we submit that a reassignment of the molecular mechanism is unnecessary; in fact if the two sets of data are examined carefully the agreement is excellent. The reliable conformational energies for (II) are $\Delta H^{\ddagger}_{ae}$ and $\Delta S^{\ddagger}_{ae}$; in addition n.m.r. studies over a wide temperature range have shown that equilibrium 11e $\rightleftharpoons$ 11a is anancomeric and it is, therefore, reasonable to assume that $\Delta G°(a\text{-}e) \approx \Delta H°(a\text{-}e) \gg 2.0$ kcal/mole.[7] In order to compare the results for (I) and (II), it is necessary to compare the respective Free Energies of activation at -107°C. For (II) the Free Energy of activation in question should be $\Delta G^{\ddagger}_{ea}$ and, consequently, for (I) $\Delta G^{\ddagger}$ at -107°C = 8.1 kcal/mole and (II) $\Delta G^{\ddagger}_{ea}$ at -107°C $\gg$ 7.6 kcal/mole. The agreement between these figures is excellent; furthermore if we allow for the fact that two substituents at the 5- position are known to increase the barrier, the agreement is even better.

References

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2. G. Wood, J.M. McIntosh and M. Miskow, Tetrahedron Letters, No. 56, 4895 (1970).
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4. K.R. Crook, E. Wyn-Jones and W.J. Orville-Thomas, Trans. Faraday Soc., 66, 1597 (1970) and references quoted therein.

5. G.C. Eccleston, Ph.D. Thesis, Salford (1970).

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7. It is reasonable to assume that $\Delta S°(a\text{-}e)$ is zero for chair/chair equilibria; however the magnitude and signs of $\Delta S^{\ddagger}$(activation) can vary substantially as has been shown experimentally. This, in turn, means that footnote (2) in reference 2 is misleading.