The cis-trans-Dibenzoylstilbene Equilibrium. Cyclic Hemiketal Anion Formation in Strong Base[1]

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The base- and light-catalyzed cis-trans equilibria between the stereoisomers of dibenzoylstilbene have been determined in 95% ethanol solution. Photoequilibrium is shown to be close to the true thermodynamic equilibrium in which the trans isomer predominates in a ratio of approximately 2:1. The apparent deviation from this ratio toward subordination of the trans isomer in a ratio of ca. 1:3 in 10% potassium hydroxide is attributed to extensive combination of the cis isomer with hydroxyl or methoxyl ions to form cyclic 2,5-hemiketal anions.

Many substituted cis-trans unsaturated 1,4-diketone pairs show a marked "cis-effect," that is, a tendency for the cis isomer to undergo certain reactions much more readily than the trans isomer, reactions which seemingly involve ring intermediates and lead to furan, dihydrofuran, or furanone ring closure—[2]e.g., cyclic ketal formation,[2e] reductive-furanization,[2f,d] addition-furanizations,[2a,b,d] furanone formation,[2a] halogen displacement,[2e] and most recently, oxidative-rearrangement.[1b,2g,h] The phenomenon holds regardless of which stereoisomer is the thermodynamically labile and which the stable form.[2b]

In the cis- and trans-dibenzoylstilbenes (I, II) with their high degree of group overlaps in both configurations, it seemed possible that there might be an appreciable contribution toward stabilization of the cis configuration by the carbonyl group interaction or quasichelation indicated in I, enough perhaps to render the cis isomer the stable form. We were thus led to reconsider the long-standing supposition[1c] that trans-dibenzoylstilbene is the lower-energy isomer. Actually the conversion of the cis to the trans isomer by the action of boiling alcoholic potassium hydroxide[3] did not in itself prove the greater stability of the latter because the efficiency of the conversion conceivably might be the result of solubility differences and precipitation of the very difficulty soluble trans isomer. The following study was therefore made, working at dilutions high enough to retain the trans isomer in solution at all times, thus to determine the true solution equilibrium and the nature of the participating species.

A series of such equilibrations was established starting from both the cis and the trans isomers each at dilutions of 1 g. of compound per 750 ml. of refluxing 95% ethanol; the amounts of potassium hydroxide were varied from 10% downward to 0.022% where the molar ratio of base to compound was 1:1 and as close to truly catalytic amounts as could be used and still maintain a feasible reaction rate. Analysis after each equilibration was accomplished by quantitative separation of the isomer-mixture by fractional crystallization and column chromatography on alumina where the very much stronger adsorption of the more soluble cis isomer shows the relatively very high polarizability predicted by the postulated cis-group interaction (I).

The total yields of isolated isomers given in the table differed somewhat in the several experiments because of differences in the extent of deterioration of material; however, the cis-trans yield ratios were the same in each pair of equilibration experiments and they must represent very closely the actual equilibrium ratios of the total cis and trans species in solution including any compounds formed by reversible combination with base. When the base concentration was 10%, the 78:22 yield ratio of the isolated cis and trans isomers showed predominance of the cis species in the equilibrium, a result which at first had seemed to support the cis effect pictured in I. However, as the concentration of base was lowered to 0.022% the cis-trans yield ratio changed dramatically with reversal to 42:58. This demonstrated that the trans isomer actually was the more stable isomer as originally had been supposed.[3] The equilibrium mixture in 10% base obviously includes a very considerable proportion of one or more species of complex anion produced by combination of the cis isomer with base, and the total amount of cis isomer isolated must be inordinately greater than the true equilibrium amount of uncombined cis-dibenzoylstilbene in solution.

