Conformational Analysis. LXXXVI. The Equilibrium between the Cis and Trans Isomers of 2-Decalone[1,2]

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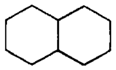
Abstract: When heated in the presence of palladium at elevated temperatures, the 2-decalones undergo equilibration between the cis and trans forms, in addition to many other side reactions leading to additional products. The thermodynamic parameters for the reaction *trans-* $\rightleftarrows$ *cis*-2-decalone are $\Delta G°_{488} = 2.22 \pm 0.04$ kcal/mol, $\Delta H°_{488} = 2.51 \pm 0.31$ kcal/mol, and $\Delta S°_{488} = 0.6 \pm 0.6$ eu. These values, in marked contrast to those found by earlier work, are in good agreement with both theoretical calculations and experimental observations on related systems.

The decalin ring system **1** is a simple parent component of a great many more complicated systems



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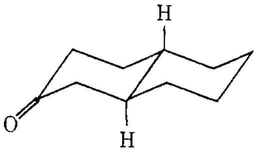
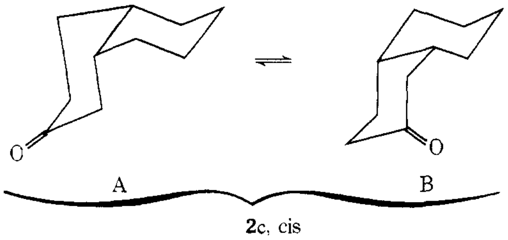
which have been studied theoretically and experimentally with respect to their thermodynamic properties.[3] Both direct equilibration experiments and heat of combustion measurements, together with symmetry considerations, are consistent with the enthalpy of *cis*-decalin being 2.7 kcal/mol greater than that of the trans isomer, which can be conveniently interpreted in terms of gauche interactions. The entropy of the cis form, since it is a *dl* mixture, is found to be approximately 1.4 eu greater than that of the trans form. These numbers have been thoroughly discussed previously and are pretty well understood.

When a ketone function is placed in the 2 position of decalin, the resulting compound (2-decalone) is also a parent compound of many structures found in nature. Particularly, the 3-keto steroids have the features of a 2-decalone in the A/B ring system. With the 2-decalones (**2**), the conformational situation is still fairly simple. The trans isomer (**2t**) is unexceptional and has a single double-chair conformation.[4] On the other hand, the cis isomer consists of two conformations (which were enantiomers in the decalins) which here are diastereomerically related. (Both the cis and trans forms are *dl* mixtures in all of the work considered in this paper, so that entropy effects due to the entropy of mixing the *d* and the *l* isomers cancel out when equilibria are considered.)



2t, trans



2c, cis

The two conformations of *cis*-2-decalone (**2c**) are expected to be different in energy, because one of them (A) has the second ring carbon which is in the β position to the ketone located in an equatorial arrangement, while the other one (B) has it in an axial arrangement. The 3-alkyl ketone effect[5] is therefore expected to favor B over A by approximately 0.5 kcal/mol.

The elementary principles of conformational analysis therefore suggest that the enthalpy difference between the *cis*- and *trans*-2-decalones should slightly favor the cis, relative to what happens with the hydrocarbons. The entropy difference between the isomeric 2-decalones should be pretty small, favoring the cis isomer by the amount of the entropy of mixing of the two conformations, which should be of the order of 1 eu.

There are in the literature some indications that the simple results predicted by the elementary principles of conformational anaylsis are in fact not to be found experimentally. First, there is the optical rotatory dispersion work reported by Djerassi and coworkers.[6] It was concluded originally that the *cis*-10-methyl-2-decalones were somehow abnormal, because the sign of the Cotton effect curve was opposite from what would be expected on simple grounds. It was suggested that perhaps ring A was in a boat form. Further studies, however, led to the conclusion that in fact the nonsteroid form (like **2c**, conformation B) is the predominant conformer.[7-9] It has been said[9] that "the sign of the Cotton curve must be controlled by a conformer pres-

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(2) This research was supported in part by Grant No. GP 15263 from the National Science Foundation.

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ent in minor amounts and which has a large rotational value." Thus, while the source of the Cotton effect curve remains unproven, the conformation of the molecule seems firmly established as being quite normal. It was calculated[8] that in this molecule the nonsteroid and steroid forms exist in a 70:30 ratio at room temperature, which corresponds to an energy difference of about 0.5 kcal/mol, which is consistent with a 3-alkyl ketone effect of that magnitude as indicated by other data.

Because of the similarity between 2-decalone and 10-methyl-2-decalone, one would expect to obtain a similar value for the 3-alkyl ketone effect in each case.

There is reported in the older literature[10] heat of combustion measurements that indicate the trans isomer has a more negative enthalpy than the cis by 2.3 kcal/mol. This value is consistent with what one would expect, but the data are old.

