Tetrahedron, 1963, Vol. 19, pp. 2123 to 2133. Pergamon Press Ltd. Printed in Northern Ireland

CONFORMATIONAL STUDIES—I*

CONFORMATIONAL TRANSMISSION

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(*Received* 21 *June* 1963)

Abstract—A semi-qualitative approach to the interpretation of the factors effecting conformational transmission is described.

OUR interest in the correlation of subtle conformational effects in cyclohexanones[1] and cyclohexenones[2] with optical rotatory dispersion data has lead us to examine the conformational effects responsible for variations in the rate of condensation of triterpenoid and steroid 3-ones with benzaldehyde to furnish derivatives of type (I).[3–5]

The work of Barton *et al.*[3–5] has provided extensive kinetic data for various ketones and has elegantly and conclusively demonstrated that the differences in rates (using lanost-8-en-3-one = 100 as an arbitrary standard (arise principally from conformational distortion produced by unsaturated substituents rather than by the operation of polar or inductive effects. This effect has been described as "conformational transmission". We now present two mutually complementary methods of approach which provide a semi-qualitative interpretation of the experimental data, a pertinent selection of which is summarised in Table 1.

The mechanism of benzylidene formation has been established[6,7] as follows:

$$—CH_2—CO— + OH^- \rightleftharpoons —C\bar{H}\cdot CO + H_2O \qquad \text{(i, ii)}$$

$$—\bar{C}H—CO— + PhCHO \rightleftharpoons PhCH(O^-—)CH—CO— \qquad \text{(iii, iv)}$$

$$PhCH(—O^-)CH\cdot CO— + H_2O \rightleftharpoons PhCH(OH)—CH\cdot CO— + OH— \qquad \text{(v, vi)}$$

$$PhCH(OH)\cdot CH—CO— + OH^- \rightleftharpoons PhCH(OH)\cdot\bar{C}—CO— + H_2O \qquad \text{(vii, viii)}$$

$$PhCH(OH)C^-—CO— \rightarrow PhCH{=}C—CO— + OH^- \qquad \text{(ix)}$$

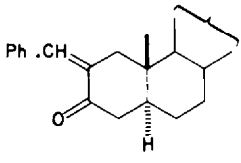
* This work was reported in part at the I.U.P.A.C. Symposium on Natural Product Chemistry held in Brussels from June 12–15, 1962.

[1] J. S. E. Holker and W. B. Whalley, *Proc. Chem. Soc.* 464 (1961).
[2] W. B. Whalley, *Chem. & Ind.* 1024 (1962).
[3] D. H. R. Barton, A. J. Head and P. J. May, *J. Chem. Soc.* 935 (1957).
[4] D. H. R. Barton, The Kekulé Symposium, Theoretical Organic Chemistry p. 127. Butterworths, London (1959).
[5] D. H. R. Barton, F. McCapra, P. J. May and F. Thudium, *J. Chem. Soc.* 1297 (1960).
[6] D. S. Noyce and W. L. Reed, *J. Amer. Chem. Soc.* **81**, 624 (1959).
[7] M. Stiles, D. Wolf and G. V. Hudson, *J. Amer. Chem. Soc.* **81**, 628 (1959).

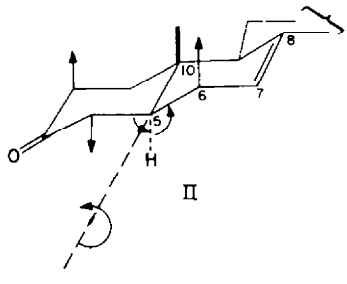
TABLE 1

Compound	Rate
1. Cholestanone	182
2. Cholest-6-enone	645
3. Cholest-7-enone	43
4. Ergosta-8,22-dien-3-one	280
5. 9(11)-Dehydrotigogenone	221
6. 11(12)-Dehydrotigogenone	380
7. 7-Methylenecholestanone	365
8. Cholestan-3,7-dione	615
9. Ergost-8(14)-en-3-one	94
10. 10-Methyl-Δ^6-*trans*-2-octalone	56
11. Tigogenone	174
12. Hecogenone	328
13. Lanostanone	55
14. Lanost-7-enone	17
15. Lanost-8-enone	100
16. Lanost-9(11)-enone	73
17. α-Onoceradiendione	117

