169. *Entropy Changes in Isomerisations.*

By R. M. Gascoigne.

The assumption that relative stabilities of isomers can be assessed from enthalpy data alone is valid for several types of isomerisation for which thermodynamic data are available. It is not valid for the chain-branching rearrangements of the higher paraffins or for certain keto-enol isomerisations. The structural and other factors which determine the magnitude of entropy changes in isomerisations are examined.

Thermodynamic aspects of the cyclisation-rearrangement reactions of terpene biosynthesis are evaluated.

In current theoretical developments in organic chemistry, particularly conformational analysis,[1] much attention is paid to assessment of relative stabilities of isomers. Recently, Allinger [2] has pointed out that confusion may arise from inexact use of the word " stability " and Wheland [3] has discussed the different and sometimes contradictory meanings of the word. Strictly, " stability " can mean only thermodynamic stability: thus in comparing two isomers, A and B, the isomer B is more stable if it predominates at equilibrium, *i.e.*, if the free-energy change, ΔG, is negative for the reaction A $\longrightarrow$ B in specified conditions. The free-energy change, and hence the relative stability, is determined by the enthalpy (heat content) change and the entropy change in the relation $\Delta G = \Delta H - T\Delta S$.

The word " stability " is still frequently used in the old, discarded sense of " thermochemical stability " [3] or at least the tacit assumption is made that entropy changes are sufficiently small to permit relative stabilities of isomers to be estimated from thermochemical (enthalpy) data alone. Often this assumption is made because enthalpy differences can, in general, be estimated from structural considerations whereas free-energy differences usually cannot. Thus, enthalpy differences are often determined by fairly well-known structural factors such as non-bonded repulsions, angle strain, resonance, polar repulsions, etc. Conformational analysis, for example, consists largely of comparisons of stability based essentially on enthalpy data (which have, however, been supplemented by data from equilibration experiments with the assumption that the two types of data are comparable).

What is generally required is a knowledge of the sign, and if possible the approximate magnitude, of ΔG for an isomerisation (hypothetical or real), given the sign, and often the magnitude, of ΔH. Thermodynamic data are now available for many organic compounds, particularly hydrocarbons,[4] and in Tables 1 and 2 are listed the values of ΔH, $T\Delta S$, and ΔG for a variety of isomerisation reactions. Generally $T\Delta S$ is numerically less than ΔH, so that ΔG and ΔH have the same sign; hence the assumption that relative stabilities can be qualitatively assessed from enthalpy data is, in many cases, justified.

In other cases, however, $T\Delta S$ is greater than ΔH. Such cases are, as yet, hardly predictable because only a limited approach can be made towards assessment of entropy changes caused by structural changes.* The structure-dependent contributions to the entropy of a molecule are those due to rotation and vibration.[5] Hence arise the applicability of qualitative ideas of molecular symmetry, compactness and rigidity, and the large effects of certain structural changes, particularly chain branching, ring formation,

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* For reactions in solution changes in solvation are also to be considered since these can cause large entropy (and enthalpy) changes. Some instructive examples are discussed by Chatt and Wilkins, *J.*, 1952, 273, 4300.

[1] Recent reviews: Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44; Dauben and Pitzer, " Steric Effects in Organic Chemistry " (ed. Newman), Wiley, New York, 1956, Ch. 1.

[2] Allinger, *J. Org. Chem.*, 1956, **21**, 915.

[3] Wheland, " Advanced Organic Chemistry," Wiley, New York, 2nd Edn., 1949, pp. 366 *et seq.*

[4] Rossini, Pitzer, *et al.*, " Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," Carnegie Press, Pittsburg, 1953.

[5] Cf. Janz, *Quart. Rev.*, 1955, **9**, 229.

and ring expansion. (Alternatively, the effect of these structural changes could be attributed to the large decrease in degrees of freedom of the molecules undergoing reaction.) The magnitude of the entropy changes in these three reactions, as compared with other isomerisations, is shown by comparison of the $T\Delta S$ values in Tables 1 and 2.

