

## 236. The Application of the Method of Electrostatic Energy Differences. Part I. Stereochemistry of the Diterpenoid Resin Acids.

By D. H. R. BARTON and (in part) G. A. SCHMEIDLER.

The potential applicability of dissociation-constant measurements in the elucidation of molecular structure is emphasised. As an example of the utility of this method of approach it is shown that rings A and C of abietic acid must be *trans*-fused, previous conflicting evidence on this point being without value.

THE use of dissociation-constant measurements in the elucidation of the configuration of symmetrical dicarboxylic acids in solution has received much attention, particularly in the thorough investigations of Ingold (see Gane and Ingold, *J.*, 1931, 2153; Ingold, *ibid.*, p. 2179, and references there cited). The general interpretation of the experimental results may be conveniently summarised by the equation

$$\log_{10} K_a^2/4K_a'^2 = N_0 \epsilon^2 / 2 \cdot 3RT D_E r \quad \dots \quad (i)$$

where  $K_a^2$  and  $K_a'^2$  are respectively the first and the second measured thermodynamic dissociation constants,  $N_0$  is the Avogadro number,  $\epsilon$  the electronic charge,  $R$  the gas constant, and  $D_E$  the effective dielectric constant for the space between the two carboxyl groups separated by the distance  $r$ . The derivation of this equation from simple electrostatic and statistical theories is well known (Bjerrum, *Z. physikal. Chem.*, 1923, 106, 219; Maxwell and Partington, *Trans. Faraday Soc.*, 1937, 33, 670) and is readily extended to the relative dissociation constants of an unsubstituted acid as compared with the same acid substituted by various unit polar and dipolar groups. In the latter case we may write

$$\log_{10} \frac{K_a^0}{K_a'} = \frac{N_0 \epsilon}{2 \cdot 3RT} \left[ \sum_{i=1}^{i=n} \frac{\epsilon}{D_E r_i} + \sum_{j=1}^{j=m} \frac{\mu_j \cos \theta_j}{D_E r_j^2} \right] \quad \dots \quad (ii)$$

where  $K_a^0$  is the measured thermodynamic dissociation constant of the unsubstituted acid,  $K_a'$  refers in the same way to the acid when substituted by  $n$  unit polar groups and  $m$  dipolar groups,  $\mu_j$  is the dipole moment of the  $j$ th substituent, and  $\theta_j$  is the angle that the line joining the seat of the charge in the acidic group to the centre of the dipole makes with the dipole itself. The other symbols have the obvious significance and the appropriate attention must be paid to the signs to be attached to each term.

It is convenient when dealing with unit polar substituents to define

$$N_0 \epsilon^2 / 2 \cdot 3RT D_E r = p\omega = -\log_{10} \omega \quad \dots \quad (iii)$$

There has been a number of interesting attempts to calculate values of  $p\omega$  in suitable cases from first principles. Of these, the most comprehensive is that of Kirkwood and Westheimer (*J. Chem. Physics*, 1938, 6, 506, 513; compare Sarmousakis, *ibid.*, 1944, 12, 277), which expresses  $D_E$  as a function of the molecular dimensions and of the external and internal dielectric constants. Although this theory has, on the whole, been well received (compare, however, Wynne-Jones and Rushbrooke, *Trans. Faraday Soc.*, 1944, 40, 99, and see also Westheimer and Kirkwood, *ibid.*, 1947, 43, 77), it is still too complex and too unreliable to be applied by the organic chemist in the elucidation of molecular structure. Nevertheless, this does not prevent the application of tables of  $p\omega$  values provided these are drawn from the empirically determined dissociation constants of suitable model substances. Such use may be described as "The Application of the Method of Electrostatic Energy Differences". In Table I various  $p\omega$  values are recorded for subsequent employment in this paper.

TABLE I.\*

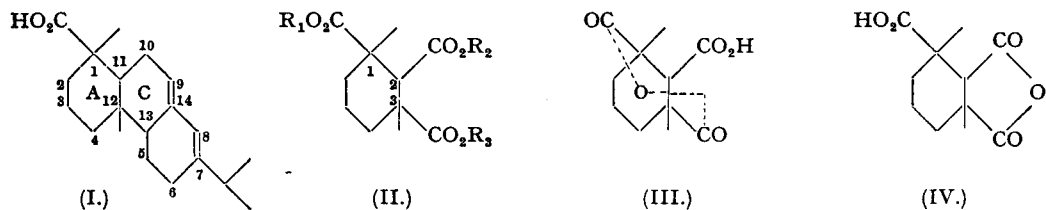
| Substance.                                                  | Solvent.                        | $p\omega$ . |               |
|-------------------------------------------------------------|---------------------------------|-------------|---------------|
|                                                             |                                 | <i>cis.</i> | <i>trans.</i> |
| <i>cyclo</i> Hexane-1 : 2-dicarboxylic acid .....           | H <sub>2</sub> O                | 1.80        | 1.15          |
|                                                             | 50 : 50-MeOH-H <sub>2</sub> O † | 2.34        | 1.33          |
| 1 : 2 : 3 : 4-Tetrahydronaphthalene-2 : 3-dicarboxylic acid | H <sub>2</sub> O                | 1.89        | 1.10          |
|                                                             | 50 : 50-MeOH-H <sub>2</sub> O † | 0.76        | 0.82          |
| <i>cyclo</i> Hexane-1 : 3-dicarboxylic acid .....           | H <sub>2</sub> O                | 0.76        | 0.82          |
|                                                             | 50 : 50-MeOH-H <sub>2</sub> O † | 0.98        | 1.32          |

