15. *Macrocyclic Compounds. Part III.*[1] *Conformations of Cycloalkanes and Other Flexible Macrocycles.*

By JOHANNES DALE.

A simple modification of ordinary space-filling molecular models to permit only the construction of molecules with staggered single bonds has proved valuable in selecting those conformations of macrocyclic hydrocarbons which are completely strain-free and therefore assumed to be preferred; such conformations are only possible for even-membered rings with 14 or more carbon atoms. Conformations of medium-sized strained rings are also discussed. Replacement of a $>CH_2$ group by –O–, –NH–, $>C=O$, etc., does not disturb the conformation of the ring skeleton, whereas multiple bonds in the ring drastically change the geometry. On this basis, variations in ease of formation, stability, and melting point (or sometimes transition point) are explained for cycloalkanes, cyclic ketones, alcohols, acyloins, imines, lactones, polyesters, lactams, polyamides, anhydrides, olefins, acetylenes, etc.

IN Part I [2] conformational considerations were used to explain the variation in melting points and in ease of formation of macrocyclic poly-ynes. The best strain-free conformations were relatively easily found in that series because the acetylenic (or conjugated poly-yne) systems with its two neighbouring saturated carbon atoms have to lie on a straight line, whereby large parts of the ring system are fixed unambiguously.

Many other series of macrocyclic compounds show a variation in melting point with ring size, although this is in general less regular and less pronounced than the strong alternation found in the cyclic diyne and tetrayne series. The most complete, and theoretically most interesting, is the cycloalkane series. With our recent syntheses of the C_{19}- and C_{25}-ring described in the preceding papers [1,2] this series is complete up to C_{30}. Accurate *X*-ray determinations of the conformations of rings larger than cyclohexane have been carried out recently by Dunitz and his co-workers, for cyclododecane [3]

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[1] Part II, preceding paper.

[2] Part I, Dale, Hubert, and King, *J.*, 1963, 73.

[3] Dunitz and Shearer, *Helv. Chim. Acta*, 1960, **43**, 18.

with the solid hydrocarbon, for cyclodecane[4] and cyclononane[5] with solid derivatives. Their results demonstrate the insufficiency of ordinary molecular models with free rotation about single bonds.[6] The surprisingly high energy barrier for internal rotation in ethane and its derivatives is well established,[7] although not yet adequately explained theoretically, and all commonly used models are therefore seriously unrealistic. For cyclododecane, for example, a variety of molecular models without angle strain (Baeyer strain) can be constructed, yet the real molecule[3] is so shaped as to avoid as much torsional strain (Pitzer strain) as possible, all bonds being roughly staggered (±8—25°) with acceptance of some angle strain by opening of certain CCC angles (from 109° to 117°). Another illustration is the ease of rearrangement of the highly Pitzer-strained perhydrogenated cyclopentadiene dimer into the strain-free adamantane.[8]

In consequence we have slightly changed ordinary space-filling Stuart–Briegleb–Leybold models by drilling three holes on one surface and placing one pin on a second surface, so that single bonds can be constructed only in the three staggered positions (Fig. 1a). Admittedly, such models represent an extreme, but have a better balance of Baeyer and Pitzer strain: the resistance to opening of CCC angles as well as to torsion around bonds is exaggerated. However, these properties make models of this type useful for selecting those conformations (rather few as it turns out) of big rings which are completely strain-free and therefore can be reasonably assumed to be preferred. For example, Fig. 1b shows the only conformation for cyclotetradecane which can be constructed with these modified models; in addition to being strain-free, it is also compact and centrosymmetric. Perspective drawings of the possible conformations up to $(CH_2)_{18}$ * are shown in Figs. 2—4 and schematic drawings of the best possibilities up to $(CH_2)_{30}$ in Fig. 5. For medium-sized rings, models are also included in which the carbon skeleton is strain-free, but which have to be deformed to make room for some of the hydrogen atoms. In absence of models, an easy aid in drawing and deducing the possible conformations is to trace them off a good perspective drawing of the diamond lattice; a similar device has been used by Natta and Corradini[9] to derive strain-free helical conformations of polymer chains. To judge van der Waals distances, it can be assumed that if two CH bonds meet

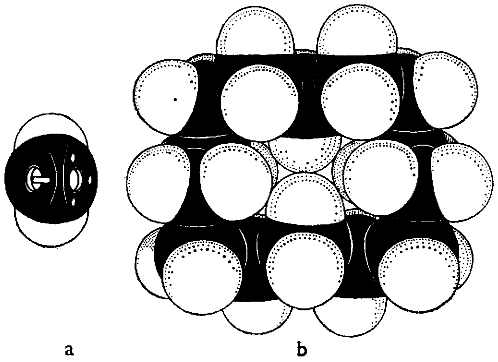

FIG. 1. Molecular models without Pitzer strain: (a) CH_2 group showing positions of pin and three holes; (b) the only possible model of cyclotetradecane.

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* In this paper we use parentheses to denote cyclo-derivatives; *e.g.*, $(CH_2)_{18}$ denotes cyclo-octadecane, in place of the more conventional $\lfloor[CH_2]_{18}\rfloor$.

[4] Huber-Buser and Dunitz, *Helv. Chim. Acta*, 1960, **43**, 760; 1961, **44**, 2027; Dunitz and Venkatesan, *ibid.*, p. 2033; Huber-Buser, Dunitz, and Venkatesan, *Proc. Chem. Soc.*, 1961, 463.
[5] Bryan and Dunitz, *Helv. Chim. Acta*, 1960, **43**, 3.
[6] Prelog, *Bull. Soc. chim. France*, 1960, 1433; Dunitz and Prelog, *Angew. Chem.*, 1960, **72**, 896.
[7] Wilson, *Proc. Nat. Acad. Sci. U.S.A.*, 1957, **43**, 816; Pauling, *ibid.*, 1958, **44**, 211; Eyring, Stewart, and Smith, *ibid.*, p. 259.
[8] Schleyer and Nicholas, *Tetrahedron Letters*, 1961, 305, and references cited therein.
[9] Natta and Corradini, *Nuovo cim.*, *Suppl.*, 1960, **15**, 9.

in one point when stretched to a full C–C distance, they are too close and strain is set up.

The first important conclusion is that strain-free conformations are impossible for any cycloalkane having an odd number of ring atoms. The second is that no ring size between cyclohexane and cyclotetradecane can have a strain-free conformation. A typical feature for the lower macrocycles is that there are four " corners," each consisting of one carbon atom, which is unique in that it can always carry two substituents, adjoined by two *gauche* bonds; the remaining carbon atoms have in general no room for an interior substituent, and the remaining bonds are all *trans.* For some larger rings, there may be conformations with six " corners; " each of these corners is made up of two *gauche*-linked carbon atoms, and the remaining bonds are *trans.** As to the relative probability of the various conformations deduced for one particular macrocyclic alkane, there may exist an additional factor which favours the most compact conformations over those with a large hole in the interior. It is evident that those which consist effectively of two parallel straight chains linked by two bridges of minimum length fill space most efficiently. Further, it is known that some more complex nitrogen-containing macrocyclic compounds, which probably have to form a hole in their most stable conformation, cocrystallize with solvent molecules trapped in the interior.[10-13] These occluded molecules are very firmly held, and, when they are removed, the host molecule often becomes amorphous or liquid [12] and sometimes even loses chemical stability; [10] the reason may be that the molecule collapses in order to fill space, whereby it has to adopt a strained conformation. Whether this " *horror vacui* " principle is of sufficient importance in cycloalkanes to favour the compact but strained conformations indicated by dotted lines in Fig. 5, and drawn in

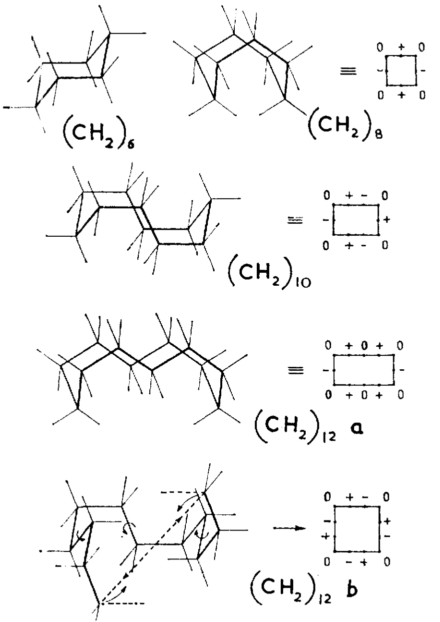

FIG. 2. Conformations of even-membered cycloalkanes, C_6 to C_{12}.