From the data available, the chain-branching rearrangements of *n*-octane (Table 1, A; similar data are available[4] for several such rearrangements of this compound), and presumably also of higher paraffins, are the only set of examples where $T\Delta S$ is greater than ΔH for a *skeletal* isomerisation at ordinary temperature. Above certain temperatures, up to *ca.* 200°, $T\Delta S$ is greater than ΔH for the chain-branching rearrangements of most of the lower paraffins also. Isomerisations involving a change in *bond type* may be expected to exhibit appreciable entropy (and enthalpy) changes. This is the case, generally, in keto-enol equilibria of β-keto-esters, for which thermodynamic data are available (for the gaseous state).[6] Here $T\Delta S$ is often greater than ΔH;[6] thus there is no

TABLE 1. *Isomerisations involving large entropy changes.*

Values are in kcal./mole at 25° and atmospheric pressure; data were taken from ref. 4 unless otherwise indicated.

	State	ΔH	$T\Delta S$	ΔG
A. *Chain-branching rearrangements*				
n-Butane → *iso*butane	gas	− 2·00	− 1·10	− 0·90
n-Pentane → *neo*pentane	gas	− 4·67	− 3·06	− 1·61
n-Hexane → 2 : 3-dimethylbutane	gas *	− 2·53	− 1·61	− 0·92
n-Heptane → 2 : 2 : 3-trimethylbutane	gas *	− 4·07	− 3·18	− 0·89
n-Heptane → 3-ethylpentane	gas *	− 0·45	− 1·18	+ 0·73
n-Octane → 4-methylheptane	gas *	− 0·87	− 0·96	+ 0·09
n-Octane → 3-ethyl-2-methylpentane	gas *	− 0·66	− 1·82	+ 1·16
n-Octane → 2 : 2 : 3 : 3-tetramethylbutane	gas *	− 4·17	− 5·52	+ 1·35
n-Butan-1-ol → 2-methylpropan-2-ol[a]	liq.	− 9·80	− 2·76	− 7·04
n-Pentan-1-ol → 2-methylbutan-1-ol[a]	liq.	−10·40	− 1·86	− 8·54
B. *Ring formation and fission*				
*cyclo*Propane[b,c] → propene	gas	− 7·83	+ 2·09	− 9·92
*cyclo*Butane[b] → but-1-ene	gas	− 6·26	+ 2·88	− 9·14
Pent-1-ene → *cyclo*pentane	gas	−13·46	− 3·77	− 9·69
Hex-1-ene → *cyclo*hexane	gas	−19·47	− 6·16	−13·31
Hept-1-ene → *cyclo*heptane[d]	gas	−13·63	− 5·79	− 7·84
Oct-1-ene → *cyclo*octane[d]	gas	−10·24	− 6·82	− 3·42
Hept-1-ene → methyl*cyclo*hexane	gas	−22·10	− 5·72	−16·38
Oct-1-ene → *trans*-1 : 2-dimethyl*cyclo*hexane	gas	−23·20	− 6·54	−16·66
Oct-1-ene → ethyl*cyclo*hexane	gas	−21·23	− 5·71	−15·52
Eicos-1-ene → *n*-tetradecyl*cyclo*hexane	gas	−21·28	− 5·85	−15·43
Penta-1 : 4-diene → *cyclo*pentene	gas	−17·35	− 3·13	−14·20
Hexa-1 : 5-diene[e] → *cyclo*hexene	gas	−21·96	− 6·60	−15·36
trans-Deca-1 : 5-diene[e] → *trans*-decalin[f]	gas	−44	−13·6	−30
C. *Ring expansion and contraction*				
Methyl*cyclo*pentane → *cyclo*hexane	gas *	− 3·93	− 2·99	− 0·94
1-Methyl*cyclo*pentene → *cyclo*hexene	gas	—	− 1·11	—
1 : 1-Dimethyl*cyclo*pentane → methyl*cyclo*hexane	gas *	− 3·94	− 1·14	− 2·80
trans-1 : 2-Dimethyl*cyclo*pentane → methyl*cyclo*hexane	gas *	− 4·32	− 1·67	− 2·65
trans-1 : 3-Dimethyl*cyclo*pentane → methyl*cyclo*hexane	gas *	− 4·52	− 1·67	− 2·85
Ethyl*cyclo*pentane → methyl*cyclo*hexane	gas *	− 6·62	− 2·49	− 4·13
*cyclo*Heptane[d] → methyl*cyclo*hexane	gas *	− 8·47	+ 0·07	− 8·54
*cyclo*Octane[d] → ethyl*cyclo*hexane	gas *	−10·99	+ 1·13	−12·12

* Data for the liquid state are available and are very similar.