\* The  $p\omega$  values given are calculated from the results of Speakman (*J.*, 1941, 490) and of Kuhn and Wassermann (*Helv. Chim. Acta*, 1928, 14, 50). When the carboxyls are in the 1 : 2-positions this may be indicated by writing  $p\omega_{1:2}$ , and similarly for  $p\omega_{1:3}$ .

† By volume.

The first application of this method has been made in the diterpenoid resin acid field. The formula (I) for abietic acid has received abundant confirmation in recent years, but the nature of the ring fusion between rings A and C is still uncertain as also is the stereochemistry at C<sub>13</sub>. With regard to the former problem, Campbell and Todd (*J. Amer. Chem. Soc.*, 1942, **64**, 928) have suggested that the fusion is *trans*-, whilst Lombard (*Bull. Soc. chim.*, 1946, **13**, 428) asserts that it is *cis*-. Campbell and Todd's evidence is based upon a study of the relative degree of steric hindrance towards alkaline hydrolysis of the esters of podocarpic acid and dehydroabietic acid. It is only correct if *cis*-decalin is assumed to have the conventional Sachse-Mohr configuration and not that of the energetically more stable two-chair *cis*-decalin (see Barton, this vol., p. 340, where these two *cis*-decalins are conveniently illustrated). This may easily be seen by an inspection of molecular models. Since the latter alternative is the more probable, Campbell and Todd's reasoning is not admissible.

Lombard's conclusion is based on the following evidence. When abietic acid is vigorously oxidised it furnishes, amongst other products, a tricarboxylic acid, C<sub>11</sub>H<sub>16</sub>O<sub>6</sub>, to which the formula (II; R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H) must be assigned. This acid has been studied in some detail by Ruzicka, Goldberg, Huyser, and Seidel (*Helv. Chim. Acta*, 1931, **14**, 545), who showed that the 1 and the 3 carboxyl group must be in the *cis*-relationship. On treatment with acetyl chloride the tricarboxylic acid furnished a mixture of two anhydrides, m. p. ca. 100° and m. p. 170—172°. On symmetry grounds the higher-melting anhydride must now be given the formula (III) and the lower-melting one the formula (IV). [Formulae (II), (III), and (IV) have no stereochemical significance as written here.] Although both these anhydrides could be smoothly reconverted into the parent tricarboxylic acid by hydrolysis, the method of their formation with acetyl chloride does not provide evidence as to the stereochemistry of the carboxyl attached to C<sub>2</sub> (compare Werner and Conrad, *Ber.*, 1899, **32**, 3046).



Subsequently, Lombard (Thesis, Paris, 1943, p. 43) showed that the action of heat alone at about 250° on the tricarboxylic acid furnished an anhydride, m. p. 175°, admitted to be identical with that of m. p. 170—172° prepared earlier by Ruzicka *et al.* (*loc. cit.*). If this anhydride had been derived from two carboxyls attached at the 1:2-positions in the cyclohexane ring its method of formation would indeed have proved them to be in the *cis*-relationship. Since, however, it is doubtless derived from the 1:3-carboxyls, its formation by the action of heat only serves to confirm that these are in the *cis*-relationship (it is well known that *trans*-cyclohexane-1:3-dicarboxylic acid does not furnish a monomeric anhydride) and provides no evidence as to the stereochemistry of the carboxyl attached at C<sub>2</sub>.