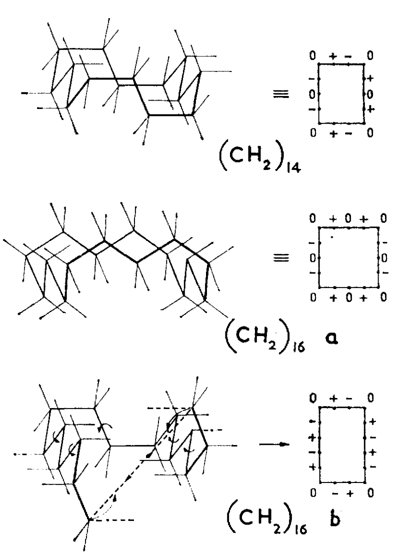

FIG. 3. Conformations of cyclotetradecane and cyclohexadecane.

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* If additional *gauche* bonds are accepted there exist, from C_{20} and upwards, some further possibilities not given in Fig. 5.

[10] Stetter and Roos, *Chem. Ber.*, 1955, **88**, 1390.

[11] Huisgen, Ugi, Rauenbusch, Vossius, and Oertel, *Chem. Ber.*, 1957, **90**, 1946.

[12] Zahn and Spoor, *Chem. Ber.*, 1959, **92**, 1375.

[13] Faust and Pallas, *J. prakt. Chem.*, 1960, **11**, 146.

Fig. 3b for cyclohexadecane, in preference to the less compact unstrained conformations, cannot yet be decided.

Before we discuss in detail the implications for the interpretation of physical properties and ease of formation, the conformational effects of modifying the skeleton by introducing heteroatoms and multiple bonds will be treated. Simple substituents would not be expected to influence the conformation of the ring itself, except by their bulk. If a CH_2 group is replaced by NH or O, the skeleton type should also remain the same, but since some hydrogen atoms are thereby eliminated a proper disposition of one or more such groups may reduce or eliminate the repulsive strain present in 8- to 12-membered cycloalkanes. In higher members the preferred positions should be next to the corner atoms (in " rectangular " conformations), as thereby the two unfavourable *gauche*-oriented dialkyl-substituted C–C bonds become replaced by a C–N or C–O bond and an alkyl-imino- or alkyl-alkoxy-substituted C–C bond, which both accept more readily (and perhaps even prefer) a *gauche*-orientation.[14]

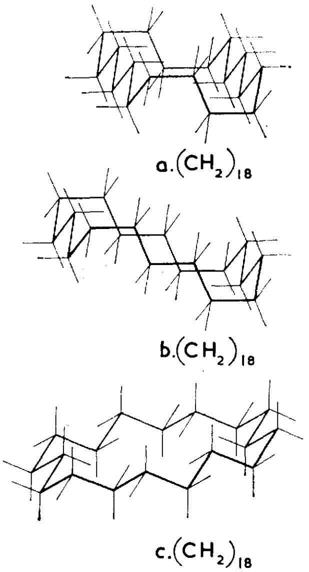

FIG. 4. Conformations of cyclo-octadecane.

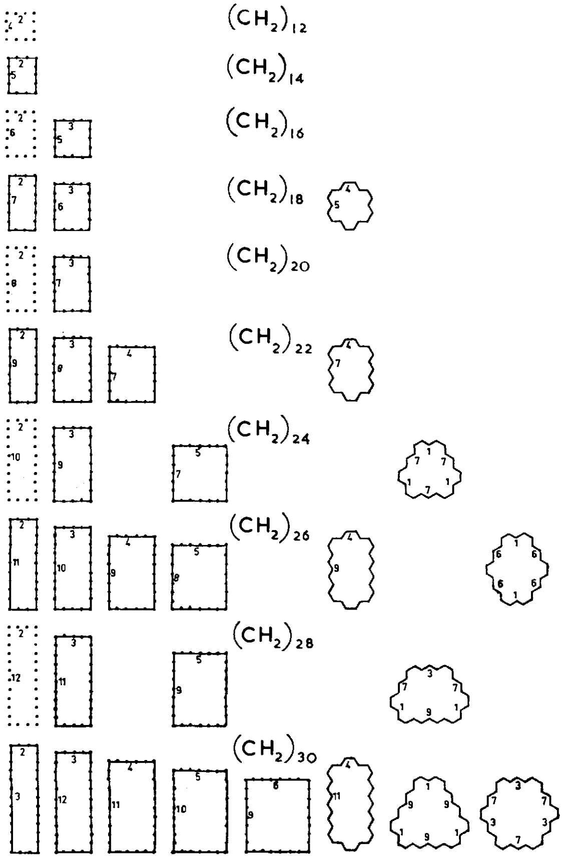

FIG. 5. Strain-free conformations (schematic) of cycloalkanes up to C_{30} (bonds drawn), and strained compact conformations (bonds not drawn).

An sp^2-hybridized carbon atom should have a similar tendency to stay next to a corner atom and, likewise by elimination of one hydrogen atom pointing inwards, should relieve repulsive strain in medium-sized rings (as already discussed by Brown *et al.*[15]). If such

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[14] See, for example, Sheppard, in *Adv. Spectroscopy*, 1959, **1**, 288.

[15] Brown, Fletcher, and Johannesen, *J. Amer. Chem. Soc.*, 1951, **73**, 212.

an atom forms part of a double bond, the ring-conformation should remain unchanged as long as the double bond is external ($>C{=}O$, $>C{=}CH_2$, $>C{=}N{\cdot}OH$, etc.), because the two CH bonds have simply been replaced by the two " bent bonds " of the double bond; this is contrary to the opinion of certain authors [16,17] but in agreement with that of Pitzer and Donath.[18] However, if the double bond forms part of the ring chain, an entirely new situation arises as the chain must change direction to obey the principle of staggered bonds. There is ample justification for considering the double bond sterically as two bent bonds in a staggered conformation with respect to its substituents.[19] For instance, microwave spectra prove that the preferred conformation of propene [20] (and similar compounds such as acetaldehyde,[21] etc.) is that in which one hydrogen atom of the methyl group eclipses the centre of the " double " bond (Fig. 6a). Further, *X*-ray studies of *trans*-polybutadiene [9,22] show that a single bond in a saturated chain cannot simply be replaced isosterically by a *trans*-double bond, but that it fixes four carbon atoms and four hydrogen atoms in one plane, out of which the continuing chain has to bend at an angle ~55° (Fig. 6b). The same feature is found in *cis*-polybutadiene,[9,23] *cis*- and *trans*-polyisoprene,[24] and geranylamine hydrochloride.[25]

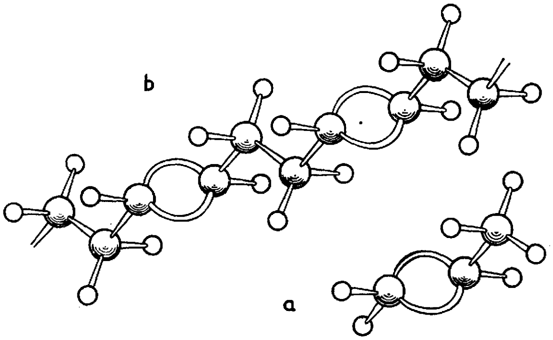

FIG. 6. Established conformations of (a) propene [20] and (b) *trans*-polybutadiene.[22]

The introduction, therefore, of one double bond into a macrocyclic ring immobilizes four successive carbon atoms, but the direction thereby imposed on each of the continuing chains is such that no absolutely strain-free conformation of the saturated chain can be found. Introduction of a second double bond does not improve the situation, except when placed diametrically opposite in certain even-numbered rings. Such conformations must have two equal, odd-numbered, and parallel polymethylene chains connected by two bridges of either both-*trans*- or both-*cis*-double bonds, as illustrated in Fig. 7. It can be seen that in the di-*cis*-olefin two rows of hydrogen atoms come rather close; hence the di-*trans*-configuration is favoured. A third double bond again prevents construction of strain-free conformations, while four double bonds may be accepted in certain even-membered rings when properly placed.

Introduction of one triple bond perturbs the ring, as does a double bond, and no ideal conformation is possible. To re-establish order a second triple bond must be diametrically

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[16] Brown, Brewster, and Shechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467.

[17] Billeter, Bürer, and Günthard, *Helv. Chim. Acta*, 1957, **40**, 2046.

[18] Pitzer and Donath, *J. Amer. Chem. Soc.*, 1959, **81**, 3213.

[19] Pauling, in " Theoretical Organic Chemistry," Kekulé Symposium, London, 1958, p. 1 (Butterworth's Scientific Publns., 1959).

[20] Herschbach and Krisher, *J. Chem. Phys.*, 1958, **28**, 728; Lide and Christensen, *ibid.*, 1961, **35**, 1374.

[21] Kilb, Lin, and Wilson, *J. Chem. Phys.*, 1957, **26**, 1695.

[22] Natta, Corradini, and Porri, *Atti. Accad. naz. Lincei*, 1956, **20**, 728.

[23] Natta and Corradini, *Nuovo cim., Suppl.*, 1960, **15**, 111.

[24] Bunn, *Proc. Roy. Soc.*, 1942, *A*, **180**, 40, 67, 82; *Trans. Faraday Soc.*, 1942, **38**, 372; Jeffrey, *ibid.*, 1944, **40**, 517.