[a] Parks and Huffman, " The Free Energies of Some Organic Compounds," Chemical Catalog Co., New York, 1932. [b] Rathjens, Freeman, Gwinn, and Pitzer, *J. Amer. Chem. Soc.*, 1953, **75**, 5634. [c] Ruehrwein and Powell, *ibid.*, 1946, **68**, 1063. [d] Finke, Scott, Gross, Messerly, and Waddington, *ibid.*, 1956, **78**, 5469. [e] ΔH_f and S estimated by the method of Souders, Matthews, and Hurd, *Ind. Eng. Chem.*, 1949, **41**, 1048. [f] ΔH_f and S for the gaseous state estimated as *ca.* −46 kcal./mole and 81 cal./degree/mole (see Appendix).

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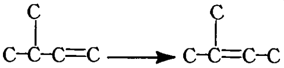
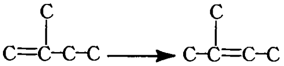
[6] Briegleb, Strohmeier, and Höhne, *Z. Elektrochem.*, 1952, **56**, 240; *Z. Naturforsch.*, 1953, **8***b*, 53; 1952, **7***b*, 184; 1951, **6***b*, 6.

qualitative correlation between the enthalpy differences and the relative stability of the isomers; hence the numerous attempts to explain the equilibrium positions on purely thermochemical grounds are necessarily inadequate.

The small entropy changes in *cis–trans*-isomerisations (Table 2, A) are particularly striking. Thus, large variations in molecular shape can be accompanied by quite small variations in molecular degrees of freedom. It is noteworthy that *trans*-isomers do not always have the lower entropy; *e.g.*, *trans*-decalin is more symmetrical and more rigid than *cis*-decalin and so might be expected to have the lower entropy but the opposite is the case. Clearly, qualitative considerations cannot predict the sign of small entropy changes. Recently, Allinger[2] has suggested that the discrepant stability relations in the

TABLE 2. *Isomerisations involving small entropy changes.*

Values are in kcal./mole at 25° and atmospheric pressure; data were taken from ref. 4 unless otherwise stated.

