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STRUCTURAL REQUIREMENTS FOR INTRAMOLECULAR PROTON TRANSFERS

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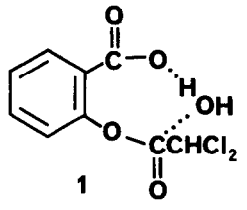
Recent findings in this laboratory have suggested certain structural requirements for intramolecular proton transfers involving a solvent bridge.[1,2] It is the purpose of this communication to present a hypothesis which predicts when intramolecular proton transfer will most likely occur. Succinctly stated, the hypothesis is that the highest probability for intramolecular proton transfer will occur when the cyclic transition state formed can accomodate a linear arrangement of donor-proton-acceptor of appropriate length. This most easily occurs when the ring size is eight.

Fersht and Kirby[3] in their now classic studies on aspirin derivatives proposed, for all the compounds they studied except one, a mechanism for spontaneous hydrolysis involving intramolecular attack of a carboxylate via a solvent bridge (1). This was later confirmed by Minor and Schowen, by application of the proton inventory method.[1] Dinitroaspirin was the only exception and Fersht and Kirby proposed, following the rapid and reversible transfer of the acetyl group, an intramolecular attack of phenoxide ion via a solvent bridge at the benzoyl carbon (2a). This intramolecular attack by phenoxide ion via a water molecule at the benzoyl carbon has been proposed for other systems.[4] A proton inventory study on dinitroaspirin has revealed that the solvent isotope effect for spontaneous hydrolysis arises from two parallel mechanisms, one intramolecular and the other intermolecular.[2] Outlined below are the reasons intramolecular phenoxide general base catalysis would not occur at the benzoyl carbon (2a) (for the case of dinitroaspirin, would occur at the acetyl carbon (2b)).



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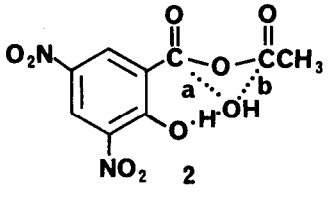

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Space-filling molecular models[5] indicate extreme difficulty when trying to place a molecule of water between an oxygen and a carbonyl group substituted *ortho* on a benzene ring. Figure 1

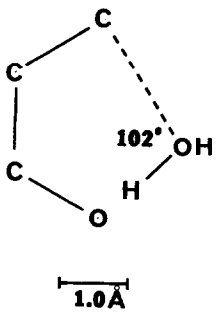

Figure 1

depicts an idealized skeletal representation of the *ortho* carbonyl aryloxide system. It is assumed that the oxide oxygen is sp^3 and that the best overlap for attack on the sp^2 benzoyl carbon is in the plane of the pi-electron system. In Figure 1, the six atoms are coplanar. This gives a good angle, 102°, for overlap in the forming C-O bond. The resulting O-O distance, 1.45 Å, is clearly too close for a hydrogen bonded system.[6] Trying to lengthen the O-O distance,while maintaining a linear O-H-O arrangement by moving the bridge molecule in or out of the plane of the other four atoms, causes distortions in the overlap in the forming C-O bond (e.g., an O-O distance of 2.2 Å reduces this angle to 83°). This can be best seen with the use of stick models.[7] The conclusion reached from this extensive model building in conjunction with what is believed to be the minimum energetics of hydrogen bonds and the best approach for orbital overlap is that proton-bridge catalysis of nucleophilic attack of the incipient hydroxide does not occur intramolecularly in a six-membered ring transition state.

Fife and Hutchins have proposed a seven-membered ring solvent bridge transition state for the intramolecular aryloxide catalysis in ethyl-2-hydroxy-5-nitrophenyl carbonate.[8] Models indicate that a linear hydrogen bond can be accomodated in this ring system almost as well as in the eight-membered ring. Cyclic transition states involving a solvent bridge have been proposed in systems other than the *ortho* aryloxide, which involve six-[9a,b] and seven-[10] membered ring transition states. The usual basis for invoking these mechanisms is the magnitude of the solvent isotope effects.[11] However, interpretation of the role of solvent from the magnitude of the isotope effect alone can be insufficient.[2]

Intramolecular proton transfers in systems other than those involving a solvent bridge seem to support the idea of a linear hydrogen bond in an eight-membered ring. Hine, Cholod, and Jensen[12] observed for the dedeuteration of $(CD_3)_2CO$, catalyzed via the immonium ion by diamines, that only those amines capable of forming eight-membered ring cyclic transition states showed intramolecular catalysis. Recent gas-phase basicity studies on diamines support the idea that a linear hydrogen bond is favored in proton bridged diamines and that cyclic structures of between seven and nine are favored thermodynamically over six and smaller rings.[13]

However, six-membered rings have been favored for intramolecular proton transfer reactions. Wilson and Lewis proposed a six-membered ring cyclic transition for intramolecularly catalyzed

ionization of $CH_3CHNO_2CH_2CH_2COO^-$ to the nitrocarbanion.[14] Molecular models indicate that this could not occur easily if a linear proton transfer is required. Bell and co-workers studied a number of keto-acids and proposed six-membered cyclic transition states involving proton transfers for those cases where they expected this mechanism to occur.[15] Molecular models indicate in these cases, also, the difficulty of accomodating a linear proton transfer in these transition states. One possibility not discussed by the above workers is the mediation of these transfers by a hydroxylic solvent bridge. Molecular models show that the two linear proton transfers needed with the solvent bridge can be accomodated without much strain in an eight-membered ring. The idea of multiple linear hydrogen bonds in eight-membered rings is not new and has been suggested for intermolecular reactions involving structured water[16] and bifunctional catalysis.[17]

The question of intramolecular bifunctional catalysis in a six-membered ring complex has been raised for proton transfers via a water bridge in $(NH_3)_5PtNH_2^{3+}$ [18] and $RCH(OH)NH_2$.[19] Molecular models of these systems suggest distortions in overlap if linear hydrogen bonds of appropriate length to both protons are to be maintained simultaneously (Figure 2). It was pointed out that the transfers could occur in stepwise manner followed by a rotation of the bridge molecule for alignment of the next proton transfer.[18] This mechanistic idea is a good one and may apply to the cases previously discussed. The hypothesis presented in this letter would apply to cyclic transition states only, i.e., those having either a proton transfer or hydrogen bond as part of a ring.

