from one member of the series to the next since the molecular refractions were not all taken at the same temperature.

Melting Points.—The melting points of the known macrocyclic compounds show little regularity in the nature of the change produced by increasing molecular weight but in the range of 8 to 14 atoms there is generally an oscillation from one member to the next.[5] The cyclic carbonates show a similar oscillation, the melting points and ring size for some of the monomeric polymethylene carbonates being

11	12	13	14	15	16	17
23°	35°	11°	41°	12°	25°	22°

Summary

Macrocyclic esters and anhydrides have odors closely resembling those of the ketones and lactones of the same ring size. The rings in the neighborhood of fifteen atoms have musk-like odors. The molecular refractions show a negative exaltation. Melting points in the carbonate series oscillate from one member to the next.

WILMINGTON, DELAWARE

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Studies of Polymerization and Ring Formation. XXII. Stereochemistry and Mechanism in the Formation and Stability of Large Rings

BY WALLACE H. CAROTHERS AND JULIAN W. HILL

A great deal of discussion has been devoted to stereochemistry and mechanism in the formation of rings, but on account of the limited range of experimental facts available, fruitful discussion has been largely restricted to rings containing fewer than eight atoms. The only important series exemplifying closure of long chains hitherto has been the macrocyclic ketones which Ruzicka obtained by heating salts of the higher dibasic acids. As a basis for theoretical inferences this general reaction suffers from two disadvantages. The macrocyclic ketones are formed in such small yields (0.1 to 5%) that they can hardly be regarded as major reaction products, and the nature of the reaction (thermal destruction at high temperatures) is such that its mechanism is inherently obscure. Data on the polyesters and anhydrides now provide the possibility for a much clearer insight into the mechanism of the formation of large rings.

Following the demonstration of the stable existence of large carbon rings, Baeyer's theory of negative strain has been generally abandoned and replaced by the idea of Sachse and Mohr[1] that large rings may exist in

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(1) Mohr, *J. prakt. Chem.*, **98**, 348 (1918).

strainless and non-planar forms. A carbon chain constructed from conventional wire tetrahedra in such a way as to allow free rotation about each single bond clearly shows that the chain can assume a great multiplicity of shapes. If the number of atoms is five or six, the model is readily rotated so that the ends collide once in each complete rotation. If the number is more than six the ends can be brought together arbitrarily without any difficulty to produce a non-planar ring, which is quite flexible and can be bent into a variety of shapes without any appreciable strain. Considering the chain model as a representation of the bifunctional molecule, it is evident why rings of 5 and 6 atoms are readily formed and stable. Larger rings should be equally stable, but it is obvious that their formation may present some difficulties. The chain can assume a great multiplicity of shapes; the particular configurations requisite for ring closure are relatively few. If then the molecule is placed under conditions where mutual reaction of its terminal groups can occur, the probability of *inter*molecular reaction is very much greater than that of *intra*molecular reaction. Hence, as has been demonstrated in previous papers of this series, reactions that might conceivably yield large rings from open chains almost invariably yield linear polymers instead. It is necessary again to emphasize this point since even some of the most recent writings on the subject of forming large rings still convey the impression that attempts to close long chains do not result in any clear-cut reaction at all. In fact, in most cases, reaction occurs perfectly smoothly without any difficulty but the reaction is intermolecular not intramolecular.

What means are available for controlling this situation? Obviously nothing much can be expected from any modification of the nature of the terminal groups. Even if these groups are of such a nature (*e. g.*, NH_2 and COOH) as to exercise a strong attraction for each other, this pre-existing attraction may itself be intermolecular rather than intramolecular.[2]

There is in fact no method known for controlling experimentally the shape that molecules assume. The possibility of such control may perhaps exist in the use of surface forces, but nothing is known about this matter. There are however two possible methods of controlling the result of the reaction. (1) High dilution will increase the *relative* probability of intramolecular reaction.[3] (2) If a series of mutually dependent and quantitatively reversible reactions is involved, constant removal of any traces of cyclic product will cause a displacement of the equilibrium with the ultimate conversion of the entire sample into the cyclic product. This is the principle involved in the synthesis of the cyclic esters and anhydrides described above.

In speculations devoted to Ruzicka's ketone synthesis it has been sug-

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(2) The idea that such attractions may favor intramolecular reaction has been suggested by Mills, "Proceedings, Fourth International Solvay Conference," 1931, p. 20.

