2-Aminodiphenyl sulfone. A mixture of 2.0 g. of 2-nitrodiphenyl sulfone,[6] 5.0 g. of ferrous oxalate dihydrate, and 50 g. of granulated lead was heated for 15 minutes in a bath at 285–290°. Vacuum sublimation gave 0.53 g. of a sparkling yellow compound melting at 118–119°. Two recrystallizations from 50% alcohol gave pure white prisms or rhomboids, m.p. 122–124°. The recorded m.p. of 2-aminodiphenyl sulfone is 122°.[7]

Anal. Calc'd for $C_{12}H_{11}NO_2S$: C, 61.8; H, 4.74; N, 6.07; S, 13.7. Found: C, 61.7; H, 4.75; N, 6.11; S, 13.4.

2-Amino-4-chlorodiphenyl sulfone. A mixture of 2.0 g. of 4-chloro-2-nitrodiphenyl sulfone,[8] 2.6 g. of ferrous oxalate dihydrate, and 20 g. of granulated lead was heated for 8 minutes in an oil-bath at 264–270°. Vacuum distillation of the product gave 0.9 g. of light orange material. This, on two recrystallizations from 50% ethanol, formed short white prisms or rods, melting at 120–121°. Analysis agreed with values for aminochlorodiphenyl sulfone:

Anal. Calc'd for $C_{12}H_{10}ClNO_2S$: C, 53.9; H, 3.74. Found: C, 53.5; H, 3.94.

2-Amino-5-chlorodiphenyl sulfone. A mixture of 2.0 g. of 5-chloro-2-nitrodiphenyl sulfone,[9] 2.6 g. of ferrous oxalate dihydrate, and 20 g. of granulated lead was heated in an oil-bath at about 270° for eight minutes. Vacuum distillation of the product gave 0.8 g. of an orange-colored solid, which on two recrystallizations from 50% ethanol formed small white rods, melting at 111–112°. Analysis agreed with values for aminochlorodiphenyl sulfone:

Anal. Calc'd for $C_{12}H_{10}ClNO_2S$: C, 53.9; H, 3.74. Found: C, 53.6; H, 3.68.

This 2-amino-5-chlorodiphenyl sulfone was photosensitive, darkening appreciably on long exposure to visible light. The 2-amino-4-chlorodiphenyl sulfone shared this property to a lesser degree, but the unhalogenated 2-aminodiphenyl sulfone was not light-sensitive, and remained pure white.

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The Relative Stabilities of *Cis* and *Trans* Isomers. II. The Decalin and Hydrindan Ring Systems[1]

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Received April 30, 1956

The relative stabilities of *cis* and *trans* isomers in fused ring systems of the decalin and hydrindan types are of theoretical and practical interest, and they have recently been the subject of an appreciable amount of work and discussion.[3-8] In spite of this widespread interest, no general rationalization of the relative stabilities of the *cis* and *trans* isomers of these ring systems under various circumstances has been advanced. It would be useful to be able to predict which isomer would be the more stable in different situations, but this can hardly be done at present. For instance, *trans*-decalin is by any criterion more stable than its *cis* isomer,[9] while with 9-methyldecalin the *cis* isomer predominates at equilibrium.[3] When the *cis* and *trans* structures were assigned respectively to the *normal* and *allo* series in steroids, the unsubstituted decalins were used as models, and the assignments are known to be correct.[10] Yet, had the more closely analogous 9-methyldecalins been used as models, the reverse and incorrect conclusions would have been reached. Turning to the hydrindans, certain curiosities are again to be found. It is reported that *trans* hydrindan and its 2-keto derivative have lower heats of combustion than the corresponding *cis* compounds,[11,12] while 1-keto-hydrindan and 4-keto-hydrindan both furnish *cis* isomers upon equilibration.[13]

Actually the confusion evident in the examples mentioned is more apparent than real. Much of the difficulty results from the fact that proper differentiation between heat contents and free energies has not been made in the past. Generally these quantities are lumped together as "stabilities." As long as the relative heat contents and free energies have the same sign, as they do in the vast majority of cases, no difficulties are encountered in qualitative discussion. However, in the systems at present under consideration there is good evidence for the fact that even an approximate parallelism between these properties does not exist.

Ordinarily we are most interested in the correspondence between the free energy and the *cis* and *trans* relationships of compounds, the goal being to predict which isomer will have the lower free energy or conversely, to assign the structures from the free energies. Frequently the free energy

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of the isomerization can be measured by equilibration experiments, but to understand these free energies they must be separated into their component parts by the relationship $\Delta F = \Delta H - T\Delta S$.