Photoequilibration by sunlight irradiation under the above conditions required only four hours, but

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(2) (a) R. E. Lutz and C. E. McGinn, J. Am. Chem. Soc., 64, 2585 (1942); (b) R. E. Lutz and P. S. Bailey, ibid., 67, 2229 (1945); (c) L. Kuhn, R. E. Lutz, and C. R. Bauer, ibid., 72, 5058 (1950); (d) R. E. Lutz and C.-K. Dien, J. Org. Chem., 23, 1861 (1958); (e) R. E. Lutz and M. G. Reese, J. Am. Chem. Soc., 81, 3397 (1959); (f) R. E. Lutz, C. R. Bauer, R. G. Lutz, and S. S. Gillespie, J. Org. Chem., 20, 218 (1955); (g) R. E. Lutz, R. G. Bass, W. J. Welstead, and C. L. Dickerson; a paper presented at the Southeast Regional ACS Meeting, Richmond, November, 1959 [Abstr. The Bulletin, Va. Section, ACS, 36, 203 (1959)]; (h) R. E. Lutz, W. J. Welstead, R. G. Bass, and J. I. Dale, J. Org. Chem., 27, 1111 (1962).

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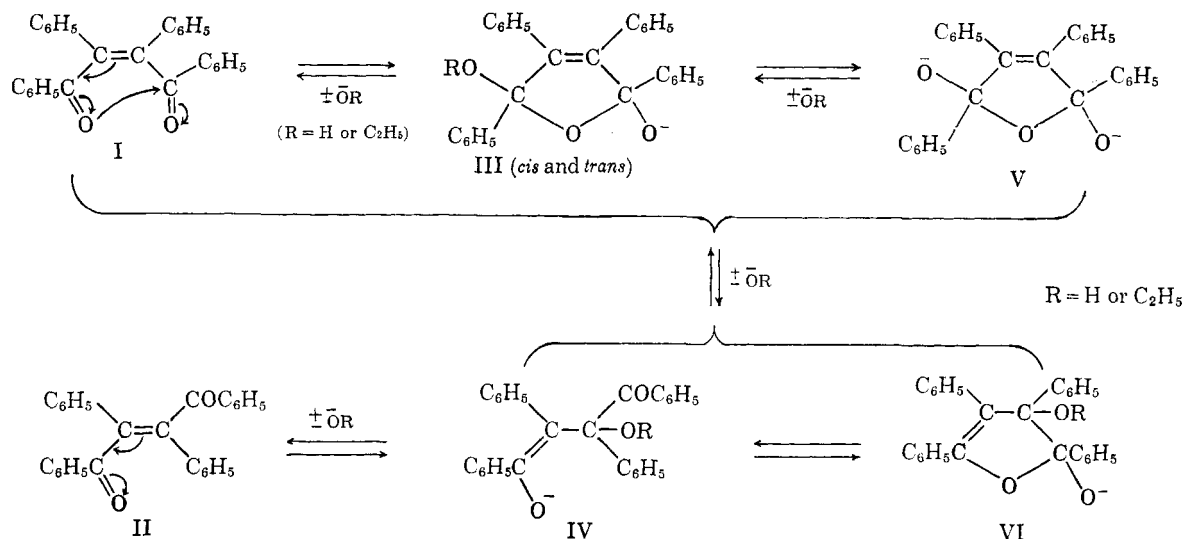
it involved more deterioration of material than the base-catalyzed equilibrations. The *cis-trans* steady state ratio of 32:68 differed slightly from the 1:1 base-catalyzed equilibrium ratio of 42:58 and it represents an equilibrium displacement of about 10% in the direction of the thermodynamically more stable *trans* isomer. It seems unlikely though theoretically possible that the equilibrium would be shifted by irradiation toward the lower-energy *trans* form. It seems probable therefore that in the 1:1-base-catalyzed equilibrations the base even in this small concentration combines with the *cis* isomer to a significant extent. The *cis-trans* photoequilibrium ratio of 1:2 is therefore believed to be close to the true thermodynamic equilibrium between the uncombined *cis* and *trans* molecules.

