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NONCHAIR CONFORMATIONS. CONFIGURATION AND EQUILIBRATION OF *CIS*- AND *TRANS*-2,5-DIMETHYL-1,4-CYCLOHEXANEDIONE

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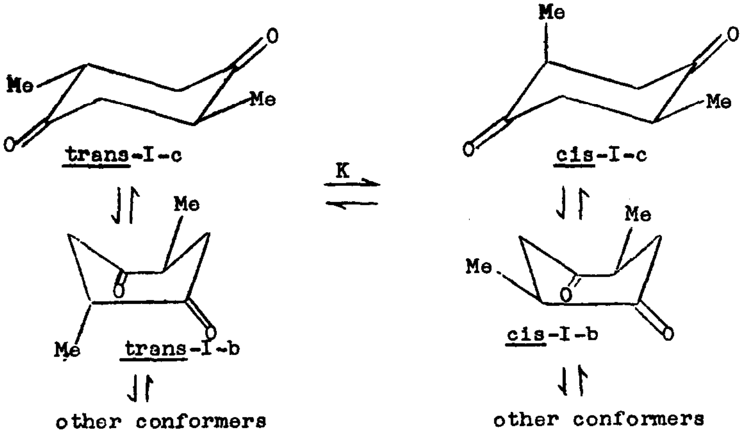
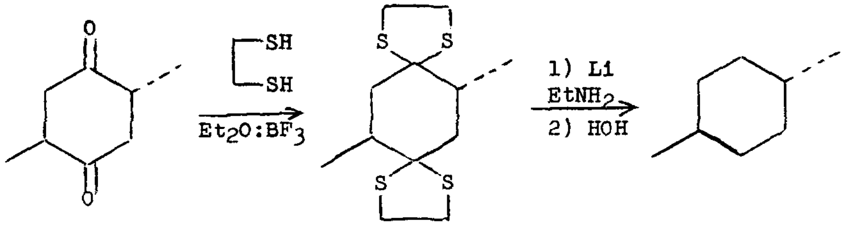
This communication presents evidence in support of the suggestion that nonchair conformations may *predominate* for simple 1,4-cyclohexanediones (1,2). In the equilibration of *cis*- and *trans*-2,5-dimethyl-1,4-cyclohexanedione (*cis*-I and *trans*-I), the *cis*-isomer is the more stable. The conclusion is drawn from the enthalpy of equilibration that for *cis*-I, nonchair conformations such as *cis*-I-b predominate, and from the entropy of equilibration that for *trans*-I, nonchair conformations such as *trans*-I-b probably predominate in spite of the fact that *trans*-I can exist in a chair conformation with both methyl groups equatorial (*trans*-I-c).

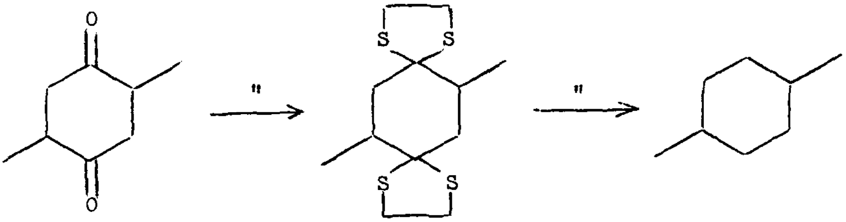


The diones, *cis*-I and *trans*-I, have been reported previously (3,4). The dione, m.p. 119-120°, prepared as reported (3), was nearly pure, while the "dione," m.p. *ca.* 90°, prepared by both of the reported procedures (3,4), was essentially an equilibrium mixture of *cis*- and *trans*-I containing *ca.* 25% of the dione, m.p. 119-120°, plus *ca.* 75% of its stereoisomer (gas chromatographic analysis). Therefore, it seems likely that samples reported previously as the lower melting "isomer" were in fact mixtures (3,4). Partial purification by column chromatography on charcoal-celite with benzene as eluent gave a fair yield of lower melting stereoisomer of *ca.* 90% purity. A small sample of the lower melting stereoisomer, collected by gas chromatography, was 96% pure and gave m.p. 85-87°.