The irreversible step (ix) is the rate controlling reaction. Hence it may be anticipated that any factor which favours the formation of a trigonal atom at C(2), or the geometrically similar 3-oxo-2-methylene derivative (I) will increase the reaction rate at C(2) and conversely. If it be correct that the different rates of reaction with benzaldehyde are due very largely, if not entirely, to conformational transmission of angle strain, it should be possible to make qualitative interpretations and predictions by comparing the difference in strain between a ketone and the corresponding transition state. In most ketones the 2,3-doubly bonded compound, i.e. the Δ^2-enol, or the equivalent enolate anion which is mesomeric with the corresponding carbanion, appears to be as satisfactory a model for the transition state as the 2-methylene-3-oxo-derivative (I). Since the mathematical treatment of even very simple systems, such as Δ^1- and Δ^2-*trans*-octalins[8] presents severe difficulties, it appears necessary and even desirable to interpret the available data in terms of strain effects which may be discerned in models (we have used Dreiding models), or inferred for polycyclic systems from the shape of very simple cyclohexane derivatives whose geometry may be calculated with accuracy.[8]

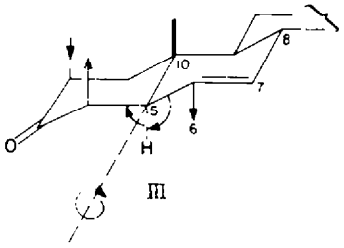


I

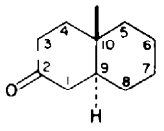


II

[8] E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.* **77**, 2505 (1955).



III



IV

In the first method we have compared strained and unstrained systems and it may be illustrated by reference to two examples. Thus, in a Δ^7-3-oxo-steroid comparison with the saturated 3-oxo-5α-steroid clearly shows that C(6) is displaced upwards i.e. in a β-direction (cf. II) by the distorting influence of the 7,8 bond. This distortion is relayed to the C(6), C(5), C(5) hydrogen angle which is expanded with the subsequent introduction of angle strain at this point. This strain is compensated, in part, by an increase in the C(4), C(5), (C5) hydrogen angle. This in turn is relayed to C(4) which is moved downwards (i.e. in an α-direction). It should be emphasised that when C(4) is displaced *downwards*, transmission of the strain across the carbonyl group simultaneously displaces C(2) *upwards* and *vice versa*. The sequence of strains initated by the 7:8-double bond and the directions in which they are exerted can be conveniently represented by arrows as in (II), and may effectively be reduced by the conversion of C(4) into trigonal atom. The formation of the Δ^4-enol is thus facilitated and the reaction rate at C(4) increased. Simultaneously the tendency for Δ^2-enol formation and condensation at C(2) is correspondingly diminished. Although the 7,8 bond favours enolisation towards C(4), condensation at a reduced rate (in accord with our prediction), occurs at C(2) (cf. examples 3 and 1 in Table 1). The explanation for the exclusive production of the C(2)-benzylidene derivative, even under conditions which facilitate formation of the Δ^4-enol has been given by Barton[5] and we concur.

Movement of the double bond to the 6:7-position reverses the effect upon ring A (cf. III). Here the tendency is to displace C(2) downwards, i.e. to aid the formation of the Δ^2-enol and hence to increase the speed of reaction at C(2) (cf. examples 2 and 1 in Table 1). Similar considerations apply, though with increasing difficulty of interpretation, to other positions of the double bond. However, it is clear that as this bond is moved around ring B, positive (i.e. activating) angle strain is alternately transmitted to C(2) and C(4) in agreement with the alternating exaltation and depression of the observed rates of condensation (cf. examples 2, 3 and 4 in Table 1). The insertion of a trigonal atom (carbonyl or methylene) at C(7) in a 3-oxo-steroid stimulates a sequence of angle displacements similar to that produced by the 6:7-bond: thus the effects of the trigonal atom at C(7) and of the 6:7-bond are similar—they displace C(6) *downwards* and increase the rate of reaction at C(2) (cf. examples 2, 7 and 8 in Table 1). As the trigonal atom is moved around ring B an alternating rise and fall in the rate of condensation similar to that produced by movement of the double bond around ring B, should be produced, although strain effects due to rings C and D will modify the effects of 8(14) and 9(11) double bonds. Experimental results (cf. examples 14, 15 and 16 and 7, 9 and 5 in Table 1) are in agreement with this prediction. This alternating effect of a trigonal atom in ring B of a steroid should *not* be produced in a 2-decalone (IV) since in this system the effects upon ring A

of such substituents at C(5) and C(8) are equivalent. Similarly *exo*cyclic double bonds at the C(6) and C(7) positions are equivalent.