Finally, there is to discuss a paper by Augustine and Caputo[11] in which a direct equilibration experiment was carried out on 2-decalone. The thermodynamic parameters reported by those workers are as follows for the equilibrium *trans*- $\rightleftarrows$ *cis*-2-decalone: $\Delta G°_{531} = +1.33$ kcal/mol; $\Delta H°_{531} = -2.25$ kcal/mol; and $\Delta S°_{531} = -6.74$ eu.

These numbers appear to be most unusual indeed. The large value for $\Delta S°$ is striking. It indicates a very high degree of freedom in the trans isomer, relative to the cis, which is without parallel as far as the authors are aware. In addition, it indicates that the trans isomer is *higher* in enthalpy than is the cis, by 2.25 kcal/mol. The elementary principles of conformational analysis clearly demand that the trans isomer should have a more negative enthalpy than does the cis.

After careful perusal of the work by Augustine and Caputo, it seemed likely to us that, since a lot of decomposition was observed in the equilibration, what was in fact being examined was a steady-state process. The apparent equilibrium amounts of material under these conditions would then be determined by the relative rate at which each isomer was formed, compared to the rate at which it decomposed to give other products. To have in existence experimental results that are apparently so contradictory to the basic principles of conformational analysis seemed an unhappy situation, and one which we felt was in need of clarification.

Results and Discussion

It was decided to essentially repeat the work of Augustine and Caputo,[11] but with attempts to minimize side-product formation, or allow for it, so that one could ascertain the equilibrium values, rather than what we believe to be steady-state values. More recently, we have developed force field methods for the calculation of energies of molecules such as these which we believe to be quite reliable for systems such as 2-decalone.[12,13] These calculations essentially put on a quantitative basis the more rough-and-ready type of conformational calculation alluded to in the introductory section. What was found was that the relative enthalpies of the *trans*-2-decalone and the *cis*-2-decalone (steroid **2c**, conformation A, and nonsteroid **2c**, conformation B) are, respectively, 0.0, 2.5, and 2.2 kcal/mol. These values are calculated for isolated molecules in the gas phase. They should be only slightly different from the enthalpy values measured in solution or in the liquid phase. They predict a 3-alkyl ketone effect in the cis isomer of 0.3 kcal/mol, and predict the trans isomer to be more stable (that is, of lower free energy) by 1.92 kcal/mol at room temperature. The enthalpy and entropy for the isomerization are calculated to favor the trans and cis isomers, respectively. These calculations are, in other words, quite consistent with all that has been said before based on principles, but not consistent with the experimental work of Augustine and Caputo.

Experimentally, what was done was to try to establish equilibrium between the decalones according to the recipe given by Augustine and Caputo.[11] It was found that it was essentially impossible to obtain reproducible results. The problem was that the rate of further reaction of the ketones to give 2-naphthol, naphthalene, and other side products was comparable to the rate at which the equilibration occurred. A search was made for conditions under which the rate of production of side products could be reduced relative to the rate at which equilibration occurred. Temperatures down to 150°, below which equilibration essentially ceased, did not improve the situation very much. Equilibration at quite low temperatures in xylene with Raney nickel, or variations thereof, a method which has been used successfully for 3,5-dimethylcyclohexanone,[14] did not give equilibration in our hands (although 3,5-dimethylcyclohexanone was equilibrated under these conditions). The use of rhodium in place of palladium was found to be ineffective in establishing equilibrium. It was finally ascertained that equilibration using palladium on carbon in acetic acid as a solvent often was successful in giving equilibrium with very little decomposition. Equilibrium was approached from both sides at several temperatures over the range of 459–516°K. Above 516°K, severe decomposition of the samples was typically observed. At lower temperatures, an occasional sample would decompose badly, in which case the points were discarded. The decomposition reaction seemed to be one in which there was an induction period. If the initiation did not occur, equilibrium proceeded smoothly. On the other hand, once initiation of the decomposition occurred, the rate of decomposition was very fast compared to the rate of equilibration.

For the points where little or no decomposition had occurred, the samples were analyzed by vpc, a plot was made of ln K *vs.* $1/T$, and a line was fitted to the points by the method of least squares. The slope of this line gave $-\Delta H°/R$ and the intercept at $1/T = 0$ gave $\Delta S°/R$. The values obtained by this method were $\Delta H°_{488} = 2.51 \pm 0.31$ kcal/mol and $\Delta S°_{488} = 0.6 \pm 0.6$ eu for the *trans*- $\rightleftarrows$ *cis*-2-decalone equilibrium. The $\Delta H°$ value is in good agreement with the value calculated by the method of molecular mechanics (2.31 kcal/mol[12,13]), with the heat of combustion by Hueckel, and with what one expects. The entropy of the change is small,

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(11) R. L. Augustine and J. A. Caputo, *J. Amer. Chem. Soc.*, **86**, 2751 (1964).

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(13) N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, **28**, 1173 (1972).

(14) E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965).

which is typical for an equilibration involving two rigid molecules. It does favor the cis isomer by +0.6 eu, while the calculation says it should favor the cis isomer by + 1.32 eu.