In explanation of the effect of strong base on the equilibrium it is postulated: (a) that hydroxide or methoxide ion adds reversibly to the dibenzoyl-stilbenes with formation of complex anions of the types III–VI; (b) that the 2,5-cyclic hemiketal anion III is the most stable of these, is present in relatively high concentration, and upon hydrolysis reverts exclusively to *cis*-debenzoylstilbene; and (c) that the other anions involved are relatively unstable and are present in small and negligible concentrations. The 2,3-cyclic hemiketal anion VI with its serious 2,2,3,3,4-group interferences, and the inherently unstable 1,4-addition enolate VI, are doubtless intermediate in stereoisomerization. The presumption that secondary ionization to the di-anion V is negligible seems supported by rough calculations based on the data in the table which indicate first rather than second order dependence of the *cis* isomer upon base concentration.

Induced changes in ultraviolet absorptivity upon acidification of neutral 5×10^{-5} M ethanol solutions of the *cis* but not of the *trans* isomer qualitatively suggest a considerable degree of reversible *acid*-catalyzed addition of solvent with formation of a 2,5-cyclic alcoholate corresponding to III,

precursory to the formation of the cyclic ketals VIIb and VIIIb which predominate at equilibrium.[2e] Because *cis-to-trans* inversion did not occur, it is evident that a 1,4-addition enol corresponding to IV did not form to any significant extent under acid conditions.

It will be noted that both 2,5- and 2,3-cyclic hemiketal intermediates corresponding to III and VI must be involved in numerous of the reactions in which the *cis*-effect is observed. 2,3–2,5-Tautomerism must be assumed, for example, in the conversions of *cis*-dibenzoyldichloroethylene, on the one hand to 2,5-cyclic ketals, and on the other to 3-furanones.[2e] A limited number of 2,5-cyclic ketals have been rigorously established, e.g., VIIa and VIIIa, but no authentic 2,3 types such as IX are known. The pair of isomeric cyclic ketals in the tetraphenyl series have been presumed to be 2,5 stereoisomers VIIb and VIIIb[2e] on steric grounds and by analogy to VIIa and VIIIa.[1b] Proof was sought and found in the n.m.r. spectra of these two isomers which showed lines relative to tetramethylsilane at 7.6 and 7.7 p.p.m. and doublets of 2:3 intensity ratio, indicating two kinds of protons in each phenyl group. Since the lines appearing at 3.9 p.p.m. due to the methoxyl protons involve essentially no chemical shifts, and since only one methyl line appears in each spectrum, there is no evidence for a *cis-trans* effect involving the two methoxyls. Had the two methoxyls
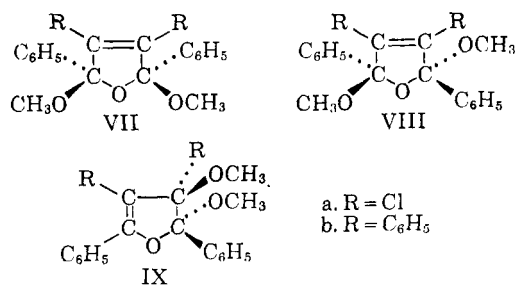
been 2,3 in one or both compounds, a shift stemming from the 2- vs. the 3-methoxyl would have been expected. The existence of only one line therefore supports the 2,5 rather than the 2,3 relationship in these cyclic ketals and establishes the stereoisomeric relationship VIIb and VIIIb.

Experimental

cis-trans-Dibenzoylstilbene equilibrations of 1-g. samples in 750 ml. of 95% ethanol were carried out under reflux and an atmosphere of nitrogen (see table). For the base-catalyzed equilibrations, hot 86% aqueous potassium hydroxide was added to achieve the specified weight-per cent concentrations. After heating, the solutions were poured into 12 l. of ice water and the mixtures were allowed to stand overnight. The precipitates were filtered, washed, dried, dissolved in benzene, and chromatographically separated (see below). The irradiation experiments in 95% ethanol were carried out at reflux in strong sunlight; work-up of these solutions, however, was by evaporation to *ca.* 30 ml., seeding with *trans* isomer, allowing to stand overnight, filtering the crop of *trans* crystals, evaporating the filtrate to dryness, dissolving the residue in benzene, and chromatographing.