In addition to distortion of bond angles the 7:8 double bond produces an anti-clockwise rotation, about the C(5)–C(10) axis, of the groups attached to C(5) and C(10) (cf. II). The 6:7- and 8:9-double bonds [and the trigonal atom at C(7)] rotate these groups in a clockwise direction about the same axis (cf. III). This rotation of substituents about the C(5)–C(10) axis is a significant factor in both our methods of approach to the problem and emphasizes their general correspondence (see later). Examination of the geometry of the 3-oxo-5α-steroid system clearly shows that changes in angle strain at C(2) and C(4) are inseparably associated with this rotation about the C(5)–C(10) axis. Thus when the substituents at C(5) and C(10) are rotated about the C(5)–C(10) axis in a clockwise direction (cf. III), relative to the positions occupied by these substituents in any arbitrary reference compound an enhanced rate of condensation at C(2) with respect to that reference compound should occur and conversely.

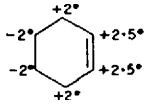
In the second and more quantitative method of approach we treat the steroids and triterpenoids as decalin derivatives, as a first approximation; the decalin moiety containing rings A and B is then derived by the hypothetical fusion of the appropriate pair of monocyclic cyclohexane derivatives. The primary assumption is that the strain in the bicyclic system may be estimated from the strain in the two isolated, component rings *together with the strain resulting from the more or less conflicting demands made by the two rings on the common bridge head atoms*, i.e. C(5) and C(10) (steroid numbering). This additional strain may conveniently be called "the degree of misfit". Since the basic premise is that variation in chemical reactivity, as measured by the formation of benzylidene derivatives, is due to transmitted strain it is obvious that this division of the strain can only be a rough approximation. A further simplification is to postpone consideration of 4:4-dimethyl compounds because of complications introduced by the additional non-bonded interactions.[1,9]

To the extent that it is justifiable to apportion the strain, the *change* in strain between a ketone and the transition state is constant for a hypothetically isolated A-ring; the strain is constant for the B-ring. Estimating the energy differences between the various possible ways of combining rings A and B therefore reduces to estimating the changes in strain due to the varying degrees of "misfit" for the bridgehead atoms [i.e. C(5) and C(10)].

If the normal state of the tetrahedral bridgehead atoms is that with unstrained angles and perfectly staggered substituents (i.e. adopting *trans*-decalin with regular tetrahedral angles at all carbon atoms as the standard), then the strain imposed by the A- and B-rings may be divided into (a) bending of the equatorial bonds in the plane of each ring (in-plane bending) and (b) out-of plane bending, the effect of which is to twist the substituents attached to C(5) and C(10) away from the perfectly staggered arrangement about the C(5)–(C10) bond (cf. page 2126). This division of strain into two types immediately leads to two predictions concerning *cis*-fused compounds. Firstly, out-of-plane bending of small distortions should have equal but opposite effects in *cis*- and *trans*-fused systems. Secondly, in-plane bending should be about half as important in *cis*-fused compounds because each ring uses only *one* equatorial

[9] cf. E. L. Eliel, *The Stereochemistry of Carbon Compounds* p. 291. McGraw-Hill, New York (1962).

bond of the other and axial bonds should be relatively unaffected by in-plane distortion. It would be surprising if these simple relationships were valid for larger distortions in e.g. hydrindan-5-ones, but it is noteworthy that a variety of evidence, which will be discussed in detail elsewhere,[10] suggests that the orientation of enolisation of *cis*-2-decalone derivatives is less sensitive to transmitted strain. In *cis*-2-decalones there may be complications occasioned by changes in skew interactions when benzylidene groups are introduced at C(1) or C(3). Probably allowance should also be made for conformational equilibria in this series.