We thus conclude that 2-decalone is quite unexceptional in its conformational behavior. The numbers reported by Augustine and Caputo are erroneous, because they measure steady-state concentrations rather than true equilibrium values, due to the unfortunate occurrence of side reactions at competing rates.[15]

Experimental Section

***cis*- and *trans*-2-Decalone.** These compounds were prepared by the oxidation of *cis*- and *trans*-2-decalol using CrO_3 as reported.[11] The isomers were separated by gas chromatography using a Varian Aerograph Model 700 with a $^3/_8$ in. × 20 ft 15% SE-30 on 30–60 Chromosorb W column at a temperature of 150° and a helium flow rate of 105 cc/min. The retention times of the cis and trans isomers were 104 and 78 min, respectively.

Equilibration. The equilibrations were carried out in 3-mm Pyrex ampoules. A sample of 2-decalone was mixed with an equal amount of acetic acid. The decalone–acetic acid solution (0.2 ml) was sealed in the ampoules with 25 mg of 5% Pd/C. The total volume of material in the ampoule was slightly over half of the volume of the ampoule. The ampoules were heated in metal tubes in an oven at constant temperature until equilibrium was reached (2–7 days). The metal tubes were then plunged into ice water, the ampoules were opened, and the samples were each taken up in 1 ml of hexane. The acetic acid was extracted with aqueous NaOH and the organic layer was washed with water. The hexane–decalone solution was allowed to stand for a few minutes, and then was decanted to separate any remaining catalyst.

Analysis. The analysis was carried out by gas chromatography using a Perkin-Elmer F-11 flame ionization instrument with a 50 ft × 0.02 in. Carbowax 20 M capillary column. The analyses were carried out at 150° using 4 lb of nitrogen carrier gas pressure. The retention times of *cis*- and *trans*-2-decalone were 12.7 and 9.9 min, respectively.

The relative areas under the peaks were determined by multiplying the peak height by its half-height width. It was found that the composition of a mixture of *cis*- and *trans*-2-decalone could be determined to a precision of 0.13%.

The equilibrium was approached from both sides. It was found that the mixtures which started on the trans side proceeded smoothly to equilibrium with very little formation of by-products, while most of the mixtures which started on the cis side formed a great deal of by-product and equilibrium was not attained. In the few cases where little by-product was formed, the same equilibrium mixtures was obtained as from the trans starting material. For this reason we have omitted from our study all samples which had a great deal of by-product. The remaining data are tabulated in Table I.

Table I

Temp, °K	$1/T$	ln K^a
459	0.00218	2.38 ± 0.05
463	0.00216	2.36 ± 0.01
468	0.00214	2.41 ± 0.03
477	0.00210	2.30 ± 0.05
483	0.00207	2.38 ± 0.03
489	0.00204	2.29 ± 0.05
503	0.00119	2.17 ± 0.06
513	0.00195	2.18
516	0.00194	2.14 ± 0.08

[a] The values in the table are standard deviations.

In order to obtain $\Delta H°$ and $\Delta S°$ for the reaction of *trans*- ⇄ *cis*-2-decalone, the inverse of the temperature (°K) and natural logarithm of the equilibrium constant were calculated, and the best straight line through these points was calculated by the method of least squares. The slope is $-\Delta H°/R$ and the intercept is $\Delta S°/R$. The values obtained are $\Delta H°_{488} = 2.51 \pm 0.31$ kcal/mol and $\Delta S°_{488} = 0.6 \pm 0.6$ eu.

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(15) After completion of this work, we were informed by Dr. Gerhard Mann in a private communication dated April 20, 1969, that he had independently come to conclusions rather similar to those which we reached and have reported herein. We are indebted to Dr. Mann for this information.

Condensations of Acyldiazomethanes with Aldehydes, Ketones, and Their Derivatives

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Abstract: Hydroxide-catalyzed condensations of ethyl diazoacetate and diazo ketones with aldehydes in alcohol solution yielding α-diazo-β-hydroxycarbonyl compounds are described. Similar condensations between the diazo esters and ketones of the small ring and α-dicarbonyl types are illustrated. Reactions of acyldiazomethanes with ketones under the influence of *n*-butyllithium and lithium diisopropylamide are depicted. Formation of α-diazo-β-amino esters by the condensation of aldehyde and ketone enamines with diazoacetic ester in alcohol solution as well as under metal ion catalysis in aprotic medium is portrayed. Hydrogenations, acid treatments, and pyrolyses of the condensation products are described.

While the thermal interaction of ethyl diazoacetate and aldehydes or ketones accompanied by nitrogen extrusion has been known for a long time,[2] three reports have indicated that reaction may occur even without nitrogen loss.[3,4] One observation, the base-catalyzed addition of the ester to isatins,[4] is especially interesting, since it suggests that condensations of the

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(1) U. S. Public Health Service Postdoctoral Fellow, 1969–1971.

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