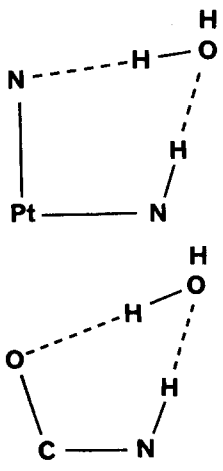

Figure 2

In summary, of all the cases in the literature supporting intramolecular or intracomplex catalysis involving proton transfer, a large number of these cases propose seven- or eight-membered cyclic transition states. Cyclic transition states of this size can support a linear arrangement of donor-proton-acceptor whereas this arrangement is only possible with considerable strain, as indicated by molecular models, in six-membered cyclic transition states. This strain might be accomodated in the more flexible alkyl cases[9b,14,15] but should not be accomodated in the rigid aromatic cases.[4,9a] The relative importance of (1) linear versus a nonlinear proton transfer, (2) the entropy required for a six- versus an eight- membered ring, and (3) the involvement of a hydroxylic molecular bridge (i.e., a second molecule) in determining a possible mechanism is crucial for an understanding of these

systems. At present, there is no convincing evidence that one single factor is the determining one, although as indicated from theoretical studies,[6] a linear arrangement of donor-proton-acceptor is energetically favorable when compared to non-linear arrangements. With this in mind, it is suggested that when intramolecular proton transfers occur, cyclic transition states of proper size to accomodate this linear arrangement are a necessity.

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REFERENCES

(1) S. S. Minor and R. L. Schowen, *J. Amer. Chem. Soc.*, 95, 2279 (1973).

(2) R. D. Gandour and R. L. Schowen, accepted for publication, *J. Amer. Chem. Soc.*

(3) For a good review of this work, see: A. J. Kirby and A. R. Fersht, *Progress in Bioorganic Chemistry*, 1, 1 (1972).

(4) M. L. Bender, F. J. Kezdy, and B. Zerner, *J. Amer. Chem. Soc.*, 85, 3017 (1963); T. C. Bruice and D. W. Tanner, *J. Org. Chem.*, 30, 1668 (1965); B. Capon and B. C. Ghosh, *J. Chem. Soc., Sect. B*, 1966, 472; F. M. Menger and J. A. Donohue, *J. Amer. Chem. Soc.*, 95, 432 (1973).

(5) CPK® Precision Molecular Models, The Ealing Corp.

(6) For a nice discussion of the theory of the hydrogen bond, see: P. A. Kollman and L. C. Allen, *Chem. Rev.*, 72, 283 (1972).

(7) Framework Molecular Models, Prentice Hall, Inc.

(8) T. H. Fife and J. E. C. Hutchins, *J. Amer. Chem. Soc.*, 95, 2837 (1972).

(9)a) F. M. Menger and C. J. Johnson, *Tetrahedron*, 23, 19 (1967); b) G. Aksnes and P. Frogen, *Acta. Chem. Scand.*, 16, 1927 (1962).

(10) P. Y. Bruice and H. G. Mautner, *J. Amer. Chem. Soc.*, 95, 1382 (1973).

(11) For a good explanation of mechanistic deductions from solvent isotope effects, see: R. L. Schowen, *Progr. Phys. Org. Chem.*, 9, 275 (1972).

(12) J. Hine, M. S. Cholod, and J. Jensen, *J. Amer. Chem. Soc.*, 93, 2321 (1971).

(13) D. H. Aue, H. M. Webb, and M. T. Bowers, *J. Amer. Chem. Soc.*, 95, 2699 (1973); R. Yamdagni and P. Kebarle, *ibid.*, 95, 3504 (1973).

(14) H. Wilson and E. S. Lewis, *ibid.*, 94, 2282 (1972)

(15) R. P. Bell and M. A. D. Fleundy, *Trans. Faraday Soc.*, 59, 1623 (1962); W. J. Albery, R. P. Bell, and A. L. Powell, *ibid.*, 61, 1194 (1964); R. P. Bell and H. E. F. Ridgewell, *Proc. Roy. Soc. (London)*, 298A, 178 (1967).

(16) For examples, see: L. Menninger and J. B. F. N. Engberts, *J. Phys. Chem.*, 77, 1271 (1973); and R. P. Bell, F. P. Millington, and J. M. Pink, *Proc. Roy. Soc. A*, 303, 1 (1968), and references cited in both.

(17) For a nice brief summary of bifunctional catalysis, see: J. P. Li, *Aldrichimica Acta*, 5, 5 (1972).

(18) E. Grunwald and D.-W. Fong, *J. Amer. Chem. Soc.*, 94, 7371 (1972). I thank the referee for pointing this out.

(19) M. I. Page and W. P. Jencks, *ibid.*, 94, 8818, 8828 (1972).