[25] Jeffrey, *Proc. Roy. Soc.*, 1945, *A*, **183**, 388; Cruickshank and Jeffrey, *Acta Cryst.*, 1954, **7**, 646.

placed as in Fig. 7, and the two saturated chains must be equal and contain an odd number of CH_2 groups, as found in the high-melting cyclic diynes discussed in Part I of this series.[2] Again, three triple bonds introduce strain, while some cyclic tetraynes are strain-free. It should be noted that a triple bond cannot be considered sterically as three bent bonds, as proposed by Pauling [19] (the evidence cited in favour of this is, in any case, not convincing *). If this proposal had been correct, the two " corner " methylene groups at each side of the triple bond should have been eclipsed with respect to each other. The observed centre of symmetry requires them to be staggered as if the C–C≡C–C group acted sterically merely as an elongated single bond. This difference between a double and a triple bond may be connected with the orbital degeneracy resulting in cylindrical symmetry around the triple bond. A formally analogous difference is found between butadiene and benzene: in butadiene, localized double bonds represent the structure most correctly, whereas the orbital degeneracy in benzene leads to cylindrical symmetry and identical bonds.

Melting Point and Ease of Ring Formation.—The melting process being an equilibrium process ($\Delta G = \Delta H - T\Delta S = 0$), the melting point can be expressed as $T_m = \Delta H_m/\Delta S_m$.

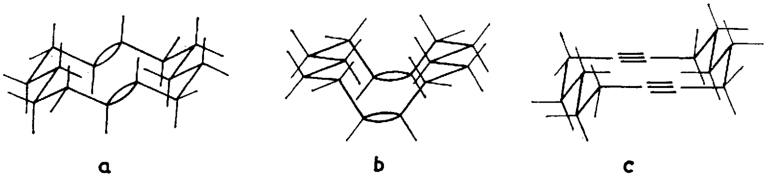

FIG. 7. Conformations of the 14-membered symmetrical cyclic dienes [(a) *cis*; (b) *trans*] and (c) diyne.

If the heat of fusion does not change much in a series, a high entropy of fusion therefore means a low melting point and *vice versa*.[26] The entropy of fusion of flexible macrocyclic compounds is composed of: (1) the positional entropy change, which, reflecting the disorder in the liquid compared with the three-dimensional crystalline lattice order, does not vary much; (2) the orientational entropy change which, depending mainly on the molecular symmetry, cannot vary much in a homologous series; and (3) the conformational entropy change. Part (3) will be small if the molecule has a preferred and unique conformation persisting in the crystal and the liquid; it will be great if there are many equivalent conformations because the liquid will contain the equilibrium mixture of them all, while in the crystal lattice there will generally be only one. As most other physical properties, such as vibrational spectra, refractive index, density, dipole moment, etc., are rather insensitive to ring size in macrocyclic compounds (from C_{13} upwards), the sensitivity of the melting point may provide information valuable for conformational studies. It should be stressed that a high melting point, strictly, indicates only that there is a single favoured conformation and not that it is strain-free, although the latter may generally be the case for the larger flexible rings.

On the other hand, the yields in cyclizations should depend on the same factors as determine conformational stability of the formed ring, as the probability of having the ring preformed in the final cyclization step must be high if the conformation of the resulting ring is to be strain-free in every sense. Thus, it can be understood why high cyclization yields and high melting points are often found together.

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* The spectroscopic evidence for dehydrocarotenes (Inhoffen *et al.*, *Annalen*, 1950, **569**, 226; **570**, 54) leads actually to the opposite conclusion; the absence of a *cis*-peak (Zechmeister, Pauling, *et al.*, *J. Amer. Chem. Soc.*, 1943, **65**, 1940) proves that the configuration around the triple bond is *trans*-like (Dale, *Acta Chem. Scand.*, 1957, **11**, 265).

[26] Ubbelohde, *Quart. Rev.*, 1950, **4**, 356.

In the following sections, various classes of macrocyclic compounds are discussed separately, and observed properties are compared with predictions based on the probable conformations indicated by our models.

Cycloalkanes.—As the modified molecular models do not allow construction of a strain-free carbon skeleton for the odd-numbered rings, a strong alternation, even (high)–odd (low), of the melting point would be predicted. Superimposed on this, a slighter alternation in the higher-melting series would be expected, at least for the higher " flexible " members (from C_{14}), because the series C_{14}, C_{18}, C_{22}, . . ., have strain-free compact conformations, whereas those of the series C_{16}, C_{20}, C_{24}, . . ., must either form an inner hole to become strain-free (Fig. 5, second column), or be strained to become compact (first column, dotted lines). However, the melting-point curve in Fig. 8, which is based on literature data [27,28] completed and corrected by our own values,[1,2] does not correspond to this prediction. This is because most of the apparent melting points in this series, and in some other macrocyclic series containing one, or a few, non-immobilising groups in a flexible saturated hydrocarbon chain, are not true melting points, inasmuch as the heat (or rather entropy) of fusion is abnormally low.[29,30] In compensation, there is at least one transition point at lower temperatures in the solid state, with a correspondingly high entropy of transition, so that the upper solid phase has to be regarded as already more than " half-melted." The known transition points [29-31] have been included in Fig. 8, and when these are considered together with the two known cases, C_{10} and C_{12}, for which the heats of fusion are normal,[30] the predicted strong even–odd alternation is found, as is the expected secondary alternation in the series C_{14}, C_{16}, C_{18}.[31] For the larger of these rings, of which several conformations may coexist in the liquid, this means that the final selection of conformation for the crystal lattice, with which our prediction is concerned, must take place at the transition

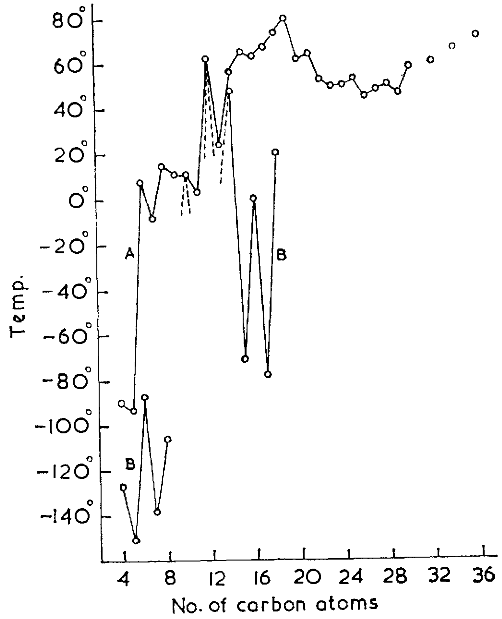

FIG. 8. (A) Melting points and (B) transition points of cycloalkanes.

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[27] Ruzicka, Plattner, and Wild, *Helv. Chim. Acta*, 1946, **29**, 1611.

[28] Sondheimer, Amiel, and Wolovsky, *J. Amer. Chem. Soc.*, 1959, **81**, 4600.

[29] Kaarsemaker and Coops, *Rec. Trav. chim.*, 1952, **71**, 261; Finke, Scott, Gross, Messerly, and Waddington, *J. Amer. Chem. Soc.*, 1956, **78**, 5469.

[30] Van Kamp, Thesis, Vrije Universiteit, Amsterdam, 1957; Coops, Van Kamp, Lambregts, Visser, and Dekker, *Rec. Trav. chim.*, 1960, **79**, 1226.

[31] Billeter and Günthard, *Helv. Chim. Acta*, 1958, **41**, 338.

point and not at the melting point. It has in fact been found [31] that the infrared spectrum of the upper solid phase is practically identical with that of the liquid, but there is a striking spectral simplification below the transition point, except just in the case of cyclotetradecane which has only one probable conformation. For the larger rings, therefore, it must be supposed that the entropy of transition corresponds to the conformational entropy change plus some, but not all, of the orientational entropy change, as the upper solid phase is not isotropic. For the lower members, C_4—C_9, the entropy of melting is only 10—25% of the entropy of the main transition,[29] and the upper solid phase is isotropic; hence only the positional entropy change is involved when the substance finally melts macroscopically. There has been much discussion [32] about the nature of the upper " plastic " phase of spheroidal molecules, whether they rotate freely or merely have random orientation as in the liquid. From Fig. 8 it can be seen that there is a group of high " apparent " melting points from C_6 to C_{11}, *i.e.*, just around cyclo-octane for which the proposed conformation (Fig. 2) resembles adamantane and has a practically spheroidal shape. Then, there is a second group from C_{15} to C_{21}, *i.e.*, around cyclo-octadecane, for which one possible conformation is that of an almost circular disc (Fig. 4c). Between these groups the true melting points of C_{10} and C_{12} (and essentially also of C_{14}) emerge. In the first group, the spheroidal molecules, after having undergone most of the " melting " at the transition point, can have the full orientational freedom of the liquid (whether it is called free rotation about all axes or random orientation does not matter) but still remain in rather well-defined relative positions. Slightly larger molecules cannot become sufficiently spherical; but in the next group the approximately circular disc-like shape allows " rotation " about the perpendicular axis but not about the two others (compare benzene [33] and polysubstituted benzenes [34]), so that the molecules remain oriented in one dimension but not in the other two. Finally, above about C_{20} the interior hole of such rings becomes too large, and the molecule collapses to the shape of two parallel straight chains bridged at both ends. Some experimental evidence supports these ideas; first, the cycloalkanes of the first group crystallize as spheroidal aggregates [27] (all directions of growth equivalent); from cyclododecane on, and including the second group, they crystallize as long, soft needles [27] (one preferred direction of growth), and the higher ones from about C_{22} form thin plates [35] (two preferred directions of growth by stacking of the long molecules side by side). The cycloalkanones, which should behave conformationally as the cycloalkanes, show a surface-film coverage [36] for the highest members (C_{29}—C_{30}) as is to be expected for two close-lying parallel chains; but the members from about C_{15-16} to C_{21} have a larger cross-section and the film is more easily compressed; the 14-membered ring is again normal. This may be taken as an indication of a circular open shape of these intermediate rings, rather than an inclination of the long axis with respect to the surface, as suggested by the original authors. A characteristic change in the *X*-ray diagrams of liquid cycloalkanones takes place between the 12- and 13-membered ring; [37] it may be linked with the onset of " rotation " of the larger rings. Finally, *X*-ray data for crystalline cyclic diketones with 24 and 28 carbon atoms indicate two parallel chains with bridges consisting of 1·5—2·3 carbon atoms.[38]