(3) *Cf.* Ruggli, *Ann.*, **392**, 92 (1912).

gested[2,4] that the peculiarity of the reaction which makes possible this very exceptional closure of large rings lies in the ability of the metal ion (*e. g.*, thorium) to bring the ends of the chain into a position of close intramolecular approach. But no reason is offered to explain why the metal ion should have such a peculiar effect; and the force of this suggestion is moreover considerably weakened by the claim[5] that macrocyclic ketones are obtained by thermal destruction not only from salts of dibasic acids but also from the acids themselves and their anhydrides. It appears to have been taken for granted in these speculations that reaction *is* intramolecular and leads directly to the cyclic ketone. This is a point that appears to be open to test and the following experiment was accordingly made.

Thermolysis of Thorium Octadecanedioate in Dixylylethane.—Twenty-five grams of thorium octadecanedioate, prepared by the method of Ruzicka, and 150 cc. of unsymmetrical dixylylethane were placed in a 300-cc. flask fitted with a stirrer and thermometer. The mixture was heated by means of a metal bath to 325°. In the course of ten minutes the suspended solid became gummy and attached itself to the stirrer. At the end of fifty minutes the mixture had become homogeneous but very viscous. At the end of two hours, heating was stopped. On cooling, the melt solidified to a slightly elastic gel. Some solid material (apparently unchanged salt) around the top of the flask was discarded. The gel was continuously extracted with ether for eighteen hours, whereupon it disintegrated to a light gray powder. It was further extracted for four hours with benzene, dried, heated with concentrated hydrochloric acid for three hours, separated, ground in a mortar, extracted for three hours with hot hydrochloric acid, then twice with hot alcohol and once with ether. The dried residue (10 g.) was an almost pure white powder. It was practically free of ash and melted at 126–128°; soluble in hot toluene, butyl alcohol and acetylene tetrachloride.

Anal. Found: C, 78.22, 78.89; H, 12.29, 12.41.

When triturated with aqueous sodium carbonate and thoroughly washed and dried it was converted to a salt (Na found, 1.16, 1.36%). The analytical data are consistent with the formula $HOOC[(CH_2)_{16}CO]_7OH$, the calculated values for C and H being 78.9 and 12.4% while a monosodium salt would contain 1.25% Na.

A sample of this material was placed in a molecular still and heated by a metal bath at 300–305°. At the end of one day a film of white solid distillate had collected on the condenser. It had a very pronounced fragrant musky odor.

Our interpretation of this experiment is that the thorium salt of the acid, as in other bifunctional reactions involving long chains, breaks down with the formation of a linear polymer

$$\ldots\text{—RCO—RCO—RCO—RCO—RCO—}\ldots$$

The resulting polyketone comprises the solid product remaining from the extraction. When the polyketone is heated in the molecular still, it cracks and appreciable amounts of the monomeric cyclic ketone (cycloheptadecanone) are produced; the characteristic musk-like odor therefore first makes its appearance at this point in the experiment.

The facts recited above place the macrocyclic ketones, esters (including

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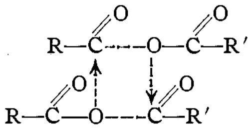
(4) Ruzicka, Stoll and Schinz, *Helv. Chim. Acta*, **11**, 670 (1928).

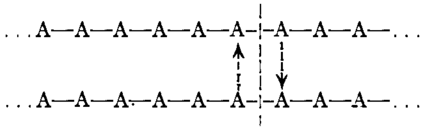
(5) Ruzicka, Brugger, Seidel and Schinz, *ibid.*, **11**, 496 (1928).

lactones) and anhydrides on a common basis for discussion so far as the stereochemistry and mechanism of formation are concerned.