A stereospecific method for the reduction of keto groups to methylene groups was reported as applied to hydroanthracene-9,10-diones (5). This method was employed to establish the configuration of the diones *cis*-I and *trans*-I. The reaction of the higher melting isomer of I, m.p. 119.5-120°, with excess 1,2-ethanedithiol and boron trifluoride-ether gave a bisdithioketal, m.p. 186.5-188.5°, after recrystallization from dioxane-methanol. The bisdithioketal, with lithium metal in ethylamine, gave *trans*-1,4-dimethylcyclohexane, identified by its infrared spectrum.



trans-I



cis-I

A mixture, m.p. 84-87°, of cis- and trans-I, containing 90% of the lower melting isomer, gave a bisdithioketal, m.p. 119-125°, containing a few percent of the higher melting epimer. The bisdithioketal was reduced with lithium in ethylamine, to give cis-1,4-dimethylcyclohexane, (containing a few percent of the trans isomer) identified by comparison of its infrared spectrum with that of an authentic sample (6). Therefore, the dione, m.p. 119.5-120°, is trans-I; its lower melting stereoisomer is cis-I. We conclude that the configurational assignment made for the higher melting dione by Fishman, et al. (4) was incorrect. One might speculate that the erroneous assignment resulted in part because the authors expected a priori that trans-I would be more stable than cis-I, an hypothesis that might seem logical if one thought exclusively in terms of chair conformations.

The results of acid catalyzed equilibration under the conditions previously reported (1) are given in Table I.

TABLE I

Equilibration: trans-I $\rightleftharpoons$ cis-I

T, °C.	% cis[a]	K[b]	ΔF
25°	72.9	2.59	-0.56
85°	66.5	1.97	-0.48

[a] Analyses by gas chromatography were carried out at 100° with a 60 cm., 0.25 in. copper column packed with 3% 1,2,3-tris-(2-cyanoethoxy)propane on 60-80 mesh "HMDS treated Chromosorb W." The area under the curve was measured with a planimeter.

[b] From a graph of ln K as a function of 1/T, the approximate values of the enthalpy and entropy of equilibration were determined: ΔH = -0.97 kcal/mole, ΔS = -1.3 e.u.

Given the fact that cis-I is more stable than trans-I, the conclusion that nonchair conformations predominate for cis-I is based upon the same reasoning presented in the case of the analogous 2,5-di-t-butyl-1,4-cyclohexanediones (1).

With the conclusion in mind that non-chair conformations predominate for cis-I, one can consider at least two hypothetical situations. First, suppose that the predominant conformation for trans-I were the diequatorial chair. Then, the entropy of equilibration, estimated in Table II, would be positive.

TABLE II

Estimation of ΔS for Hypothetical Equilibria of 2,5-Dialkyl-1,4-Cyclohexanediones

	ΔS, Calculated[a]			
	sym	d,l	x	Total
meso-e,e-trans chair ⇌ d,l-cis nonchair	-1.4	1.4	ca. 2	ca. 2
d,l-trans nonchair ⇌ d,l-cis nonchair	-1.4	0	0	-1.4[b]

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[a] The entropy of equilibration, ΔS, is calculated as the sum of three factors: 1) change in symmetry number, 2) change in optical isomerism, and 3) *x*, an estimate of the entropy factor favoring more flexible nonchair conformations relative to the chair conformations. The factor due to a change in internal rotation of the alkyl substituents has been neglected. This factor might be significant for alkyl groups other than methyl. See E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N.Y., 1962, Sec. 8-3.

[b] Rickborn's suggestion that this value would be expected to be Rln 2 (*i.e.*, +1.4) is erroneous (ref. 8, footnote 14).

Next, suppose that nonchair conformations predominate for *trans*-I. Then the entropy of equilibration, estimated in Table II, would be negative. The experimental entropy of equilibration, -1.3 e.u. (Table I), is not consistent with the first hypothetical situation, but is consistent with the second. Therefore, we conclude that the diequatorial chair conformation does not *predominate* for *trans*-I (7).

The suggestion that nonchair conformations predominate for *trans*-I as well as *cis*-I requires further examination. Assuming that the equatorial methyl groups would not be expected to destabilize the chair conformation of *trans*-I significantly with respect to the possible nonchair conformations (8), then the suggestion that nonchair conformations predominate for *trans*-I would seem reasonable only if for 1,4-cyclohexanedione itself a nonchair conformation exists which is more stable than the chair conformation. Clearly, such is the case (2).

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7. For *cis*- and *trans*-2,5-di-*t*-butyl-1,4-cyclohexanedione (1), the entropy of equilibration (ΔS, 0.2 e.u.) may be compared with the calculated values given in Table II. If models are

used to judge a value for the neglected factor due to internal rotation of the *t*-butyl group, an additional positive term seems appropriate in each hypothetical case in Table II. If so, the experimental value, 0.2 e.u., is not consistent with predominance of the diequatorial chair conformation (Calcd.: $\Delta S >$ *ca.* 2 e.u.), but may be consistent with predominance of nonchair conformations for the *trans* dione (Calcd.: $\Delta S > -1.4$ e.u.). Based upon these considerations, the tentative conclusion was reported (1) that nonchair conformations may predominate for *trans*-2,5-di-*t*-butyl-1,4-cyclohexanedione, and possibly, for simple 1,4-cyclohexanedione derivatives in general.

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