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ON THE DEHYDRATION OF *trans*-1,2-DIHYDROPHTHALIC ACID

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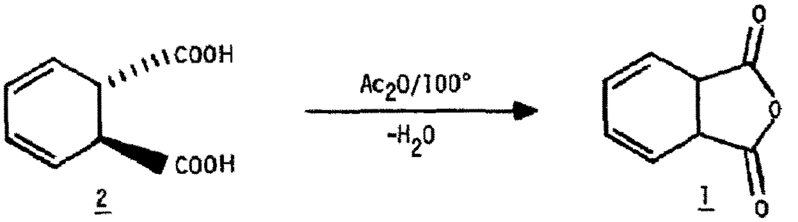
ABSTRACT: The epimerization/dehydration of the title compound occurs by way of an enolization rather than a pair of concerted, suprafacial [1,5] hydrogen shifts.

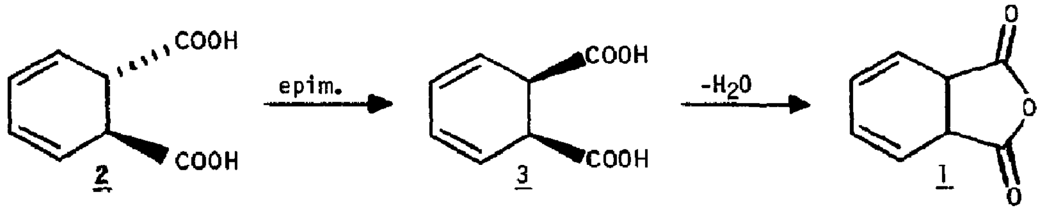
Unimolecular rearrangements may often be described by several reaction mechanisms. In such cases a deuterium labeling experiment may provide an efficient and unambiguous distinction between mechanistic possibilities. We report here results of experiments designed to elucidate the pathway by which the title compound is converted to *cis*-1,2-dihydrophthalic anhydride, 1 (eq. 1). This cyclodehydration reaction, which was first uncovered by von Baeyer in 1892,[1] is a key step in the syntheses of Dewar benzene[2] and its dihydro-[3a] and tetrahydro-[3b] derivatives. It has also been exploited independently by Fuchs and Scharf,[4] and Goldstein and coworkers[3b, 5] for the preparation of regiospecifically deuterated materials.



(eq. 1)

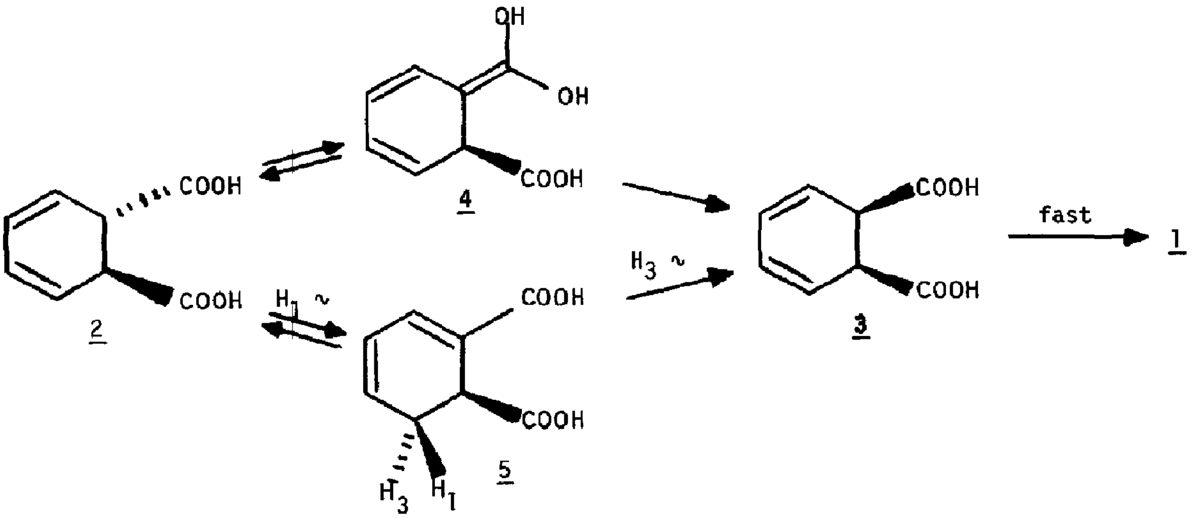
Trans-1,2-dihydrophthalic acid, 2, is transformed to 1 in 85% yield upon dissolution in acetic anhydride at 100°. While this is the conventional method for dehydration of 1,2-diacids, the current example is of mechanistic interest because the loss of water is accompanied by inversion of configuration at one of the tetrahedral centers.