The heat contents can be determined in various ways, most simply from heats of combustion. The necessary data are available for only a limited number of compounds, however. Of wide application in this connection is a rule which was stated as follows:[1] For liquid[14] *cis* and *trans* isomers in cyclic systems,[15] that isomer which has the highest boiling point, highest index of refraction, and highest density is the isomer which possesses the least stable configuration.[16,17]

Finally the entropy of the isomerization must be considered. An examination of models of the *cis* and *trans* isomers of the decalins and hydrindans shows that the *cis* isomer is invariably less constrained than the *trans*, and that it is more disordered. Consequently, the *cis* isomer will have the more positive entropy of formation.

In Table I are summarized the reported physical properties of several simple members of the ring systems in question, and these data may now be examined in the light of the preceding discussion.

The decalins may first be considered as an established case and as a point of reference. The *trans* isomer has the more negative heat content by 2.1 kcal.,[9] and this difference is large enough to be the controlling factor in determining the relative free energies, thus the *trans* isomer predominates in the equilibrium mixtures with various derivatives.[13]

In the case of 9-methyldecalin, conformational analysis predicts that the *trans* isomer will have a lower heat content than the *cis*, but only by 0.8 kcal.[8] The physical constants[6] in Table I are in qualitative agreement with this conclusion; unfortunately heat of combustion data are not available. It is clear, however, that the difference in heat content between the 9-methyldecalins is rather small, and since the *cis* isomer has the more positive entropy it is not surprising that (with the 1-keto compound) the *cis* isomer predominates in the equilibrium mixture,[3] especially at the high temperature used.

TABLE I

PHYSICAL PROPERTIES

Compound	n_D^{25}	d_4^{25}	H_f[a]	F_f[a]
Decalin,				
cis-	1.4811^{20}	0.8963^{20}	2.1	—
trans-	1.4697^{20}	0.8699^{20}	0.0	—
9-Methyldecalin,				
cis-	1.4791	0.8924	—	—
trans-	1.4764	0.8857	—	—
cis-1-keto-	1.4893	—	—	0.00
trans-1-keto-	1.4882	—	—	0.42
(*cis*) coprostane	$1.4884^{87.7}$	$0.9120^{87.7}$	—	—
(*trans*) cholestane	$1.4887^{87.7}$	$0.9091^{87.7}$	—	—
Hydrindan,				
cis-	1.4713_{He}^{20}	$0.8815^{20.7}$	1.8	—
trans-	1.4638_{He}^{20}	$0.8630^{20.2}$	0.0	—
cis-1-keto-	—	—	—	0.00
trans-1-keto-	—	—	—	positive
cis-2-keto-	$1.4846^{16.7}$	$1.0022^{15.5}$	2	—
trans-2-keto-	1.4769^{17}	0.9807^{17}	0	—
8-Methylhydrindan,				
cis-	1.4671	0.8756	—	—
trans-	1.4672	0.8756	—	—

[a] H_f and F_f are, respectively, the relative heats and free energies of formation of the compounds in kcal./mole. For a given isomeric pair these quantities were determined at the same temperature with the substances in the same state, but the temperatures and states vary throughout the Table. These quantities are consequently not strictly comparable, but the errors thus introduced appear to be small enough to neglect in the present comparison.

When the 9-methyldecalin part of the steroid ring system (rings A and B) is considered, it is predicted that the magnitude of the difference in entropy between the two isomers will be smaller than that found with the 9-methyldecalins themselves. The reason for this difference is that since the *trans* isomer is fairly rigid in the simple molecule, its fusion into a larger system is of little consequence, while the *cis* isomer which is relatively free in the simple molecule, becomes more rigid in the steroid system with the consequent larger loss of entropy. Experimentally it is found that the density (liquids) of cholestane is appreciably lower than that of coprostane,[18] and that derivatives of the latter are isomerized to those of the former. Hence, as with the 9-methyldecalins, the *allo* structure has a more negative heat content than the *normal*. Although the entropy difference has reversed the free energies of the 9-methyldecalins relative to their heat contents, such a reversal has not been effected in the steroid system. Thus the assignment of *trans* and *cis* ring junctures to the *allo* and *normal* series, respectively, by analogy to the decalins themselves led to the correct result only through a fortuitous cancelling of opposing effects.

A similar argument is applicable to the hydrindan ring system. With the parent hydrocarbons and their 2-keto derivatives the *trans* isomers, in agree-

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(14) Presumably for solid compounds the partial molal properties in inert solvents could be used.

(15) The *cis* and *trans* isomers of olefins are specifically excluded from consideration for reasons which have been remarked on previously (Ref. 1) and which will form the subject of a separate paper.