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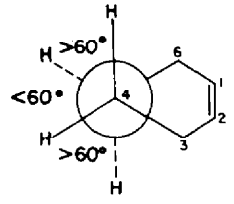
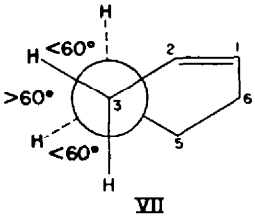


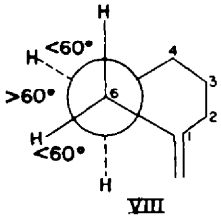
VI

Newman projection along C(4)–C(5) axis in cyclohexene.



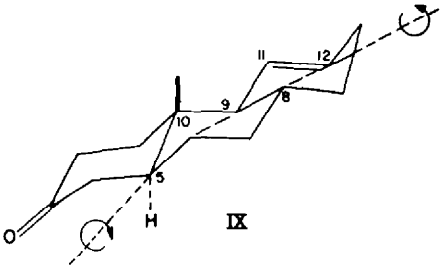
VII

Newman projection along C(3)–C(4) axis in cyclohexene

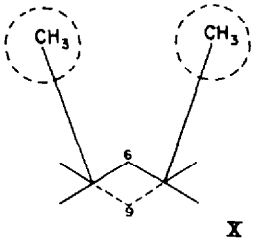


VIII

Newman projection along C(5)–C(6) axis in cyclohexylidene



IX



X

The relevant aspects, (V, VI and VII) of the geometry of cyclohexane and of the cyclohexylidene group (VIII) are emphasized in the diagrams. In the half-chair conformation of cyclohexene the bond angles are distorted from the tetrahedral values by the amounts indicated in V (rounded figures derived from Corey and Sneen[8]). Further the methylene-methylene single bonds are not perfectly staggered. In a distorted half-chair conformation (approaching the "sofa" form[11] in which five of the carbon atoms are co-planar), two of these single bonds become more or less

[10] M. J. T. Robinson, (unpublished work).

[11] cf. E. M. Philbin and T. S. Wheeler, *Proc. Chem. Soc.* 167 (1958).

completely staggered, at the cost of a slight increase in angle strain and increased eclipsing in the remaining methylene-methylene bond. This flexibility of cyclohexene (and of cyclohexenones[2]), in contrast to cyclohexane and the cyclohexylidene residue, is not apparent from Corey and Sneen's work,[8] but is immediately obvious from accurate models. We may predict, therefore, that strain resulting from out-of-plane distortion will be small if a singly fused cyclohexene ring is involved, but it will be much larger when two rings, each requiring more or less completely staggered ring junctions, are fused to a cyclohexene ring as in a Δ^6-steroid (e.g. cholest-6-en-3-one). An intermediate amount of strain would be expected in a Δ^7-steroid, where the cyclohexylidene type ring C restricts the flexibility of ring B, and in fact a Δ^7-steroid is less reactive than the analogous Δ^6-2-octalone, (cf. examples 3 and 10 in Tables 1).

Quantitatively the differences in out-of-plane distortion for the methylene-methylene bonds in cyclohexene (VI and VII) and cyclohexylidene (VIII), quite apart from differences in flexibility, are probably inaccurate since they depend upon the assumption of regular tetrahedral bond angles for Sp^3-hybridized carbon atoms and this is known to be incorrect.[12] We regard these estimates of distortion, therefore, as qualitatively valid only. Examples of out-of-plane distortion leading to strain may be found in 3,7-dioxo-steroids, 3-oxo-7-methylene-steroids and α-onoceradiendione, (examples 8, 7 and 17 in Table 1). This strain is decreased in the Δ^2-enols (or 2-methylene-3-oxo-derivatives) and so this strain is generally activating (cf. Table 1). The activating effect of *exo*cyclic double bonds at C(7) in a steroid and in α-onoceradiendione indicate that the out-of-plane distortion for C(3)–C(4) [or C(4)–C(5)] in cyclohexylidene is significant and *negative* (see below): this is readily apparent only from an inspection of a Dreiding model of the *whole* steroid molecule, when the rotation of the substituents, attached to C(5) and C(10), about the C(5)–C(10) axis is easily appreciated. The $\Delta^{8(14)}$-steroids, which react more slowly than the saturated analogues, are not comparable with α-onoceradiendione because of the very important strain effects due to the C- and D-rings (see later).