The α-polyanhydrides for example may be represented by the formula ...—CORCOO—CORCOO—CORCOO—CORCOO—.... They are apparently open chains, and contain no more than traces of cyclic anhydrides of low molecular weight. The possibility of converting the polymeric α-anhydrides into β-anhydrides of low molecular weight depends in the first place on the very great reactivity of carboxylic anhydrides and the fact that they are capable of reacting with themselves. A mixed anhydride such as that derived from acetic and butyric acids will, at least at elevated temperatures, pass into an equilibrium mixture containing a considerable proportion of the two simple anhydrides.[6] The process is analogous to ester interchange and, like that, doubtless proceeds through the formation of an addition product involving the ether oxygen of one molecule and the carbonyl carbon of another (A). A linear polyanhydride is not a chemical individual. It is a mixture of long chains of slightly differing lengths each of which bears a series of anhydride linkages. It presents a very complicated series of possibilities of reacting with itself. Adjacent chains can react with themselves to produce simultaneously longer and shorter chains (B). Reaction in a similar manner at two points will yield large rings and these may mutually coalesce by the same mechanism to produce still larger rings. Intramolecular reaction may result in the formation of cyclic monomers and dimers, etc.



(A)



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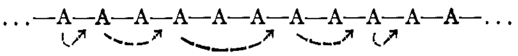

The potentialities of the situation are sufficiently complex to suggest that at equilibrium the number of entities involved will be limited only by the magnitude of the sample. No doubt a condition of genuine equilibrium is impossible to achieve; nevertheless, experiment shows that at elevated temperatures quite a considerable series of transformations occurs, and it leads chiefly to the formation of very large molecules. At the same time appreciable amounts of smaller cyclic fragments (β-anhydride) are produced. The actual concentration of these β-anhydrides present in the reaction mixture at any time must be small, since the β-anhydrides polymerize almost instantly at the temperature involved; and their rate of formation cannot be exceedingly great because even at elevated temperatures where the speed and amplitude of molecular vibrations are greatly

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(6) *Cf.* Autenrieth, *Ber.*, **34**, 168 (1901).

increased, the relative probability of the configurations necessary for the formation of such cyclic compounds must be rather low. However, in the molecular still a mechanism is provided for removing and isolating the β-anhydrides as fast as they are produced. The equilibrium is thus continuously displaced and the entire specimen is finally converted into the β-anhydride.

A precisely similar mechanism is unquestionably involved in the formation of macrocyclic esters from polyesters and it is significant in this connection that smooth transformation requires the presence of ester-interchange catalysts.

The ketones obviously present a more difficult case. No mechanism corresponding to ester interchange exists for the smooth rupture of the linkages joining the structural units in a chain of the type ...—CO—R—CO—R—CO—R—...; nor would one expect a macrocyclic ketone to polymerize with the formation of the corresponding polyketone. Since the reactions involved are not strictly reversible and there are many side reactions, the formation of cyclic ketones offers scarcely any possibilities for rational and deliberate control. The yields are therefore generally only a small fraction of those obtained with the cyclic carbonates, oxalates and anhydrides.

Steric Interferences.—The outline presented above is incomplete since the possible influence of atoms attached to the carbon chain has been ignored. Such atoms are capable of acting as obstacles to ring closure, and they may also introduce strains into rings. For the series under consideration hydrogen is the most numerous and important peripheral atom. The internuclear C–H distance is known from spectroscopic data to be 1.08 Å., and since the (aliphatic) carbon radius is 0.77 Å., the distance from the center of the hydrogen to the surface of the carbon is 0.31 Å. This indicates an atomic diameter of 0.62 Å. for hydrogen attached to carbon. But hydrogens not mutually joined will be expected to exercise a mutual repulsion preventing close approach, and data on the densities of hydrocarbons, collision areas, etc., show that the average distance between the centers of hydrogens belonging to separate molecules is always greater than 0.62 Å. The combined hydrogen atom must therefore be assigned, in addition to its internal radius of 0.31 Å., a larger external radius, which defines the closest average approach of other atoms.[7] This external radius will vary with the compound and the conditions; it will decrease with increasing temperatures and will be larger in a crystal than a gas. The most elaborate experiments and speculations on the external radius of hydrogen are those of Mack,[8] who in different cases uses values ranging from 0.49 to 1.26 Å. Stoll and Stoll-Comte[9] had, however, already made specific

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(7) *Cf.* the excellent review by Sidgwick in "Annual Reports of the Progress of Chemistry for 1932."

(8) Melaven and Mack, THIS JOURNAL, **54**, 888 (1932); Sperry and Mack, *ibid.*, 904; Mack, *ibid.*, 2141.