It is very probable that the solid-state " rotation " of the disc-like molecules is not a real rotation of a rigid ring; if it were, cyclo-octadecane should show a sharper infrared spectrum,[31] corresponding to the ideal conformation of Fig. 4c; the molecules are probably

[32] Pirsch, *Ber.*, 1936, **69**, 1323; 1937, **70**, 12; Timmermans, *J. Chim. phys.*, 1938, **35**, 331; Turkevich and Smyth, *J. Amer. Chem. Soc.*, 1940, **62**, 2468; Perdok, *Helv. Chim. Acta*, 1947, **30**, 1782; Davidson, Argersinger, and Michaelis, *J. Phys. Colloid Chem.*, 1948, **52**, 332; see also Proc. Symposium on Plastic Crystals and Rotation in the Solid State (Oxford, 1960), *J. Phys. and Chem. Solids*, 1961, **18**, 1.

[33] Andrew, *J. Phys. and Chem. Solids*, 1961, **18**, 9.

[34] Smyth, *J. Phys. and Chem. Solids*, 1961, **18**, 40.

[35] Ruzicka, Stoll, Huyser, and Boekenoogen, *Helv. Chim. Acta*, 1930, **13**, 1152.

[36] Büchner, Katz, and Samwel, *Z. phys. Chem.*, 1929, *B*, **5**, 327.

[37] Katz, *Z. angew. Chem.*, 1928, **41**, 329; Katz and Selman, *Z. Phys.*, 1928, **46**, 392.

[38] Müller, *Helv. Chim. Acta*, 1933, **16**, 155.

anyway too large to rotate.[34] Rather, there may be a " lattice imperfection " which travels around the ring, much in the same way as the out-of-plane position of one CH_2 group in cyclopentane.[18] In this way the effective symmetry of the ring increases, making understandable that there is little difference between odd- and even-numbered rings. It may also explain the nuclear magnetic resonance results,[39] which show the coexistence of a normal (crystal-like) broad peak and an abnormal (liquid-like) sharp peak in the upper solid phase; the former may be due to the fraction of the ring, decreasing with rise in temperature, which is undisturbed at a certain moment; the latter to the fraction, increasing with temperature, which constitutes the travelling imperfection.

The proposed conformations for the medium-sized cycloalkanes will next be considered in relation to observed properties and determined structures. It is encouraging for the present approach to find that three different crystal-structure determinations of cyclodecane derivatives [4] reveal the conformation of the ten-membered ring shown in Fig. 2, but, of course, with the two parallel chains somewhat curved outwards because of the transannular hydrogen repulsion. The uniqueness of this conformation is confirmed by the very similar infrared spectra of the liquid and the solid hydrocarbon.[31,40] In the case of cyclododecane, the conformation with a strain-free carbon skeleton (Fig. 2a) is apparently rendered sufficiently unstable by the increased transannular hydrogen repulsion, to make preferable the adoption of the both Pitzer- and Baeyer-strained roughly square skeleton of Fig. 2b, actually established by *X*-ray methods.[3] Again, the infrared spectrum does not undergo much change with state; [31] so this conformation must be very much preferred. The structure of cyclo-octane has not yet been determined, but the conformation derived in Fig. 2 has the symmetry required by the combined infrared and Raman studies of Bellis and Slowinski,[41] although it is not the one favoured by these authors. A certain indirect support comes from the structure determination of cyclononylamine hydrobromide; [5] the observed structure (Fig. 9) cannot be derived from cyclodecane just by removal of one CH_2 group and closing of a new link, as can the " envelope form " of cyclopentane [18] from cyclohexane; it is obtained directly from the postulated cyclo-octane conformation by insertion of one CH_2 group in such a way that a chain of seven CH_2 groups remains conformationally practically unchanged (Fig. 9). The very high dipole moments [42] of 1-oxa- and 1-thia-cyclo-octan-5-one, which are only in accordance with a " folded " conformation, may also be quoted, again with the assumption that ether oxygen and the ketone group do not change the basic stereochemistry of the ring.

Cyclic Ketones.—In accordance with the conclusion that replacement of a $>CH_2$ group by a $>C{=}O$ group should not change the conformational situation in the ring skeleton, the melting-point curve [43-45] of the cycloalkanones (Fig. 10) is strikingly similar to that of the cycloalkanes (Fig. 8); above C_{11} they are indeed almost superimposable. It is natural that the smallest rings undergo relatively larger changes, the carbonyl group constituting a larger fraction of the molecule. Unfortunately, heats of fusion have not been determined, but they can be estimated from the known [44] cryoscopic constants according to the approximate relation $K_{cr} = \boldsymbol{R}T_m{}^2M/1000\Delta H_m$. The few melting points which are thus revealed as " true " by having a normally low cryoscopic constant are indicated in Fig. 10. The other members must have upper " half-liquid " phases (except possibly C_{10}, C_{30}, and C_{34}, which have not been measured and may very well have low constants), but only in a few cases have the transition points been localized. The physical methods by which they have been found are determination of the dielectric constant [46] (which also

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[39] Bommer and Arndt, Abs. 5th European Congress on Mol. Spectroscopy, Amsterdam, 1961, p. 19.

[40] Billeter and Günthard, *Helv. Chim. Acta*, 1958, **41**, 686.

[41] Bellis and Slowinski, *Spectrochim. Acta*, 1959, **15**, 1103; 1960, **16**, 518.

[42] Leonard, Milligan, and Brown, *J. Amer. Chem. Soc.*, 1960, **82**, 4075.

[43] Ruzicka and Giacomello, *Helv. Chim. Acta*, 1937, **20**, 548.

[44] Ziegler and Hechelhammer, *Annalen*, 1937, **528**, 114.

[45] Prelog, *J.*, 1950, 420.

[46] Gäumann, Gugerli, Beguin, and Günthard, *Helv. Chim. Acta*, 1956, **39**, 132; Gäumann, Gugerli, and Günthard, *ibid.*, pp. 145, 702.

shows that the dipoles in the upper state are as free to orient themselves as in the liquid) and infrared spectroscopy.[47]

The infrared spectra are not well suited, in this case, for a decision about the conformational homogeneity of the ring skeleton, as the carbonyl group may occupy any position in the ring without disturbing its shape, although positions next to corner atoms may be preferred. The liquid and the upper solid phase may therefore contain a variety of conformations differing only in the position of the carbonyl group. A striking parallelism of the variation in splitting pattern of the CH_2 scissoring band in the infrared spectrum with ring size has been found between the series of cycloalkanes and of cycloalkanones (as well as the series of hydroxy-, chloro-, and bromo-cycloalkanes), and this has been taken to indicate conformational similarity of the carbon skeleton in all these series.[48]

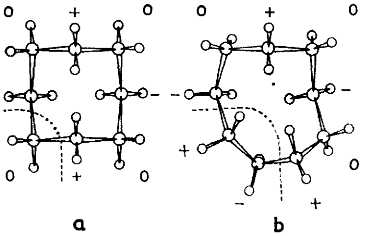

FIG. 9. Relation between (a) the proposed conformation of cyclo-octane and (b) the established conformation [5] of a cyclononane derivative.

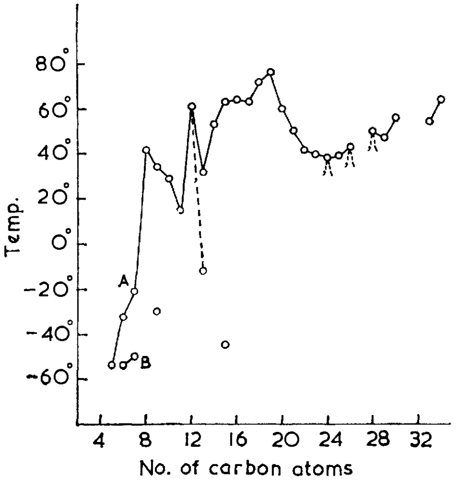

FIG. 10. Melting points (A) and transition points (B and lone points) of cycloalkanones.