Cholest-6-en-3-one is particularly interesting since it is clear from models that much of the distortion occurs in the A-ring because the doubly-fused B-ring is very rigid, unlike the analogous Δ^7-octal-2-one, which may be expected to be as reactive as Δ^5-octal-2-one. This predicted strain in the A-ring of cholest-6-en-3-one is in complete agreement with (a) its thermodynamic instability,[8] (b) the anomalous O.R.D. curve[13] and (c) the high rate of condensation with benzaldehyde[5] (Table 1). It may further be noted that the strain on the A-ring in a 3,7-dioxosteroid is in the same sense as that in the 3-keto-6-en steroids (examples 8 and 2 respectively in Table 1). This is in keeping with activation at C(2) in each case. The quantitative similarity of the strain is apparent in the comparable high reaction rate (Table 1). Further, since the $\Delta^{2:6}$-steroid system is geometrically equivalent to the $\Delta^{3:7}$-system (cf. Batron *et al.*[5]), the enhanced reactivity at C(2) with the 3-keto-6-en-steroids is in complete agreement with the diminished reactivity at C(2) in 3-keto-7-en-steroids. Even the magnitudes of differences of reactivity are in good agreement. Thus:

$$\frac{\text{The rate for cholest-6-en-3-one}}{\text{The rate for cholestan-3-one}} = 645/180 - 3{\cdot}6$$

[12] R. A. Bonham and L. S. Bartell, *J. Amer. Chem. Soc.* **81**, 3491 (1959).

[13] F. Sondheimer, Y. Klibansky, Y. M. Y. Haddad, G. H. R. Summers and W. Klyne, *Chem. & Ind.* 902 (1960).

Since cholest-7-en-3-one reacts more slowly than cholestan-3-one the appropriate ratio in this case is the *reciprocal* of the rate for cholest-7-en-3-one/the rate for cholestan 3-one

$$\text{i.e. } \frac{1}{43/180} = 4{\cdot}1.$$

The double bond in a Δ^{11}-steroid is in many ways analogous to that in a Δ^{6}-steroid, but being further from the A-ring, the magnitude of its activating effect is perhaps more remarkable. It may be appreciated, however, from the following considerations. The B/C ring system of the Δ^{11}-steroid is approximately, geometrically equivalent to the A/B system in the Δ^{6}-steroid, and hence the 11:12-bond causes rotation of the substituents attached to C(8) and C(9) about the C(8)–C(9) axis. This rotation is in an *anti-clockwise* direction, when viewed from the β-face of the molecules as in (IX). The comparative rigidity of the saturated B-ring transmits this torsional strain to the C(5)–C(10) axis with consequent rotation of the C(5) and C(10) substituents in a *clockwise* direction (viewed as in IX) with its concomitant activation at C(2). Models clearly illustrate the interdependence of the torsional strains about C(5)–C(10) and C(8)–C(9), which can only be coupled in the sense indicated.* An extension of these considerations shows that since C(7) is geometrically equivalent (for this purpose) to C(12), a trigonal atom at C(12) should activate C(2). This is in agreement with experimental facts (cf. examples 11 and 12; Table 1). Likewise C(6) is geometrically equivalent to C(11): interpretation of the C(11) trigonal atom situation is however complicated by interaction of the C(11) substituent with the C(1) β-hydrogen. The interdependence of the torsional angles about C(8)–C(9) and C(13)–C(14) associated with the flexibility of cyclohexene should make a Δ^{11}-C-ring, in contrast to its saturated analogue, effective as a transmitter of strain from the D-ring. A similar transmission of strain may be expected when the C-ring is in a boat conformation. We may predict, therefore, that whilst an 11,12-double bond will cause substantial transmission of the strain resulting from substitution in the D-ring, the transmitted strain will be much less in the analogously substituted D-homosteroid. For this reason a comparison of e.g. the Δ^{11}-3,16- and Δ^{11}-3,17-diones with their saturated analogues would be interesting.