The conversion of 2 to 1 necessarily involves two nonsynchronous steps, epimerization and dehydration. Although the actual timing of these two events is unknown, the probable order is epimerization of 2 to its cis analogue 3, followed by rapid dehydration of the latter (eq. 2). Consistent with this hypothesis is the observation that 3 cyclizes spontaneously at 100°. Thus the mechanistic problem may be reduced to analysis of the epimerization step for which two antithetical, and heretofore unconsidered, pathways may be proposed.[6]

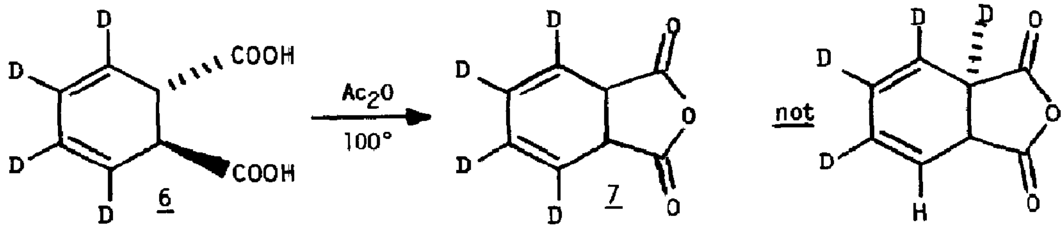


(eq. 2)

A sufficient condition for epimerization is generation of a new trigonal center α- to one of the acid functions. Two species which incorporate this structural feature are 4 and 5. Structure 4 is simply the enol form of 2 and could tautomerize to the cis acid 3. Structure 5 is the product of a [1,5] hydrogen shift;[7] a second [1,5] hydrogen shift converts 5 to 3. Note that in the sigmatropic shift pathway, as a consequence of the orbital symmetry requirement of suprafaciality,[8] the protons at C_1 and C_3 are interchanged. This permits distinction of the two mechanistic alternatives by means of a deuterium labeling experiment.



Trans-1,2-dihydrophthalic-*3,4,5,6*-d_4 acid, 6, proved to be an appropriate substrate for this purpose. Compound 6 was prepared from *o*-xylene-d_{10} (Aldrich Chemical Company, 99+ atom % D) by permanganate oxidation and the standard sodium amalgam reduction.[1] Pmr analysis of compound 6 and its immediate aromatic precursor[9] indicated that there was no loss of isotopic integrity at carbons 3 through 6 in the oxidation-reduction sequence. Dehydration of 6 in hot acetic anhydride then afforded a dihydrophthalic anhydride, 7, which within limits of pmr detection,[10] was free of contamination from protium at the vinylic positions (eq. 3).

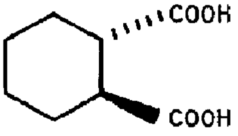


(eq. 3)

This result is incompatible with the [1,5] shift alternative and is most economically explained by an enolization process. Consistent with the above conclusion is the observation that dehydration of 2 (nondeuterated) in freshly distilled acetic anhydride containing four molar equivalents of acetic acid-d_1 provided a dihydrophthalic anhydride in which was incorporated *ca.* 0.5 deuterium atom per molecule at the allylic position. Other attempts to trap the putative enol intermediate have not met with success.[11]

On the basis of the above experiment we estimate that the [1,5] shift mechanism intervenes at a level of less than 0.5% in the epimerization reaction. However it should be pointed out that an isomorphic labeling experiment leads to a less definitive conclusion. Dehydration of *trans*-1,2-dihydrophthalic-*1,2*-d_2 acid-d_2 produced a dihydrophthalic anhydride in which the ratio of protons at the allylic and vinylic carbons was 0.08 ± 0.01, rather than the expected ratio (assuming the enolization mechanism) of <0.005. These data coincide with the results of an earlier experiment by Fuchs and Scharf who reported that "deuterium was incorporated in the angular positions to the extent of 87%."[12] We conclude that these results reflect rapid exchange of the hydroxylic deuteria with adventitious protic contaminants in the dehydrating medium, and have no bearing on the actual reaction mechanism.