The high, emerging, true melting point of cyclododecanone (as in the case of cyclododecane) is noteworthy and might be taken as a confirmation of the rigid square structure, unable to " rotate " either as the smaller compact spheroidal molecules or as the larger flexible circular rings. Further indications of the semi-liquid nature of the upper phase of the large rings are the observations that the cycloalkanones with large cryoscopic constants are soft solids, and those with small constants particularly hard.[44] Indications from studies of unimolecular surface films have been discussed above in the section on cycloalkanes.

" Rotation " in the solid state seems to be effectively depressed by protruding side-groups, as is already known [34] for certain benzene derivatives. Thus, whereas the melting points of cyclic ketones (and alcohols) are very sensitive to traces of impurities, this property is not extended to the derivatives used for identification.[49] *cis*- and *trans*-Civetone (heptadec-9-enone), as well as a mixture of the two, melt at ~30°, and the mixture is inseparable; the corresponding ethylene ketals have different melting points and their mixture is separable by crystallization.[50]

In the monoketones discussed so far, the strong dipole of the keto-group can orient

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[47] Bürer and Günthard, *Helv. Chim. Acta*, 1957, **40**, 2054.

[48] Chiurdoglu, De Proost, and Tursch, *Bull. Soc. chim. belges*, 1958, **67**, 198; Chiurdoglu, Doehard, and Tursch, *Bull. Soc. chim. France*, 1960, 1322.

[49] Stevens and Erickson, *J. Amer. Chem. Soc.*, 1942, **64**, 144.

[50] Stoll, Hulstkamp, and Rouvé, *Helv. Chim. Acta*, 1948, **31**, 543.

itself in opposition to keto-groups of neighbouring molecules without influencing the conformation of the ring itself. However, when there is more than one carbonyl group in the ring, it is necessary also to consider the mutual orientation of these dipoles within the ring. Thus, among the cyclotetradecanediones, the conformation in Fig. 3 is stabilized in the case of the symmetrical 1,8-isomer, as the carbonyl groups can be put in the " bridges " next to corner atoms and have their dipoles oppositely oriented; but there is destabilization in the case of the 1,7-isomer, because the dipoles must there be parallel. On the other hand, among the cyclohexadecanediones neither conformation a nor b of Fig. 3 will be stabilized by a symmetrical 1,9-disposition of the keto-groups, whereas the 1,8-isomer should stabilize both. The symmetrical cycloalkanediones form, therefore, a specially interesting series because dipole interaction reinforces the alternation caused by the pure conformational effect. Further, both carbonyl groups being next to corner atoms, the molecule may become fixed in one conformation so that the " rotation " or travelling of an imperfection is suppressed. Unfortunately, heats of fusion are not known in this series, or in any of the other series to be discussed below, and the series is complete only above C_{14} (but, on the other hand, all the way up to C_{34}). The highest melting point is just that of cyclotetradecane-1,8-dione,[51] the first possible unstrained conformation, and alternation is observed [52] for the descending melting points of C_{14}, C_{16}, C_{18}, and C_{20} (148°, 85°, 97°, and 52°), indicating absence of an upper solid phase. Beyond C_{20} the curve rises regularly [52] as the composition approaches that of the cycloalkane; in this region, as already mentioned, *X*-ray results for two diketones (C_{24} and C_{28}) indicate that the molecules consist effectively of two parallel chains.[38] More illustrative is the behaviour of the cyclic oligomer series $([CH_2]_6{\cdot}CO{\cdot})_x$, for which the composition remains constant.[53] An alternation in a " second dimension " is now observed (Fig. 11); the monomer and trimer are odd-membered and have lower melting points than the even-numbered dimer and tetramer. Of the last two, the 14-membered dimer is compact, strain-free, and dipole-stabilized, and therefore melts much higher than the 28-membered tetramer, which must either be strained or " open " and in either case have parallel carbonyl groups.

In the various cyclization methods which give cyclic ketones, a remarkable alternation in yield is observed, *e.g.*, in Ziegler's dinitrile condensation via cyclic ketimines [44,54] and the adapted Dieckmann diester condensation of Leonard and Schimelpfenig.[55] Of course, the yield depends strictly on the conformation of the open chain before cyclization, but this must be favourable for cyclization when the conformation of the resulting ring is strain-free. The yields of cycloalkanones are good from about the ring size (13—14) which first allows ideal conformations, and the yields in the former method alternate—high for even-membered, lower for odd-membered rings. For medium-sized rings (C_9—C_{12}) yields are very poor; instead, the dimers (cycloalkanediones) are obtained. These diketones are, of course, all even-membered; nevertheless, in the latter method,[55] they are also obtained in alternating yields, high for C_{18}, C_{22}, C_{26}, lower for C_{16}, C_{20}, C_{24}, in accordance with the postulated secondary variation in conformational stability for the even-membered cycloalkanes, which is here reinforced by the dipole effect.

Finally, a striking result obtained by Allinger and Hu [56] can be cited to show that the yield of cyclic ketimine depends more on the conformation of the dinitrile than the tension in a resulting strained ring. A polymethylene chain tends to be straight zig-zag but, when substituted by a methyl group, it does not matter for the neighbouring C–C bond whether the chain itself or the methyl group continues in the *trans*-position; hence

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[51] Blomquist and Spencer, *J. Amer. Chem. Soc.*, 1948, **70**, 30.

[52] Ruzicka, Brugger, Seidel, and Schinz, *Helv. Chim. Acta*, 1928, **11**, 496; Ruzicka, Hürbin, and Furter, *ibid.*, 1934, **17**, 78.

[53] Sondheimer and Gaoni, *J. Amer. Chem. Soc.*, 1959, **81**, 6301.

[54] Ziegler and Aurnhammer, *Annalen*, 1934, **513**, 43.

[55] Leonard and Schimelpfenig, *J. Org. Chem.*, 1958, **23**, 1708.

[56] Allinger and Hu, *J. Amer. Chem. Soc.*, 1961, **83**, 1664.

the probability of a bent chain increases (Fig. 12), and the yield with two such substituents increases from 30% to 100% (both isomers). It is not conceivable that addition of two methyl groups could relieve ring strain. The higher yield obtained on replacement of one or two CH_2 groups of the dinitrile by oxygen was observed by Ziegler and Holl [57] and was discussed in Part I of this series; [2] in these cases ring strain is indeed reduced, but it is nevertheless probably a less important factor.

Cycloalkanols.—If a single hydroxyl group is attached to the cycloalkane ring, the hydroxyl group may be situated on any carbon atom, and the conformation of the ring itself should not change. Infrared evidence [48] for the skeletal similarity with the cycloalkanes has already been cited. The melting-point curve [45, 58] again resembles that for cycloalkanes, which might be unexpected considering the possibility of hydrogen-bond formation. The group of high melting points in the region around C_{18} indicates strongly that the upper liquid-like " solid state " still exists; the formation of intermolecular hydrogen bonds cannot be reconciled with a real rotation of discs, but conforms well to the travelling of an imperfection around the ring. The appearance of alternation in the " first group," at about C_8, may indicate suppression of the upper solid phase here, although at least for cyclohexanol " free rotation " is well established [33] in the isotropic [59] solid. It is surprising that the hydroxyl group plays such an unimportant role in this small molecule. The phenylurethanes [58] would be expected to be incapable of " rotation," and in fact the melting points alternate regularly from the 8- to the 20-membered ring; even the secondary alternation C_{14}, C_{16}, C_{18}, C_{20} is indicated. Again, it may be surprising

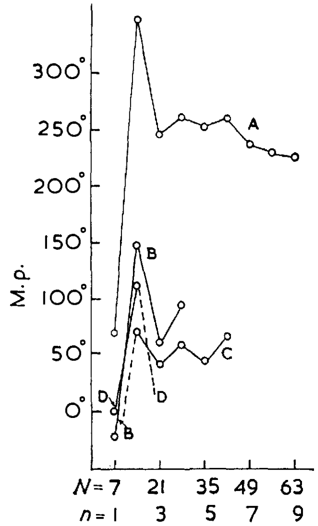

FIG. 11.