In order to make qualitative predictions it is necessary to have at least semi-quantitative parameters indicative of the relative importance of each type of strain. The following numerical values appear to be satisfactory. The in-plane distortions in cyclohexene are arbitrarily put equal to $+1$ and -1 units for the allylic and homoallylic methylenes respectively (the angles being respectively greater than and less than the normal tetrahedral angles by equal amounts cf. V), and are zero for cyclohexane and the cyclohexylidene residue. The out-of-plane distortions, taken to be positive for axial bonds bent *into* the ring and *vice versa*, are taken as zero for cyclohexane; -1 for the 2,3(5,6)- and 3,4(4,5)-bonds in the cyclohexylidene group:

* If ring B were completely rigid all the strain initiated in ring C would be transmitted to ring A and the predicted increase in strain energy in the Δ^{5}-enol would be the same for Δ^{6}- and Δ^{11}-steroids, and hence the reaction rates would be similar. However, the "flexing" of ring B undoubtedly absorbs some of the strain produced in ring C: this is reflected in the decreased rate of reaction of e.g. 11(12)-dehydrotigogenone (380)[6] compared with cholest-6-en-3-one (645).[5] Similarly the rate for 12-methylene tigogenone (218)[6] is less than that for the geometrically equivalent 7-methylene cholestanone (365).[5]

and −2 and +2 for the 3,4(5,6)- and 4,5-bonds respectively in cyclohexene, before allowing for flexibility. Since the flexibility of the cyclohexene ring is assocated with changes in the allylic and homoallylic bond angles, its effect will vary with the in-plane distortions present. When the in-plane distortions are small, e.g. in a Δ^2-7-methylenesteroid, or equal, e.g. in 1,4,5,8,9,10-hexahydronaphthalene, the flexibility of each cyclohexene ring is considered to reduce the magnitude of the out-of-plane strain by 1 unit. Because the C-ring restricts the flexibility of the B-ring no similar allowance is made for the B-ring in a Δ^7-steroid. Since flexibility alters the bond angles in opposite ways at C(5) and C(10) (steroid numbering) it will not have much resultant effect if the in-plane distortions are similar. When the in-plane strains are very different in magnitude and the flexibility of a cyclohexene ring can decrease the larger strain at the expense of the smaller, thereby reducting the strain *energy*, the effect of flexibility should be large, but there are no examples of this.

The total additional strain energy due to "misfit" is proportional to the sum of the *squares* of the total strains for in-plane distortions at C(5) and at C(10), and for out-of-plane distortions about the C(5)–C(10) bond. The results of this simple calculation for a variety of systems are set out in Table 2 and plotted against the logarithms

TABLE 2

Unsaturated group	Strain in ketone			Total strain energy in ketone	Strain in Δ^2-enol			Total strain energy in enol	Increase in strain energy in enol
	In-plane C(5)	In-plane C(10)	Out-of-plane C(5)–C(10)		In-plane C(5)	In-plane C(10)	Out-of-plane C(5)–C(10)		
Saturated 3-oxosteroid	0	0	−1	1	+1	+1	+1	3	+2
Δ^5-Steroid*	0	+1	0	1	−1	0	0	1	0
Δ^6-Steroid	+1	−1	−3	11	0	−2	0	4	−7
Δ^7-Steroid	−1	−1	+1	3	−2	−2	−3	17	+14
$\Delta^{8(9)}$-Steroid	−1	−1	−2	6	−2	0	0	4	−2
$\Delta^{9(11)}$-Steroid	0	0	−2	4	−1	−1	0	2	−2
Δ^6-Decalinoid	−1	−1	0	2	−2	−2	+2	12	+10
5,6†,7,8 Methylene-decalinoid	0	0	−2	4	−1	−1	0	2	−2
7-Methylene-steroid	0	0	−2	4	−1	−1	0	2	−2

* No data are available for 3-oxo-Δ^5-steroids, but in the 4:4-dimethyl series the rates of e.g. 17β-hydroxy-4:4-dimethylandrostan-3-one (58)[5] and 17β-hydroxy-4:4-dimethylandrost-5-en-3-one (57)[5] are in good agreement with prediction.