(9) Stoll and Stoll-Comte, *Helv. Chim. Acta*, **13**, 1185 (1930).

application of the external domain of hydrogen atoms in connection with macrocyclic hydrocarbons. They pointed out that the cyclic paraffins exhibit two anomalies. (1) When density is plotted against number of CH_2 groups a maximum appears in the range of 10 to 17 atoms, and (2) it is within this range that the yields of the cyclic ketones fall to an exceedingly low minimum. The explanation which they offer is very briefly this. Consideration of the densities of cyclic and open-chain hydrocarbons indicates a domain for the CH_2 group that can be accounted for by representing the hydrogen as spheres of diameter 2.3 Å. (compared with 1.54 Å. for carbon). Rings of 5, 6 or 7 members therefore consist of an approximately flat cyclic chain of carbon atoms with a shell of much larger hydrogen atoms around the periphery. In rings of 8 to 15 atoms the geometrical limitations imposed by the valence angles of the carbon atoms force some of the hydrogens toward the center of the ring. The space available is not sufficient to receive them; the "domain" of the hydrogens (or of the CH_2 group) is therefore reduced or compressed. The resulting strain explains the minimum in the yield of the cyclic ketones, and the compression explains the maximum in the density curve of the hydrocarbons. The turning in of hydrogens toward the center of the ring is illustrated for cyclononane by Fig. 1 in which the diameter of the hydrogens (1.18 Å.) is much smaller than that assumed by Stoll and Stoll-Comte (2.3 Å.). This configuration is quite rigid and it is evident that if the hydrogens were twice as large, the space available would not be adequate to receive them. As the size of the ring increases the number of hydrogens forced toward the center increases; above 15 atoms half of them are forced toward the inside of the ring, but there is sufficient space to accommodate them and no strains are developed.

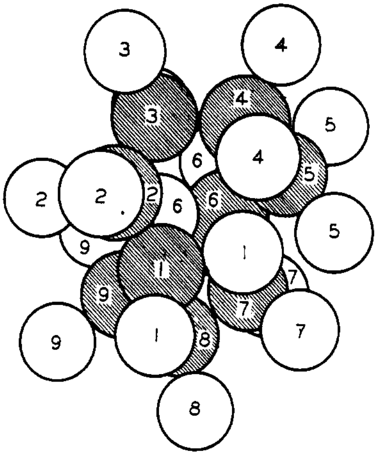

Fig 1.—Cyclononane (carbon, d = 1.54; hydrogen, 1.1). This model illustrates the cramped nature of the ring and the turning of hydrogen toward the center.

This idea of steric interferences due to "external" radii is capable of many interesting applications to the cyclic esters and anhydrides. It is unfortunately for this purpose impossible to assign any exact value to the external radius of hydrogen. Results obtained in the diphenyl problem[10] suggest that the value implied in a spherical hydrogen of 2.3 Å. is probably much too large; however, for immediate qualitative purposes the exact

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(10) *Cf.* Adams and Yuan, *Chem. Reviews*, **12**, 261 (1933).

value adopted is not particularly important. The following discussion is based on observation of models in which the hydrogen is represented as a sphere of radius 2.2 Å.

When a zig-zag hydrocarbon chain is constructed with such large hydrogens, it is immediately evident that the mobility of the chain is greatly reduced. The hydrogens interfere with many rotational movements that would present no difficulty if the hydrogens were absent. The interferences toward ring closure become exaggerated as the length of the chain is increased beyond 6 or 7 atoms. For a cycloparaffin of 9 atoms the interferences are so serious that the model is not constructible.

If an oxygen atom is inserted in the chain, the flexibility of the model is considerably increased, since this insertion is practically equivalent to the removal of two of the interfering hydrogens.[11] Actually also oxygen probably presents less resistance to the deflection of its valence angles, although this is not illustrated by the models. In the anhydrides and esters under consideration each structural unit contains in its chain at least one oxygen and at least one carbonyl carbon (which also bears no hydrogens). The result is a great increase in the constructibility of the models. Construction of models of the cyclic hydrocarbons in the range of 9 to 15 atoms requires either a compression of the hydrogen spheres or a considerable deflection of the angles. In the carbonates and anhydrides the entire series of monomers from the 5-atom ring up can be constructed from spherical wooden atoms without more than very slight deflection of the angles. From this one may infer that no maximum should appear in the curve relating density to ring-size of the carbonates. The experimental curve is shown in Fig. 2. Unfortunately data are lacking in the range of 7 to 10 atoms, but the nature of the curve makes it very improbable that any maximum exists.