The benzene solutions of the mixture of isomers were poured through an F-20 alumina column, eluting the higher-melting *trans* isomer with benzene. Acetone was then used to elute the more soluble yet more highly adsorbed *cis* isomer. Evaporation of the solutions gave pure *cis* and *trans* isomers of m.p. 212–214° and 230–232°, respectively, in total yields given in Table I. Systematic efforts were not made to work up the by-products of the reactions.

In separate experiments both the *cis* and *trans* isomers were placed on alumina columns and eluted in the above way. The samples were recovered unchanged, showing that no

isomerization or extensive deterioration occurred under work-up conditions.

Table I
cis-trans Equilibrations

Equilibrating agent, 95% ethanol[a]	Time[b] required, hr.	% Yield of mixture[c] from *cis*	% Yield of mixture[c] from *trans*	*cis-trans* equilibrium ratios from *cis*	*cis-trans* equilibrium ratios from *trans*
KOH, 10%	3.5	77	88	78:22	78:22
2.9%	12	73	77	55:45	56:44
0.71%	36	73	68	42:58	43:57
0.022%[d]	168	84	88	44:56	41:59
h*ν*	4	58	46	33:67	31:69
h*ν*(C_6H_6)[e]	48	64	42	32:68	34:66
h*ν*(C_6H_6,I_2)[e,f]	48	52	66	32:68	35:65

[a] Used except in the last two photoequilibrations. [b] These times might have been shortened somewhat. [c] The mixtures represent the bulk of crystalline materials obtained which contained only the pure stereoisomers; these were much less soluble than the by-products. Although the losses were considerable, it can be said that little of the more soluble *cis* isomer escaped, and these figures seem to be reasonably accurate. [d] This represents a 1:1 molar ratio of base to compound. To have cut the concentration further would have been impractical because of the concomitant drop in reaction rate. [e] One gram of compound per 700 ml. of benzene, at room temperature. [f] Crystals of iodine were introduced periodically to maintain a small amount throughout the reaction, for the purpose of determining its effect, if any.

Azo and Hydrazo Aliphatic Acid Derivatives. I. Alkylazoformic Acid Esters[1]

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The ethyl esters of *n*- and *t*-butylazoformic acid have been synthesized and some of their properties have been recorded.

As part of a program designed to synthesize derivatives of azo and hydrazo aliphatic acids of the general formulas $R(CH_2)_xN{=}N(CH_2)_y$—CO_2H and $R(CH_2)_xNHNH(CH_2)_yCO_2H$ as possible anticancer agents, it appeared to be of interest to investigate esters of azoformic acid. The latter, which would be represented by the case where $y = 0$ in the first general formula, should be obtainable from alkylidene carbazates, which result from the condensation of carbonyl compounds with alkyl carbazates,[2] by reduction, followed by oxidation of the intermediate hydrazo esters.

In the present work, 1-*n*-butyl-2-carbethoxy-

hydrazine was selected as a representative hydrazo ester for oxidation studies. It was thought that the carbethoxy group might stabilize the azo structure. As is known,[3] aliphatic azo compounds which have at least one hydrogen atom at an *α*-carbon tend to rearrange to the isomeric hydrazones. O'Connor[4] has shown recently that phenyl-hydrazones of aliphatic ketones and aldehydes are converted rapidly in solution to the azo tautomers.

The oxidation of 1-*n*-butyl-2-carbethoxyhydrazine by means of bromine water at temperatures below 0° afforded a yellow liquid with a sweet odor which showed an absorption maximum near 375

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