† As in α-onoceradiendione.

of "group rate factors"[5], based on cholestan-3-one as the standard, in Fig. 1. The latter shows that an approximately linear relationship exists between the "calculated" differences in strain energy and the reactivities of the selected ketones. (N.B. If the group rate factor be converted to ΔF values in k cal/mole then there would be a simple conversion factor of 12 strain energy units = 1 k cal/mole).

In principle this approach could be extended to molecules containing two or more substituents. The simplest assumption would then be to take the strains as additive for each substituent. It is obvious that this apparently conflicts with Barton's concept[5] of group rate factors, which implies additivity of strain energies. However,

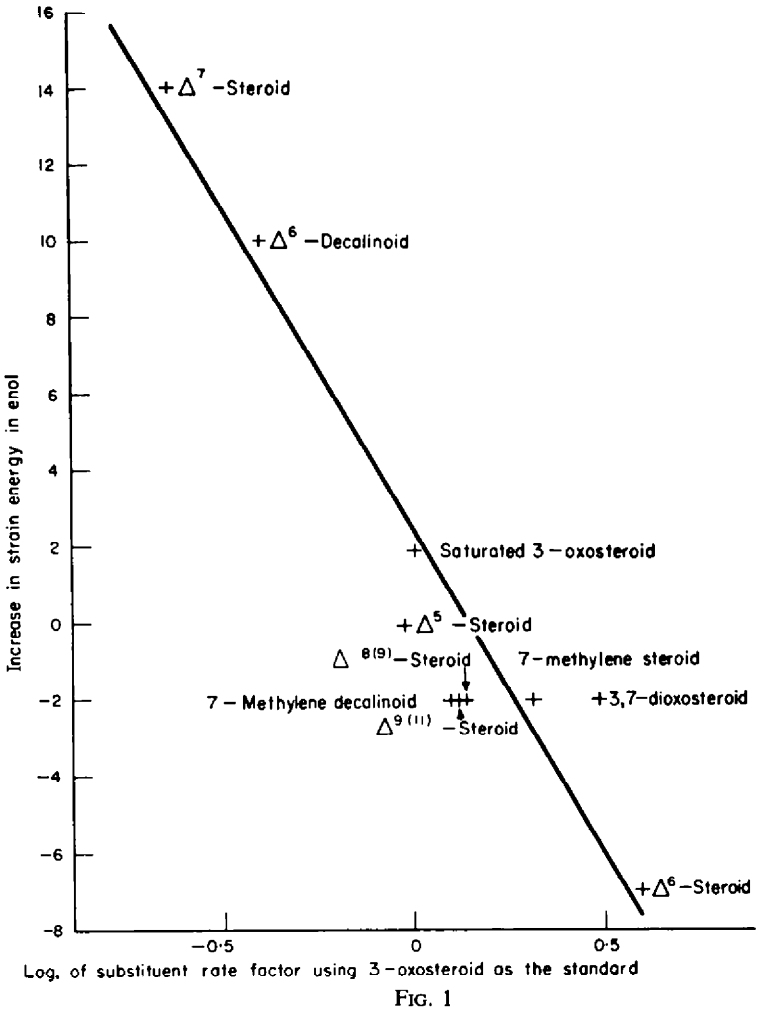


FIG. 1

examination of selected examples shows that the quantitative difference between additivity of strains and of strain energies is often not very large and may be of either sign, and could be obscured by the errors introduced by assuming additivity.

In the 2-decalones this approach predicts a quantitative similarity in the effects of Δ^5- and Δ^7-double bonds, of 5- and 8-methylene groups and of 6- and 7-methylene groups (cf. page 2128). These effects are modified in the steroids by the additional rings. The influence of ring C is reasonably straight forward only for steroids with tetrahedral atoms at C(8) and C(9) since the C-ring may then be treated as making the B-ring more rigid (a very simplified picture). The effects of this ring on the rigidity of ring B are apparent from the enhanced rates of reaction of steroids compared with