Although involvement of the diene system in an orbital symmetry controlled process has been excluded by our results, conjugative stabilization of the intermediate enol is a significant factor in the rearrangement of 2. This was established by subjecting several other trans diacids to the reaction conditions for dehydration of 2. The model compounds were chosen because they are fully saturated in the vicinity of the tetrahedral center. In accord with the literature[13] dehydration of trans diacid 8 afforded the corresponding anhydride without detectable inversion of configuration. On the other hand compounds 9 and 10, for which trans anhydrides would be prohibitively strained, were not dehydrated but rather reacted with the solvent to form mixed anhydrides.[14] Hydrolysis of these labile materials regenerated the trans diacids. Finally it should be noted that Alder and coworkers found that hot acetic anhydride converts the trans diacid 11 to the cis anhydride 12 (eq. 4).[15] Thus it appears that inversion of stereochemistry α- to a carboxyl function occurs only with those compounds in which an enol intermediate benefits from conjugation.



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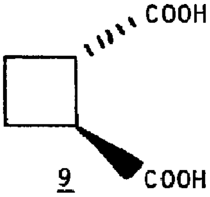

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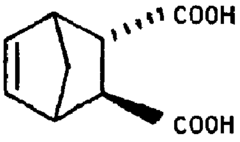

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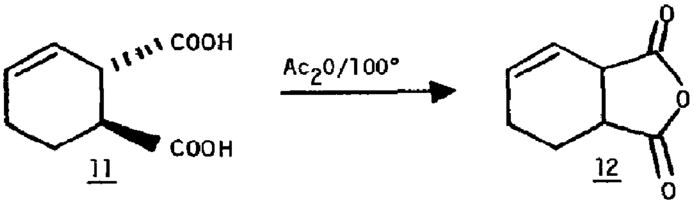

(eq. 4)

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2. van Tamelen, E.E.; Pappas, S.P.; Kirk, K.L. *J. Am. Chem. Soc.* 1971, *93*, 6092.

3a. Goldstein, M.J.; Leight, R.S.; Lipton, M.S. *J. Am. Chem. Soc.* 1976, *98*, 5717.
3b. Goldstein, M.J.; Benzon, M.S. *ibid.* 1972, *94*, 5119.

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5. Goldstein, M.J.; Leight, R.S. *J. Am. Chem. Soc.* 1977, *99*, 8112.

6. In point of fact the relative sequence of events is immaterial. Mechanisms analogous to those for the epimerization of 2 may be proposed and distinguished by the same experimental strategy in the unlikely event that dehydration (to a strained trans anhydride) precedes epimerization.

7. For a review of sigmatropic rearrangements see Spangler, C.W. *Chem. Rev.* 1976, *76*, 187.

8. Woodward, R.B.; Hoffman, R. *Angew. Chem., Int. Ed. Engl.* 1969, *8*, 781.

9. As the respective esters (prepared by esterification with ethereal diazomethane at 5°). Pmr spectrum of 6'(ester): δ 3.8 (6.0 H), δ 3.9 (2.0 H), and δ 5.6 - 6.2 (<0.01 H).

10. Pmr spectrum of 7: δ 4.0 - 4.3 (2.0 H) and δ 5.8 - 6.5 (<0.01 H).

11. An alternate mode of reaction for enol 4 might be aromatization (by [1,3] hydrogen migration)and dehydration of the *gem*-diol to afford *o*-carboxybenzaldehyde. Careful scrutiny of the crude product failed to reveal any quantities of this compound.

12. Reference 4, p. 340.

13. von Baeyer, A. *Ann.* 1890, *258*, 216.

14. Under more brutal reaction conditions compound 9 is converted to the cis anhydride (Buchman, E.R,; Reims, A.O.; Skei, T.; Schlatter, M.J. *J. Amer. Chem. Soc.* 1942, *64*, 2696). Detection of the analogous process for 10 is complicated by the retro-Diels-Alder reaction which intervenes at elevated temperatures (Pincock, R.E.; Tong, M-M.; Wilson, K.R. *ibid.* 1971, *93*, 1669).

15. Alder, K; Schumacher, M.; Wolff, O. *Ann.* 1949, *564*, 79.

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