	State	ΔH	$T\Delta S$	ΔG
A. cis ⟶ trans-*Isomerisation* (*additional to the examples listed by Chatt and Wilkins,* J., 1952, 274)				
Decalin[a]	liq.	− 2·12	+0·28	− 2·40
3-Methylpent-2-ene	gas	0·00	+0·24	− 0·24
4-Methylpent-2-ene	gas	− 1·00	−0·36	− 0·64
Propenylbenzene	gas	− 1·00	−0·24	− 0·76
1 : 2-Dichloroethylene[b]	gas	+ 0·58	+0·05	+ 0·53
Maleic ⟶ fumaric acid[c]	solid	− 6·80	+0·48	− 7·28
B. *Mutarotation and epimerisation*				
β- ⟶ α-Glucose[d]	soln.[e]	0	+0·33	− 0·33
β- ⟶ α-Mannose[d]	soln.[e]	0	+0·25	− 0·25
α- ⟶ β-Xylose[d]	soln.[e]	− 0·55	−0·18	− 0·37
α- ⟶ β-Lactose[d]	soln.[e]	+ 0·71	+1·01	− 0·30
β- ⟶ α-Glucose penta-acetate[f]	soln.[g]	− 1·39	−0·42	− 0·97
Mannitol ⟶ Dulcitol[c]	solid	− 1·20	−0·30	− 0·90
β-Maltose[h] ⟶ α-Lactose[h]	solid	− 5·9	−0·2	− 5·7
C. *Double-bond migration*				
C=C–C–C ⟶ C–C=C–C (*cis*)	gas	− 1·64	−0·34	− 1·30
C=C–C–C ⟶ C–C=C–C(*trans*)	gas	− 2·64	−0·65	− 1·99
 $C-\overset{\displaystyle C}{\underset{}{C}}-C=C \longrightarrow C-\overset{\displaystyle C}{C}=C-C$	gas	− 3·25	+0·36	− 3·61
 $C=\overset{\displaystyle C}{C}-C-C \longrightarrow C-\overset{\displaystyle C}{C}=C-C$	gas	− 1·49	−0·35	− 1·14
 $C=\overset{\displaystyle C}{C}-\overset{\displaystyle C}{C}-C \longrightarrow C-\overset{\displaystyle C}{C}=\overset{\displaystyle C}{C}-C$	gas	− 1·13	−0·21	− 0·92
C=C=C–C ⟶ C=C–C=C	gas	−12·44	−1·02	−11·42
C=C–C–C=C ⟶ C=C–C=C–C (*trans*)	gas	− 6·60	−0·98	− 5·62
3- ⟶ 1-Methyl*cyclo*pentene	gas	—	−0·30	—
1 : 5- ⟶ 1 : 2-Dimethyl*cyclo*pentene	gas	—	−0·72	—
D. 1 : 2-*Migration of methyl groups*				
3- ⟶ 2-Methylpentane	gas *	− 0·64	+0·05	− 0·69
2 : 3- ⟶ 2 : 2-Dimethylbutane	gas *	− 1·86	−0·53	− 1·33
3-Ethyl-2-methyl- ⟶ 3-ethyl-3-methylpentane	gas *	− 0·90	−0·58	− 0·32
cis-1 : 2- ⟶ 1 : 1-Dimethyl*cyclo*hexane	gas *	− 2·11	−0·68	− 1·43
trans-1 : 2- ⟶ *cis*-1 : 3-Dimethyl*cyclo*hexane	gas *	− 1·14	−0·03	− 1·11
trans-1 : 4- ⟶ *cis*-1 : 3-Dimethyl*cyclo*hexane	gas *	− 0·04	+0·41	− 0·45
cis-1 : 2- ⟶ 1 : 1-Dimethyl*cyclo*pentane	gas *	− 2·09	−0·49	− 1·60
cis-1 : 2- ⟶ *cis*-1 : 3-Dimethyl*cyclo*pentane	gas *	− 0·97	+0·05	− 1·02

* Data for the liquid state are available and are very similar.

[a] Parks and Hatton, *J. Amer. Chem. Soc.*, 1949, **71**, 2773. [b] Pitzer and Hollenberg, *ibid.*, 1954, **76**, 1493. [c] Ref. *a*, Table 1. [d] Kendrew and Moelwyn-Hughes, *Proc. Roy. Soc.*, 1940, **176**, *A*, 352. [e] In water. [f] Bonner, *J. Amer. Chem.*, 1951, **73**, 2659. [g] In acetic acid–acetic anhydride. [h] Monohydrate; Anderson and Stegeman, *J. Amer. Chem. Soc.*, 1941, **63**, 2119.

9-methyldecalin and hexahydroindane series may be due to entropy differences. However, from the nature of the data in Table 2, A, it is doubtful if this is the case.

Table 2, D, contains representative examples of methyl 1 : 2-migrations (for other examples, see ref. 4). The reactions listed, like those in Table 1, A and C, are formally equivalent to Wagner–Meerwein rearrangements. It may be concluded that in isomerisations (hypothetical or real) involving such rearrangements the relative stabilities of the isomers can safely be predicted from the relative enthalpies, with the exceptions, already noted, in the higher paraffins. Application of this principle is made in the following paper. Similar remarks apply to double-bond isomerisations, representative examples of which are listed in Table 2, C.