(16) The expression *least stable configuration* is used here in the same sense in which it is used in conformational analysis, namely in reference to energy (rather than free energy).

(17) This rule has recently been stated in other forms by various workers: (a) Siegel, *J. Am. Chem. Soc.*, **75**, 1317 (1953); (b) Darling, Macbeth, and Mills, *J. Chem. Soc.*, 1364 (1953); (c) Hewgill, Jefferies, and Macbeth, *J. Chem. Soc.*, 699 (1954); and ref. 7.

(18) Ruzicka, Furter, and Thomann, *Helv. Chim. Acta*, **16**, 327 (1933).

ment with the physical constants,[19] have the lower heat contents.[11,12] With the 1-keto and the 4-keto derivatives, the *cis* isomers have the lower free energies.[13] It seems likely that the differences here noted are not due to the position or absence of the oxygen atom, but rather are due to the fact that the entropy of the *cis* form is sufficient to cause it to predominate in the equilibrium mixture with each of the isomeric pairs mentioned even though the *trans* isomer in each case has the lower heat content. Unfortunately experimental values for both the heat contents and the free energies for the same pair of isomers are not available in a single case. There is, however, some evidence which indicates that the substitution of small hetero atoms (*e.g.* oxygen, nitrogen) in and around the above types of ring systems has no appreciable effect on the relative stabilities of the *cis* and *trans* ring junctures.[7,12,20]

When the hydrindan system is fused into a larger but still relatively non-rigid structure, little change in the relative entropy of the *cis* and *trans* isomers is to be expected. The entropy will consequently favor the *cis* form at equilibrium while the heat contents must be examined in individual cases. The lowest heat content will ordinarily be found for the isomer in which the five-membered ring is joined to the six-membered ring by the smallest number of axial bonds, regardless of *cis-trans* relationships. Consequently podophyllotoxin can be epimerized to picropodophyllin[21] as this isomerization involves both conversion of an axial to an equatorial bond, and conversion of a *trans* to a *cis* ring juncture. When the equilibrium between isodesoxypodophyllotoxin and isodesoxypicropodophyllin is considered, the energy and entropy effects work in opposite directions.[22] Clearly at very low temperatures the former compound, with its lower heat content, will predominate while the latter compound, with its greater entropy, will predominate at sufficiently high temperatures. More precise predictions cannot be made from the available data.

The 8-methylhydrindan system may be approached in the same way as were the previous cases. It is clear from equilibration studies that the *cis* isomer has the more negative free energy in this system.[23,24] Substitution of the 8-methyl group into *trans*-hydrindan would be expected to increase its heat content more than would the same substitution in the *cis* system, since only in the latter can the methyl group be put into a favorable equatorial position. The heats of combustion have not been determined for any compounds of the 8-methylhydrindan series, but again the physical constants[25] may be used to indicate the heats of formation, and it is concluded that they are virtually identical for the two isomers. Consequently, because of the entropy the *cis* isomer should and does predominate in the equilibrium mixture.

Dreiding has interpreted the known C/D stabilities of the saturated steroids in terms of axial-equatorial interactions.[5] Since in these cases the systems are rigid anyway, the entropies will not affect the conclusions drawn from the heat contents. In the Δ^8 compounds, the *cis* isomer is predicted to have a significantly higher entropy, but since the effect works in the same direction as the heat content, the correct stabilities are predicted from either. An extension of these ideas to the pyroketone of Windaus led to the suggestion that in this compound ring B might be in the boat form.[5] Subsequently it was shown that this arrangement was improbable, and an alternative interpretation of the data was offered.[4]

Actually the inconsistency in Dreiding's argument may be due to the misidentification of a kinetically controlled product with a thermodynamically stable one. There seems to be no reason to assume that the ketone initially formed in the reaction had to isomerize under the conditions employed,[26] and it is possible that the *cis* juncture is formed in a rate-controlled ketonization of an enol.[27] This point will be discussed in detail in a subsequent publication.

We may generalize these conclusions in the following way. First, we may predict the order of the heat contents of a pair of *cis-trans* isomers from their physical constants. Second, the relative entropies of the compounds may be deduced from models, and, lastly, the relative free energies may be estimated from the heat contents and entropies. Since we do not ordinarily have numerical values for these quantities, it is usually only known that one is greater than, less than, or similar to the other. Certain cases are consequently ambiguous, but for most cases of interest it is now possible to predict, especially with the aid of properly constituted model compounds, which isomer of a pair will predominate at equilibrium. These principles are independent of the size and number of rings, their arrangement, and the substitution in and around them, and consequently should be capable of considerable extension.

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