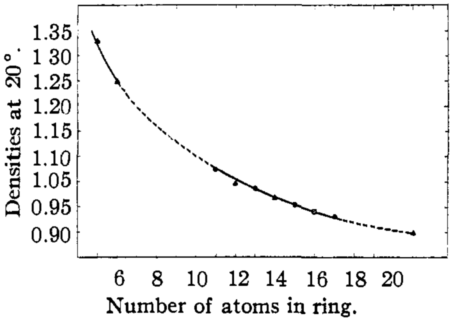

Fig. 2.—Densities of monomeric cyclic polymethylene carbonates at 20°: ⊙, values determined at 20°; ⊡, values obtained by extrapolation via molecular refractions from determinations of density made at 25°; △, values obtained by extrapolation via molecular refractions from determinations made at 50°.

Although it appears from the models that no compression of the hydrogen domains is involved in any of the cyclic ester or anhydride molecules, the manipulation of the models shows that there is a great difference in ease of ring closure depending upon the length of the chain. In the range of 8 to 14 atoms the interferences are so numerous that many trials and errors

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(11) This effect is probably considerably exaggerated in the models since the oxygens are represented only by their internal diameters.

must occur before the particular configuration that permits ring closure is found; and the ring when closed is then very rigid. In the carbonate series with the 15-membered ring the model acquires considerable flexibility.

The greater ease in constructibility of rings of 15 atoms or more explains why in the preparation of carbonates in the range of 7 to 12 atoms the products are almost exclusively the dimeric forms. At equilibrium the concentration of dimer will be large compared with the concentration of monomer. But as the ring size increases not only does the ease of monomer formation approach (and ultimately exceed) that of the dimer, but the latter becomes relatively more and more difficult to remove by evaporation. The ring-size at which the two forms begin to appear in equal amounts will depend partly upon the experimental conditions; but it will also be controlled to a certain extent by the nature of the ring. It is interesting in this connection to compare the three 14-membered rings undecamethylene carbonate, tetraethylene glycol carbonate and decamethylene oxalate. The first has two annular oxygens and one carbonyl, the second two oxygens and two carbonyls and the third five oxygens and one carbonyl. The first compound under the conditions used gave a mixture of monomer and dimer, the last two gave exclusively monomer.

The alkylene esters of dibasic acids above malonic yield chiefly dimers even when the unit length is as great as 18. The models do not furnish any very clear explanation of this fact although it appears that some advantage in ease of ring formation may be expected if the oxygens and carbonyls are all adjacent (as in oxalic esters).

The cyclic anhydrides present the same reluctance toward the formation of rings of intermediate size as do the esters, but they show some peculiarities. The products appear to be invariably either monomer or dimer, not mixtures of the two. The range of dimer formation is from 9 to 13 atoms (unit length). Very peculiar is the fact that the two even membered compounds (10 and 12 atoms) in this range appear to yield exceedingly unstable monomers rather than dimers. The result is the alternating effect shown graphically in Table I (p. 5025). The manipulation of models in this range furnished the impression that even-membered rings were more readily constructed than odd, but the geometrical peculiarity responsible for this effect was not identified. All of the cyclic anhydrides are exceedingly unstable at the high temperatures used in their formation, and the nature of the β-anhydrides produced might therefore be expected to be very sensitive to very slight differences in the ease of constructibility.

Ring Stability.—Ruzicka showed[12] that his macrocylic paraffins were not destroyed by the action of phosphorus and hydriodic acid at 250° and his cyclic ketones resisted the action of fuming hydrochloric acid at 180–

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[12] Ruzicka, Brugger, Pfeiffer, Schinz and Stoll, *Helv. Chim. Acta*, **9**, 499 (1926).

190°. This was an indication that large rings are no less stable than those of 5 or 6 atoms and a refutation of the idea that large rings are strained. It appears, however, in view of the results obtained with the cylic esters and anhydrides, that this conclusion requires some revision. The higher cyclic anhydrides all polymerize very readily. In this respect the large rings are very unstable as compared with those of 5 to 6 atoms, which do not polymerize at all. The instability rises to a maximum with the rings of 10 to 12 atoms, which polymerize rapidly even at temperatures below 0°. At elevated temperatures (*e. g.*, 200°) the macrocyclic esters also polymerize. It is therefore very difficult to accept the conclusion that large rings are entirely free from strain. Our interpretation of the facts is as follows.