The conclusions reached in this paper are relevant to certain biosynthetical reactions which are of interest essentially as skeletal isomerisations. Ruzicka and his colleagues [7] have proposed a hypothesis in which the biosynthesis of the various classes of cyclic terpenes is thought to take place by cyclisation of aliphatic prototypes; thus the numerous cyclic triterpenes are derived by oxidative cyclisation of squalene. The complex cyclisations often incorporate several 1 : 2-shifts of methyl groups, hydrogen atoms, or ring members (ring expansion or contraction) and are envisaged to be single, " non-stop " reactions. By analogy with the reactions listed in Tables 1, B, 1, C, and 2, D, these reactions should be exothermic (ΔH negative) and $T\Delta S$ should be numerically less than ΔH; hence they should also be exergonic (ΔG negative; thermodynamically spontaneous).

TABLE 3. *Estimated thermodynamic properties of representative triterpenes (hypothetical gaseous state; atmospheric pressure;* 25°).

ΔH_f and ΔS_f were calculated by the method of Souders, Matthews, and Hurd [13] and ΔH_f was corrected for various conformational features (see Appendix). Values of ΔS_f are in cal./degree/mole and other values are in kcal./mole.

	$-\Delta H_f$ (calc.)	$-\Delta H_f$ (corr.)	$-\Delta S_f$ (calc.)	Formation from squalene:		
				$-\Delta H$	$-T\Delta S$	$-\Delta G$
Squalene	12	12	534	—	—	—
Ambrein	144	137	654	125	36	89
Tetra*cyclo*squalene	92	90	628	78	28	50
Onocerin	172	169	661	157	38	119
Lanosterol	133	133	645	121	33	88
Euphol	133	127	645	115	33	82
Dammaradienol	130	126	651	114	35	79
α-Amyrin	155	147	681	135	44	91
β-Amyrin	155	146	682	134	44	90
Taraxerol	155	135	682	123	44	79
Glutinol	157	143	681	131	44	87
Friedelin	167	155	690	143	46	97
Lupeol	150	147	682	135	44	91
Taraxasterol	153	149	683	137	44	93

Clearly, the enzymic conversion of squalene into lanosterol [8] and the acid-catalysed conversion into tetra*cyclo*squalene [9] are exergonic reactions.

An estimate of the thermodynamic properties of terpenes can be made by methods used in petroleum technology. These methods have a sound theoretical basis [5] and depend upon the additivity of the enthalpy and entropy contributions of specific structural units; empirical correction factors are applied for various structural features. Thermodynamic properties of representative triterpenes estimated by one of these methods (discussed in the Appendix) are given in Table 3, together with the values of ΔH, $T\Delta S$, and ΔG for their formation from squalene; these should be correct at least in order of

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[7] Ruzicka, Eschenmoser, and Heusser, *Experientia*, 1953, **9**, 357; Eschenmoser, Ruzicka, Jeger and Arigoni, *Helv. Chim. Acta*, 1955, **38**, 1890; Ruzicka, " Perspectives in Organic Chemistry " (ed. Todd), Interscience, New York, 1956 (cf. Stork and Burgstahler, *J. Amer. Chem. Soc.*, 1955, **77**, 5068).,

[8] Tchen and Bloch, *J. Amer. Chem. Soc.*, 1955, **77**, 6085; 1956, **78**, 1516; cf. Clayton and Bloch, *J. Biol. Chem.*, 1956, **218**, 305, 319.

[9] Heilbron, Kamm, and Owens, *J.*, 1926, 1630.

magnitude. Necessarily, the estimates are for the gaseous state but the values for formation from squalene should not be significantly different for the liquid and the solid state.

As will be seen from Table 3, the reactions involved in the conversion of squalene into the various triterpenes are highly exergonic as well as exothermic. Stoicheiometrically, these reactions are not far removed from isomerisations and the $T\Delta S$ term has the same type of relation to ΔH as in the majority of examples in Tables 1 and 2; also the magnitudes of ΔH, $T\Delta S$, and ΔG are what might be expected from extrapolation of values in Table 1, B.

Some support for the principle that each representative triterpene is formed directly from squalene by a single concerted reaction [7] is provided by consideration of relative thermodynamic stabilities. Taraxerol, glutinol, and friedelin could conceivably be formed by cyclisation of squalene to β-amyrin followed by rearrangement to these three compounds by reversal of the reactions discussed in the following paper. However, since taraxerol and glutinol are thermodynamically less stable than β-amyrin (see following paper) their formation from β-amyrin would involve a positive free-energy change of several kcal./mole. Endergonic reactions are, of course, common in the thermodynamically " open " systems of living organisms,[10, 11] but it may well be doubted if they occur at the level of biosynthesis discussed here. In any case, coupling of the rearrangement of β-amyrin with a source of metabolic energy *via* energy carriers such as adenosine triphosphate [11, 12] seems unlikely on mechanistic grounds.