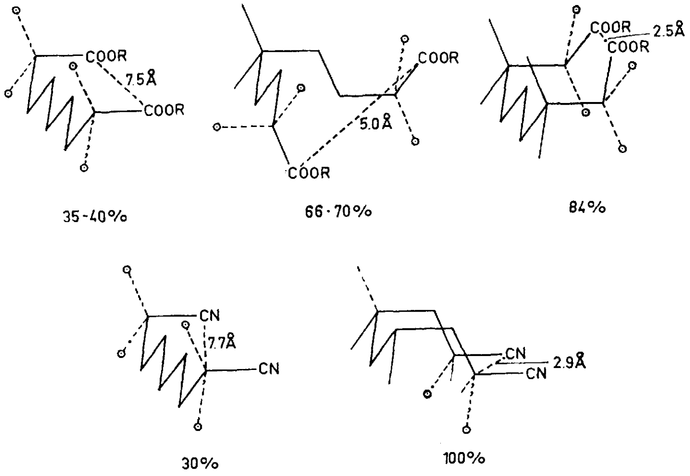

FIG. 12.

FIG. 11. Melting points of cyclic oligomers of some seven-membered units; (A) 6-hexanolactam, (B) cycloheptanone, (C) azacycloheptane, and (D) 6-hexanolactone.

N = total number of ring atoms. n = number of monomer units.

FIG. 12. Conformational effects of methyl substituents in polymethylene chains, explaining increased yields of cyclic product in the acyloin condensation and the dinitrile condensation.

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[57] Ziegler and Holl, *Annalen*, 1937, **528**, 143.
[58] Kobelt, Barman, Prelog, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 256.
[59] Hassel and Sommerfeldt, *Z. phys. Chem.*, 1938, *B*, **40**, 391.

that the phenylurethane group plays such an unimportant role compared with that of the ring skeleton.

With the introduction of more than one hydroxyl group, the situation becomes complicated by diastereoisomerism and steric difficulties with substituents on the inside of the ring, and such compounds will not be discussed here.

Cyclic Acyloins.—The cyclic acyloins (2-hydroxycycloalkanones) contain both a keto- and a hydroxyl group and may be expected to show the added effects of the two. In Fig. 13 the melting points [60,61] are given, and the strong alternation in the region C_{11}—C_{15} indicates that at least here the upper solid phase has been suppressed by the acyloin group.

An alternation in yield is again observed in the acyloin condensation of diesters,[45,60,62] even-numbered being obtained more readily than odd-numbered rings. That here also it is the probability of having the diester molecule preformed for cyclization which is of prime importance can be demonstrated from the results of Blomquist and his co-workers on the influence of methyl substituents in the formation of the strained 9-membered ring.

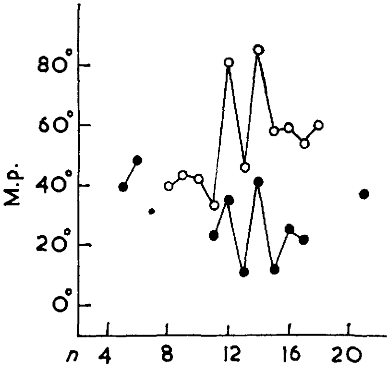

FIG. 13. Melting points of (○) cyclic acyloins and (●) monomeric diol carbonates. *n* = Number of atoms in ring.

Whereas dimethyl azelate gives the cyclic acyloin in only 35—40% yield,[63] a single methyl group in the 5-position increases the yield to 60% under the same conditions.[64] A second 5-methyl group [63] causes a further increase to 66—70%, and two *gem*-dimethyl groups in 3- and 7-position [65] to 84%. If we assume, as before, that at a C–C single bond a methylene group has an equal probability of being *trans*-oriented with respect to a methyl group as with respect to the other methylene group, then in a straight zig-zag polymethylene chain the introduction of one methyl group means that in half of the molecules the chain must change direction at this point; the introduction of one *gem*-dimethyl group must cause a bend in two thirds of the molecules. Fig. 12 illustrates how the yields can be roughly related to the distance between the reacting groups in the best conformations thus made probable.

Cyclic Ethers and Amines.—The conformational influence of heteroatoms such as oxygen and nitrogen was predicted as being negligible. Few cyclic mono- or di-ethers are known, but a series of dimeric polymethylene formals [66] $H_2C{<}\begin{smallmatrix}O\cdot[CH_2]_n\cdot O\\ O\cdot[CH_2]_n\cdot O\end{smallmatrix}{>}CH_2$, shows indications of the secondary alternation discussed for even-membered cycloalkanes.

Heterocyclic monoamines (azacycloalkanes) [67] are liquid when the ring is less than

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[60] Prelog, Frenkiel, Kobelt, and Barman, *Helv. Chim. Acta*, 1947, **30**, 1741; Stoll and Hulstkamp, *ibid.*, p. 1815; Stoll and Rouvé, *ibid.*, p. 1822.

[61] Cope, Fenton, and Spencer, *J. Amer. Chem. Soc.*, 1952, **74**, 5884.

[62] Leonard and Owens, *J. Amer. Chem. Soc.*, 1958, **80**, 6039.

[63] Blomquist, Wheeler, and Chu, *J. Amer. Chem. Soc.*, 1955, **77**, 6307.

[64] Blomquist and Meinwald, *J. Amer. Chem. Soc.*, 1958, **80**, 630.

[65] Blomquist and Miller, *J. Amer. Chem. Soc.*, 1961, **83**, 243.

[66] Hill and Carothers, *J. Amer. Chem. Soc.*, 1935, **57**, 925.

[67] Ruzicka, Kobelt, Häfliger, and Prelog, *Helv. Chim. Acta*, 1949, **32**, 544.

12-membered, indicating that the upper solid state may have been suppressed for the smaller spheroidal molecules. From the 14- to the 21-membered ring the melting points lie between 45° and 68°, with a maximum at azacyclo-octadecane, suggesting that this group of disc-like molecules " rotate " in an upper solid phase. Only the 12-membered ring stands out, as always, from its neighbours with a high, probably true, melting point.

A very large number of heterocyclic diamines (diazocycloalkanes) is known.[68] The symmetrical ones are solid above the 12-membered ring, and a melting-point alternation is observed in the series 14, 16, 18, and 20 ring members (72°, 26°, 55°, and 38°); on the other hand, 1,10-diazacyclo-octadecane has a high cryoscopic constant.[69] It is not, therefore, clear whether an upper solid state exists or not.

Melting-point variation in another " dimension " is shown in Fig. 11 for the cyclic oligomers $([\mathrm{CH_2}]_6{\cdot}\mathrm{NH})_x$. The cyclic dimer, tetramer, and hexamer are even-membered and melt higher than the odd-membered monomer, trimer, and pentamer,[12] but the situation is complicated by formation of hydrates.

Lactones and Cyclic Polyesters.—The introduction of an ester linkage into a saturated ring system may be expected to have a much more profound effect than just the sum of a ketone and an ether group because of the electronic conjugation which tends to keep the ester group and the two neighbouring carbon atoms planar. The melting-point curve of the monolactones has been given by Stoll and Rouvé,[70] and it is understandable that the first member to become solid is the 10-membered ring which is the first one of our models which can accommodate the planar *trans*-ester system of four ring atoms; this is in excellent agreement with the observed discontinuities in boiling point, dipole moment, and rate of hydrolysis, which indicate that the transition from the less stable *cis*-ester configuration to the more stable *trans*-configuration is completed in the 10-membered ring.[71] More unexpected is the low melting point for the 12-membered ring (possibly caused by non-planarity in the " square " conformation of Fig. 2b) and the group of high melting points from 14 to 19 ring atoms (suggesting the survival of the upper solid state). In the case of symmetrical dilactones, in order that there may be only *gauche* preferred bonds at the "corners," a tendency of the two ester groups to form the two bridges between the two saturated chains is to be expected; then odd-numbered polymethylene chains would give ideal conformations, whereas even-numbered ones would lead to strained conformations. This is strikingly confirmed by the most beautiful alternating melting-point curve found in the literature,[70] namely, that for the symmetrical dilactones with 14—38 ring atoms. A contributing factor to this alternation may be the mutual orientation of the strong dipoles of the two ester groups. Stoll and Rouvé [70] also reported some trilactones and, without exception, a trilactone, as well as the corresponding monolactone, melts lower than the corresponding dilactone (cf. the 6-hexanolactone oligomers in Fig. 11), even when all the oligomers must be even-membered.

The same preference for the bridge positions would be expected if one ester group of the dilactone is turned around as in cyclic esters from diols and dicarboxylic acids. An alternating melting-point curve would therefore be expected also for symmetrical cyclic diesters from a purely conformational point of view; but the dipole effect is here the opposite and may cancel the conformational effect. Although Carothers and his co-workers,[72,73] and Stoll and Rouvé,[74] prepared many cyclic diesters and tetraesters, with varying chain lengths of both diacid and diol, they have not combined acids and diols

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[68] von Braun, Blessing, and Zobel, *Ber.*, 1924, **57**, 185; Müller *et al.*, *Ber.*, 1934, **67**, 295; 1941, **74**, 416; *Monatsh.*, 1952, **83**, 386; Stetter and Marx, *Annalen*, 1957, **607**, 59; Stetter and Spangenberger, *Chem. Ber.*, 1958, **91**, 1982.

[69] Müller and Kindlmann, *Ber.*, 1941, **74**, 416.

[70] Stoll and Rouvé, *Helv. Chim. Acta*, 1935, **18**, 1087.