Rings of 3 or 4 atoms have very large strains owing to the necessarily large deflection of the annular valences. Rings of 5 atoms are practically free of strain. Most rings of 6 atoms are strained. It is true that cyclohexane can be represented as existing in two strainless forms (*cis* and *trans*) but since it has not been possible to isolate two cyclohexanes, it seems likely that the two forms are in dynamic equilibrium. On each conversion of one form into the other the ring must pass through a nearly planar position of strain. The existence of such strain is indicated by the fact that all simple 6-membered cyclic esters polymerize very readily. (Glutaric anhydride does not polymerize but the oxygen valences in this case may permit sufficient deflection to avoid strain.) Larger rings are all strained. In the range of 7 to 14 atoms where the models are very rigid the strain may be pictured as due to the mutual repulsion of non-linked peripheral atoms that are crowded against one another. In larger, more flexible rings the vibrations due to thermal agitation constantly present the possibility of introducing momentary strains. This effect is similar to that pictured for the cyclohexane ring but is probably less pronounced. At any rate, 6-membered cyclic esters polymerize more readily than macrocyclic esters.

The ease of polymerization of the macrocyclic anhydrides is unquestionably associated with the extraordinary reactivity of anhydrides generally. A facile mechanism for the rupture of the ring is provided by the nature of the anhydride linkage and hence very slight strains or distortions, which may arise merely through small interferences among substituent atoms, need not be tolerated. The macrocyclic esters polymerize by a similar mechanism (*i. e.*, by ester interchange) but less readily because they are less reactive. The apparent high stability of the macrocyclic hydrocarbons and ketones is due to the fact that they present no point of easy chemical attack; if a sufficiently delicate chemical probe were available they would probably prove to be somewhat less stable than those of 5 atoms.

Summary

It is shown that the formation of macrocyclic ketones from salts of the dibasic acids probably involves first a linear polyketone which is subsequently cracked or decomposed. The ketones thus follow a course already established for esters and anhydrides. The characteristic analogies and differences in the three series can be explained by taking into account the nature of the reactions involved and the steric effects of peripheral atoms. Rings of more than 5 atoms cannot be regarded as entirely strainless. The probable nature of the strains in large rings is indicated.

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Organic Reactions with Boron Fluoride. VI. The Reaction of Acetamide with Alcohols and Phenol

BY FRANK J. SOWA AND JULIUS A. NIEUWLAND

The purpose of this paper is to describe the formation of esters by the removal of ammonia, in the form of monoammino boron fluoride,[1] from the acetamide–boron fluoride compound[2] and a second compound of the type ROH. The reaction takes place according to the equation

$$CH_3CONH_2{\cdot}BF_3 + ROH - CH_3CO_2R + BF_3{\cdot}NH_3$$

By this method the acetates of methyl, ethyl, isopropyl, *n*-butyl and *tert*-butyl alcohols and of phenol have been prepared in yields of 71, 69, 32, 50, 38 and 50%, respectively. The percentage yield depends upon the amount of boron fluoride used (as long as the latter is not in excess). This seems to indicate that the formation of the monoammino boron fluoride is the driving force of the reaction. From the foregoing results it is predicted that the acetamide–boron fluoride compound should be a good acetylating agent.

Various amides and alcohols are being studied in connection with this reaction. The reaction of the acetamide–boron fluoride compound with amines, acids, esters and hydrocarbons is also being examined.

Experimental

One mole of the alcohol or phenol was introduced into a 500-cc. flask containing the acetamide–boron fluoride compound, prepared by passing a mole of boron fluoride into a mole of acetamide. In a few cases monoammino boron fluoride separated as a white solid almost immediately. The flask was fitted with a reflux condenser and the mixture was refluxed

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[1] Kraus and Brown, THIS JOURNAL, **51**, 2690 (1929); Mixter, *Am. Chem. J.*, **2**, 153 (1881); Pflaum and Wenzke, *Ind. Eng. Chem., Anal. Ed.*, **4**, 392 (1932).

[2] Bowlus and Nieuwland, THIS JOURNAL, **53**, 3835 (1931).