Similar considerations apply in other terpene groups. Thus, in the monoterpenes it is well known that *in vitro* acyclic hydrocarbons are readily converted into monocyclic hydrocarbons but the latter are not converted into (strained) dicyclic hydrocarbons. Probably *in vivo* the dicyclic hydrocarbons are formed in a single reaction from the acyclic prototype and not from monocyclic hydrocarbons, since this would involve a positive free-energy change. Relevant ΔH values are: myrcene ⟶ limonene, $-16{\cdot}5$;* myrcene ⟶ α-pinene, $-7{\cdot}4$; limonene ⟶ α-pinene, $+9{\cdot}1$. The free-energy changes in these reactions would have the same sign as the heat changes (cf. Table 1, B).

APPENDIX

For the estimation of thermodynamic properties of triterpenes the method of Souders, Matthews, and Hurd [13] appeared the most suitable; group contributions for hydroxyl and keto-groups were taken from the similar method of Franklin.[14] Satisfactory estimates were obtained for monocyclic hydrocarbons, *e.g.*, 1 : 1-dimethyl*cyclo*hexane: ΔH_f, $-44{\cdot}65$ kcal./mole; ΔS_f, $-172{\cdot}6$ cal./degree/mole; the experimental values [4] are $-43{\cdot}26$ and $-173{\cdot}6$, respectively. The main source of error is probably in the application of the method to polycyclic systems; experimental data for such systems are meagre and so the method cannot distinguish between *cis*- and *trans*-ring junctions. The calculated values for decalin are: ΔH_f, $-42{\cdot}3$; ΔS_f, $-214{\cdot}3$; ΔG_f, $+21{\cdot}9$; experimental values for the gaseous state are available [15] only for ΔG_f; these are: for the *cis*-isomer, $+20{\cdot}4$, and for the *trans*-isomer, $+17{\cdot}6$. Consequently, a rough correction of -4 kcal./mole per *trans*-junction was applied to the calculated values of ΔH_f. This correction is similar to the adjacency corrections to ΔH_f made by Souders *et al.*[13]

Further approximate corrections, all positive in sign, were made to the calculated values of ΔH_f to allow for the main types of conformational instability. These were: for each diaxial 1 : 3-H : Me interaction, 0·9 kcal./mole; [16, 17] for each diaxial 1 : 3-Me : Me interaction (and

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* The ΔH values are in kcal./mole and are taken from Hawkins and Eriksen's combustion data (*J. Amer. Chem. Soc.*, 1954, **76**, 2669).

[10] Cf. Gutfreund, *Ann. Reports*, 1954, **51**, 295; *Adv. Enzymol.*, 1951, **11**, 1.

[11] Cf. Street, *Sci. Progr.*, 1950, **38**, 43.

[12] Cf. Avison and Hawkins, *Quart. Rev.*, 1951, **5**, 171.

[13] Souders, Matthews, and Hurd, *Ind. Eng. Chem.*, 1949, **41**, 1048.

[14] Franklin, *ibid.*, p. 1070.

[15] Parks and Hatton, *J. Amer. Chem. Soc.*, 1949, **71**, 2773; cf. Seyer, *ibid.*, 1953, **75**, 616.

[16] Beckett, Pitzer, and Spitzer, *ibid.*, 1947, **69**, 2488.

[17] Winstein and Holness, *ibid.*, 1955, **77**, 5562; Turner, *ibid.*, 1952, **74**, 2118.

two associated 1 : 3-H : Me interactions), 5·4 kcal./mole; [16] for each half-boat ring, 2·7 kcal./mole.[18]

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[18] Beckett, Freeman, and Pitzer, *J. Amer. Chem. Soc.*, 1948, **70**, 4227.