[71] Huisgen and Ott, *Tetrahedron*, 1959, **6**, 253.

[72] Hill and Carothers, *J. Amer. Chem. Soc.*, 1933, **55**, 5031.

[73] Spanagel and Carothers, *J. Amer. Chem. Soc.*, 1935, **57**, 929.

[74] Stoll and Rouvé, *Helv. Chim. Acta*, 1936, **19**, 253.

with the same number of CH_2 groups. There remain, however, two homologous series of cyclic tetraesters which show interesting melting-point variations (Fig. 14). One is the series of dimeric cyclic esters of ethylene glycol with dicarboxylic acids,[72] for which the expected alternation is observed, odd-numbered acids allowing compact strain-free conformations with two of the ester groups in the bridges. The other is the very similar series of dimeric cyclic polymethylene succinates,[73] for which similar melting-point alternation would be predicted; here, however, the alternation for the higher members is the inverse. A possible explanation of this anomaly may be based on a consideration of dipole interactions. Two ester groups would always be very close and oriented parallel at two of the corners and must destabilize the proposed conformations. As the ester dipole is mostly concentrated in the $\rangle C=O$ group, the destabilization must be strongest in the succinates as the $\rangle C=O$ groups are here closer than in the ethylene glycol esters.

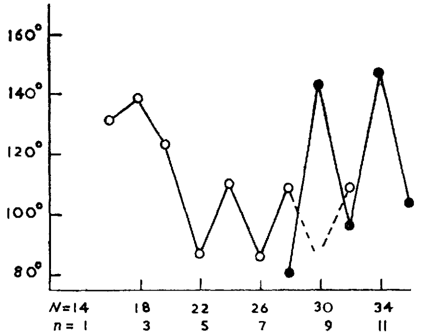

FIG. 14. Melting points of dimeric (○) polymethylene succinates and (●) ethylene dicarboxylates. N = Total number of atoms in ring; n = number of CH_2 groups in each polymethylene chain.

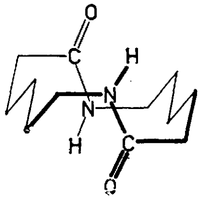

FIG. 15. Conformation of 6-hexanolactame dimer.

Lactams, Cyclic Polypeptides, and Polyamides.—The introduction of one or several amide (peptide) groups into a cycloalkane should have the conformational consequences discussed for the ester group. The conjugation in the amide group, and hence its tendency to remain planar, might be more pronounced; on the other hand, intermolecular hydrogen bonding will increase the heat of fusion and may obscure subtle variations in the conformational part of the entropy of melting. Further, dipole interactions should be still stronger than between ester groups and it should accentuate alternation in the dilactam series but counteract alternation in symmetrical cyclic diamides. Unfortunately, the melting points in the series of dilactams are incompletely known, but dielectric constants [75] and infrared and ultraviolet spectra [76] of monolactams show that the 10-membered ring is again the smallest which can accommodate the stable *trans*-amide group, as was observed for the *trans*-ester group and is to be expected from our models. A very large number of cyclic diamides has been prepared,[77] but only in two cases have diamines and diacids with the same number of CH_2 groups been combined to give symmetrical diamides.

A long series of cyclic oligomers has been synthesized by Zahn and his co-workers,[78] and by Rothe and Kunitz,[79] namely, homologues up to and including the nonamer of 6-hexanolactam, $([CH_2]_5 \cdot CO \cdot NH)_x$. The melting-point curve is shown in Fig. 11, and the

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[75] Huisgen and Walz, *Chem. Ber.*, 1956, **89**, 2616.
[76] Huisgen, Brade, Walz, and Glogger, *Chem. Ber.*, 1957, **90**, 1437.
[77] Stetter and Marx, *Annalen*, 1957, **607**, 59.
[78] Zahn and Determann, *Chem. Ber.*, 1957, **90**, 2176; Zahn and Kunde, *Annalen*, 1958, **618**, 158.
[79] Rothe and Kunitz, *Annalen*, 1957, **609**, 88.

much higher melting point of the dilactam suggests a very high conformational stability, as is to be expected for a 14-membered ring with two pentamethylene chains connected by two amide bridges having their dipoles oppositely oriented (Fig. 15). Of the higher oligomers, the odd-numbered should be less stable than the even-numbered, and among the latter only the hexamer can be both strain-free and compact; in fact, the melting point of the hexamer is somewhat higher than those of its neighbours. A more pronounced alternation has been observed [80,81] for the solubility, which usually is closely related to the melting point.

The remarkable stability of the 6-hexanolactam dimer compared with the higher oligomers and its isomer, the cyclic diamide from adipic acid and hexamethyleneamine (nylon 6,6-monomer), has been a subject of much speculation.[80,81] There has been a tendency [80,82] to explain stability in such cases by an increased possibility of forming intramolecular hydrogen bonds, though sometimes these were sterically unacceptable. The extremely high melting point, and especially the abnormally low solubility, indicate just the opposite: that intermolecular bonding is preferred. As no strain-free conformation for the cyclic nylon monomer is possible, it is much more likely that the difference is one of conformational stability. That the 6-hexanolactam dimer hydrolyzes less readily, and the cyclic nylon monomer more readily, than the open-chain polyamides, which the original authors [81] could not explain, is rationalized on this basis.

The cyclic oligomeric lactams of ω-aminoundecanoic acid [83] are all even-membered and none of them can have a compact, strain-free conformation; hence there is no striking variation in the melting points (monomer 155°, dimer 188°, trimer 184°).

Only a few cyclic polypeptides of β-alanine are known.[84] The di- and tri-peptide are rapidly hydrolyzed, but the 16-membered tetrapeptide is very stable and it is the first for which a completely strain-free conformation (of the type in Fig. 3a) with planar *trans*-amide groups becomes possible.

Several cyclic polypeptides of α-amino-acids have been reported, but as they all decompose when or before melting, one is limited to a consideration of their relative ease of formation and their stability. Simple replacement of CH_2 groups in the ideal compact cycloalkane conformations in Fig. 5 by planar *trans*-peptide groups is only possible when the number of ring members is 18, 30, 42, 54, etc. These rings correspond to cyclic hexa-, deca-, tetradeca-peptides, etc., and it is interesting that all attempts to synthesize cyclic tripeptides,[82,85-88] and in most cases also pentapeptides,[88,89] have failed; instead the hexa- and deca-peptides are readily formed. Further, the even-numbered, but still strained, tetrapeptides were obtained either not at all [88] or in much lower yield [82] and did not give the equally strained octapeptides. The remarkable stability of cyclohexaglycyl, and especially its resistance to hydrolysis, have been noted.[86]

Obviously, these deductions might be valid only for the simplest amino-acids such as glycine, etc.; bulky side chains may prevent intermolecular hydrogen-bonding and favour intramolecularly bonded structures such as those proposed for gramicidin-S.[90]

Cyclic Diol Carbonates and Anhydrides.—The melting points of the simple cyclic " monomeric " diol carbonates [72] are shown in Fig. 13, and the marked alternation in the region

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[80] Hermans, *Nature*, 1956, **177**, 127.

[81] Heikens, Hermans, and Veldhoven, *Makromol. Chem.*, 1959, **30**, 154.

[82] Schwyzer, Iselin, Rittel, and Sieber, *Helv. Chim. Acta*, 1956, **39**, 872.

[83] Zahn, Roedel, and Kunde, *J. Polymer Sci.*, 1959, **36**, 539; Zahn and Kunde, *Chem. Ber.*, 1961, **94**, 2470.

[84] Rothe, *Acta Chim. Acad. Sci. Hung.*, 1959, **18**, 449.

[85] Sheehan, Goodman, and Richardson, *J. Amer. Chem. Soc.*, 1955, **77**, 6391.

[86] Bamford and Weymouth, *J. Amer. Chem. Soc.*, 1955, **77**, 6368.

[87] Schwyzer and Sieber, *Helv. Chim. Acta*, 1958, **41**, 2190; Schwyzer and Gorup, *ibid.*, p. 2199.

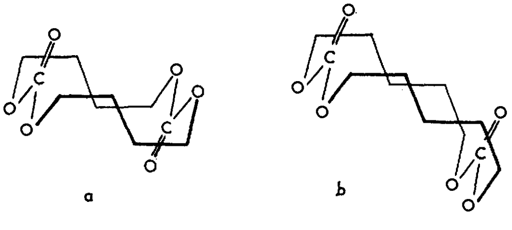
[88] Kenner, Thomson, and Turner, *J.*, 1958, 4148.

[89] Schwyzer and Sieber, *Helv. Chim. Acta*, 1957, **40**, 624; 1958, **41**, 2186.