appropriate decalones. Unfortunately there are no kinetic data available for $\Delta^{8:9}$-steroids with substituents in the C-ring, since an 8,9-double bond should effectively insulate the A/B ring system from the remainder of the molecule and cause a breakdown in the generally approximate additivity of the logarithms of "group rate" factors. The effect of the C- and D-rings in Δ^{7}- and $\Delta^{8(14)}$-steroids is complicated. By limiting the flexibility of the BC-system in the former, and increasing its buckling in the latter the CD- and D-rings should increase out-of plane distortions. Since the A-ring exhibits greater flexibility when existing as the Δ^{2}-enol rather than the corresponding ketone, the enol should be more stable than the ketone. Models show, however, that considerable angle strain pulls C(11) towards the D-ring. This makes the in-plane distortions more negative at C(10). The effect, therefore, is greater on the *enols* than on the ketones because the negative in-plane distortion at C(10) is already larger for the enol than in the decalin series. In both the Δ^{7}- and $\Delta^{8(14)}$-steroids it appears that changes of in-plane distortions (deactivating) are more important than the increased out-of-plane distortions (activating). At present the relative importance of these two effects is unpredictable.

The influence of the C(10) methyl group and of 4:4-dimethyl substitution is now considered. The available data are limited but three separate categories are recognizable.

(i) *The* C(10) *methyl effect.* The effect of replacing a C(10) methyl substituent in a 3-oxo-steroid or a 2-decalone by a hydrogen atom is to *reduce* the rate of reaction.[4] Thus *trans*-2-decalone has a rate of 35 whilst the 10-methyl analogue has a rate of 148.[4] Ring A in a *trans*-3-oxo-steroid approximates most closely to the perfect chair conformation when all the axial substituents, including the C_{10} substituent, are hydrogen, e.g. 3-oxo-19-nordihydrotestosterone. Then the factors conducive to enol formation are reduced to a minimum and reaction rate will be smallest. In the C(10) methyl derivatives the C(2)β-hydrogen-C(10)methyl and the C(4)β-hydrogen-C(10) methyl interactions will introduce angle strain—particularly at C(2), together with the associated clockwise rotation of the C(5) and C(10) substituents about the C(5)–C(10) axis, away from the fully staggered conformation. This strain is largely removed when C(2) becomes trigonal and hence the substitution of a C(10) hydrogen by a methyl residue *increases* the rate of condensation.

(ii) *The* 4:4-*dimethyl effect in steroids.* It now seems reasonably certain that non-bonded interactions in 3-oxo-4:4-dimethylsteroids produce conformational changes in ring A which result in atoms 1, 2, 3, 4 and 5 being more nearly co-planar than in the parent 3-oxo-steroid.[1,9,14] In this conformation the shape of the A-ring approximates more closely to that of the 2-methylene-3-oxosteroid. Consequently the driving force for benzylidene formation is smaller than in the original chair conformation; i.e. the 4:4-dimethyl substituents *decrease* the reaction rate.

(iii) *Tetra- and penta-cyclic triterpenes.* In addition to the 4:4-dimethyl residue the 3-oxo-tetra- and penta-cyclic triterpenes have a C(8)β-methyl group which produces 1:3-non-bonded interactions with the C(10)β-methyl substituent. The usually accepted van der Waals radius of the methyl group is 2·0 Å. But Braude and Sondheimer[15] have shown that in problems of steric interaction a more appropriate value is 1·7 Å. Thus in the 1:3-non-bonded interaction of two axial methyl groups in a cyclohexane ring the substituent bonds must be displaced laterally from the ideal, parallel positions by about 15° (compare Sandris and Ourisson[16]) as in X. X-ray

diffraction studies[17] with the iodoacetate of lanost-8-en-3β-ol have conclusively established the reality of this displacement for the C(4)β- and C(10)-methyl groups. The lateral displacement of the C(8)β- and C(10)β-methyl substituents in a tetra- or penta-cyclic triterpene flattens ring B and produces a clockwise rotation about the C(5)–C(10) axis of substituents at C(5) and C(10). It thus seems likely that the de-activation of the 4:4-dimethyl residue is partially reversed by the imposition of some activation at C(2) caused by the clockwise rotation of the substituents at C(5) and C(10) under the influence of the C(10)-methyl, C(8)-methyl interaction.

Finally, it is apparent from this discussion of conformational transmission and from the general nature of the relationship between O.R.D. and conformation that the two effects are in *general* entirely separate. No overall correlation between the sign of the O.R.D. curve and rates of reaction is to be expected.

Experimental investigation of the consequences arising from these concepts are in progress.

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