[90] Schmidt, Hodgkin, and Oughton, *Biochem. J.*, 1957, **65**, 744; Hodgkin and Oughton, *ibid.*, p. 752; Schwyzer, in Ciba Foundation Symposium on Amino Acids and Peptides with Antimetabolic Activity, Churchill, London, 1958, p. 171.

of 11—16 ring atoms indicates that the planar carbonate group is sufficiently rigid to eliminate the upper solid phase. The series of cyclic " dimers "[72] is particularly interesting as it would be expected that both the carbonate groups would form the bridges between the two saturated chains, whereby each of them with its two neighbouring carbon atoms becomes coplanar, and that *gauche* preferred bonds would fit into the corner positions (Fig. 16). That the bridges are not two- but three-membered should have the consequence that all chain lengths are equally good conformationally; no odd (high)—even (low) alternation would be expected, but rather the inverse, as even-numbered chains give centrosymmetrical molecules with a smaller change in orientational entropy during melting; also, these are stabilized by the opposite dipole orientation. A second consequence would be that only the first member, the 14-membered ring, can be compact, and the hole size must increase along the series; the initially high melting point may therefore be expected to descend. It would hardly be possible to explain the observed melting-point curve in Fig. 17 as well on any other basis, *e.g.*, by placing the carbonate groups in the long chains of the " compact " conformations and two CH_2 groups as each bridge.

FIG. 16. Conformations of dimeric diol carbonates.



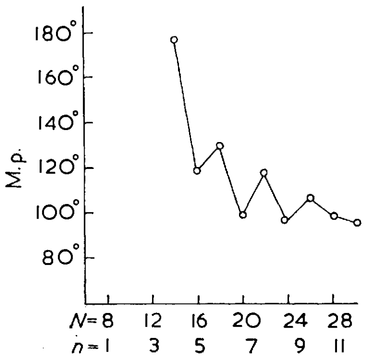


FIG. 17. Melting points of dimeric diol carbonates.

N = total number of ring atoms.
n = number of CH_2 groups in the diol.

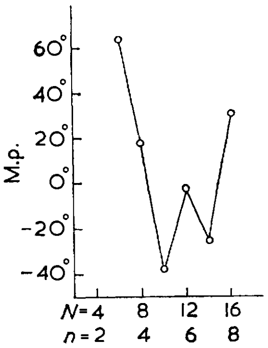


FIG. 18. Melting points of cyclic poly(dimethylsiloxanes).

N = total number of ring atoms.
n = number of monomer units.

A very similar steric situation exists in the cyclic anhydrides prepared by Hill and Carothers[91] by pyrolysis of polymeric anhydrides. Again the anhydride group and two neighbouring carbon atoms should tend to be coplanar, and this is not possible with smaller than 14-membered rings. In fact, the cyclic monomers with 14 and more ring atoms have a certain (although low) stability.

As the volatility plays a role in determining the relative yields of mono- and di-mer, some medium-sized rings are also obtained, although they are extremely unstable liquids; significantly these are the even-membered rings having 8, 10, and 12 ring atoms. Instead

[91] Hill and Carothers, *J. Amer. Chem. Soc.*, 1933, **55**, 5023.

of the 9-, 11-, and 13-membered rings, which apparently must be even more unstable, the corresponding dimers are obtained as stable solids; ideal conformations are here again possible with the anhydride groups forming the bridges, stabilizing the corners, and having their dipoles opposed.

Cyclic Olefins.—The prediction from models that one double bond makes a strain-free conformation impossible for any ring size, receives a certain support from the fact that the known *cis*-cycloalkenes [92,93] (up to C_{12}) and the *trans*-cycloalkenes [92,93] from C_8 to C_{12} are liquid at room temperature; only *trans*-cyclopentadecene [94] is solid, m. p. 37°, but it remains to be shown that this is a " true " melting point. As was also expected, a second double bond in conjugation does not improve the situation; all known cycloalka-1,3-dienes (C_8—C_{14}, C_{16}, C_{18}) are liquid.[95] Only when the double bonds are further apart, and especially when diametrically placed, are the diolefins solid, as found for the *cis,cis*-cycloalkadienes reported in Part I [2] and for corresponding *trans,trans*-dienes.

Cyclic Acetylenes.—One acetylenic bond alone is as unacceptable as one olefinic bond, and again all known cycloalkynes [93,96] (C_8—C_{12}, C_{15}, C_{17}) are liquid. The melting points of cyclic diynes and tetraynes have been discussed in Part I; [2] here it will only be emphasized that these are the only types of cyclic oligomers obtained in a reaction which in principle should also yield other oligomers. That monomers are not formed might, of course, also be ascribed to non-specified difficulties with medium-sized rings, but the complete absence of cyclic triynes [2,97] must have a purely conformational cause; no strain-free model can in fact be constructed which contains three, or any odd number, of triple bonds.

Rings containing two diacetylenic systems have also been discussed in Part I; a large number of cyclic oligomers containing more than two such systems has been synthesized by Sondheimer and his co-workers,[28,98] but the steric situation is too complicated for a sound discussion.

Miscellaneous Compounds.—The introduction of one *ortho*- or *para*-linked benzene ring in the macrocyclic chain should prevent any good conformation, whereas a *meta*-linked benzene ring might replace three ring atoms without much difficulty. When placed diametrically in pairs, all three isomeric benzenes may be able to form the bridges and give strain-free conformations. However, the large size of these groups may play a too dominant role in the crystal lattice and obscure conformational effects of the macro-ring itself. Nevertheless, it may be significant that all known *para*-polymethylenebenzenes [1,99] (C_8—C_{10}, C_{12}, C_{13}) are liquid, whereas almost all the fourteen known bis-*para*-cyclophanes [1,100] are high-melting solids. Similarly, most *ortho*-polymethylenebenzenes are liquids [1,2,101] and all known bis-*ortho*-cyclophanes [1,102] are high-melting solids. Only a few *meta*-cyclophanes are known.

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[92] Ziegler and Wilms, *Annalen*, 1950, **567**, 1; Cope, Pike, and Spencer, *J. Amer. Chem. Soc.*, 1953, **75**, 3212.

[93] Bomquist *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 3636, 3643; Prelog *et al.*, *Helv. Chim. Acta*, 1952, **35**, 1598; 1955, **38**, 1776, 1786.

[94] Ruzicka and Boekenoogen, *Helv. Chim. Acta*, 1931, **14**, 1319.

[95] Stoll and Commarmont, *Helv. Chim. Acta*, 1948, **31**, 1077; Cope and Estes, *J. Amer. Chem. Soc.*, 1950, **72**, 1128; Ingraham, MacDonald, and Wiesner, *Canad. J. Res.*, 1950, **28**, *B*, 453; Bartlett, Figdor, and Wiesner, *Canad. J. Chem.*, 1952, **30**, 291; Fawcett and Harris, *J.*, 1954, 2673; Braude, *Chem. and Ind.*, 1954, 1557; Blomquist and Goldstein, *J. Amer. Chem. Soc.*, 1955, **77**, 998.

[96] Ruzicka, Hürbin, and Boekenoogen, *Helv. Chim. Acta*, 1933, **16**, 498; Blomquist and Liu, *J. Amer. Chem. Soc.*, 1953, **75**, 2153.

[97] Wotiz, Adams, and Parsons, *J. Amer. Chem. Soc.*, 1961, **83**, 373.

[98] Sondheimer, Amiel, and Wolovsky, *J. Amer. Chem. Soc.*, 1957, **79**, 4247.

[99] Wiesner, MacDonald, Ingraham, and Kelly, *Canad. J. Res.*, 1950, **28**, *B*, 561; Cram *et al.*, *J. Amer. Chem. Soc.*, 1954, **76**, 2743, 6132; 1958, **80**, 3109; 1961, **83**, 2204.

[100] Cram *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 5691; 1954, **76**, 726, 6132; 1958, **80**, 3103; Steinberg and Cram, *ibid.*, 1952, **74**, 5388; Allinger and Cram, *ibid.*, 1954, **76**, 2362; Abell and Cram, *ibid.*, 1954, **76**, 4406.

[101] Huisgen, Rapp, Ugi, Walz, and Mergenthaler, *Annalen*, 1954, **586**, 1.

[102] Baker, Banks, Lyon, and Mann, *J.*, 1945, 27; Behr, Eglinton, Galbraith, and Raphael, *J.*, 1960, 3614.

Macrocyclic compounds containing elements of the second long period, such as thia-, and dithia-cycloalkanes, are known,[103] but too incompletely to merit discussion. Among cyclic poly(dimethylsiloxanes) [104] the larger rings will have the dimethylsilane groups at the corners of conformations of the open three-atom bridged type in Fig. 3a, the hole being needed to accommodate methyl groups from those silicon atoms that are not at the corners. An alternation, high-melting points for the octamer, decamer, etc., and low ones for heptamer, nonamer, etc., is predicted, and in the melting-point curve of Fig. 18 it seems to extend even to lower (strained ?) members. The type of conformation thus deduced for the 16-membered octamer is exactly that found by an *X*-ray determination [105] of its crystal structure.

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[104] Patnode and Wilcock, *J. Amer. Chem. Soc.*, 1946, **68**, 358.

[105] Frevel and Hunter, *J. Amer. Chem. Soc.*, 1945, **67**, 2275.