In the discussion of polybasic acids in this paper and subsequent parts of this series it is convenient to define nomenclature for dealing with the general case. For a completely asymmetric *n*-basic acid, AH<sub>*n*</sub>, there are *n* possible sites of residence for the negative charge on derived univalent anions and *n*(*n* - 1)/2 sites of residence for the two negative charges on derived bivalent anions. The first two measured (or gross) thermodynamic dissociation constants, K<sub>*a*</sub><sup>*n*</sup> and K<sub>*a*</sub><sup>*n*</sup><sub>2</sub>, may be defined by

$$K_{a_n}^n = a_{H^+} \cdot \frac{\sum_{j=1}^{j=n} [AH_{n-1}]_j^- \cdot f_-}{[AH_n] \cdot f_0} = \sum_{k=1}^{k=n} {}^k K_{a_n}^n \dots \dots \dots (iv)$$

and

$$K_{a_n}^n = a_{H^+} \cdot \frac{\sum_{i=1}^{i=n(n-1)/2} [AH_{n-2}]_i^{2-} \cdot f_-}{\sum_{j=1}^{j=n} [AH_{n-1}]_j^- \cdot f_-} = \sum_{i=1}^{i=n(n-1)/2} \frac{1}{\sum_{m=1}^{m=n} \frac{1}{i K_{a_n}^n}} \dots \dots \dots (v)^*$$

\* The use of the expression on the extreme right in (v) will be found to involve partial dissociation constants that do not *formally* exist. This difficulty is, however, easily resolved since the latter can be expressed in terms of those partial dissociation constants which do have obvious meaning.

The expression on the extreme right in (iv) represents the sum of the thermodynamic *partial* dissociation constants for the first ionisation, whilst the corresponding expression in (v) represents  $K_a^n$ , in terms of the thermodynamic partial dissociation constants for the second ionisation. The generalised nomenclature adopted for partial dissociation constants will be clear from their context.\* The symbols  $f_0$ ,  $f_-$ , and  $f_{-}$  represent the activity coefficients of the undissociated acid, the univalent anions, and the bivalent anions, respectively.

If one now considers the potentiometric titration of this  $n$ -basic acid, assuming that higher charges than two do not make contributions during the addition of  $B$  equivs. of alkali (up to a total of 2 equivs.), then

$$A = \text{molarity of the acid} = [\text{AH}_n] + \sum_{j=1}^{j=n} [\text{AH}_{n-1}]_j^- + \sum_{i=1}^{i=n(n-1)/2} [\text{AH}_{n-2}]_i^-$$

and 
$$B + [\text{H}]^+ = \sum_{j=1}^{j=n} [\text{AH}_{n-1}]_j^- + 2 \sum_{i=1}^{i=n(n-1)/2} [\text{AH}_{n-2}]_i^- + [\text{OH}]^-$$

Defining

$$\alpha = B + [\text{H}]^+ - [\text{OH}]^- = \sum_{j=1}^{j=n} [\text{AH}_{n-1}]_j^- + 2 \sum_{i=1}^{i=n(n-1)/2} [\text{AH}_{n-2}]_i^-$$

$$\beta = A - B - [\text{H}]^+ + [\text{OH}]^- = [\text{AH}_n] - \sum_{i=1}^{i=n(n-1)/2} [\text{AH}_{n-2}]_i^-$$

$$\gamma = 2A - B - [\text{H}]^+ + [\text{OH}]^- = 2[\text{AH}_n] + \sum_{j=1}^{j=n} [\text{AH}_{n-1}]_j^-$$

it is readily shown that

$$a_{\text{H}^+}^2 \cdot \left(\frac{\alpha}{\gamma}\right) \cdot \frac{f_-}{f_0} = K_a^n \cdot a_{\text{H}^+} \cdot \left(\frac{\beta}{\gamma}\right) \cdot \frac{f_-}{f_-} + K_a^n \cdot K_a^n \dots \dots \dots \text{(vi)}$$

Clearly this may be plotted as a linear equation and has, therefore, considerable advantages in the interpretation of the experimental results. All the data recorded in the experimental section for polybasic acids were obtained in this way. For a symmetrical dibasic acid (vi) takes a form previously shown to hold by Speakman (*J.*, 1940, 855), whilst for asymmetrical dibasic acids (vi) assumes a form, (vii), previously shown to be applicable by the author (*Nature*, 1947, 160, 752) :

$$a_{\text{H}^+}^2 \cdot \left(\frac{\alpha}{\gamma}\right) \cdot \frac{f_-}{f} = ({}^1K_a^2 + {}^2K_a^2) \cdot a_{\text{H}^+} \cdot \left(\frac{\beta}{\gamma}\right) \cdot \frac{f_-}{f_-} + \frac{({}^1K_a^2 + {}^2K_a^2) \cdot \frac{1}{2}K_a^2 \cdot \frac{1}{2}K_a^2}{(\frac{1}{2}K_a^2 + \frac{1}{2}K_a^2)} \dots \dots \dots \text{(vii)}$$

(vi) may be used for the evaluation of  $p\omega$  values and hence for the elucidation of molecular structure. In the important case of an asymmetric dicarboxylic acid [equation (vii)] the constant term may be simplified by the considerations that

$$\log_{10} \frac{{}^1K_a^2}{{}^2K_a^2} = \frac{N_0 e^2}{2 \cdot 3 R T D_{E'}} = \log_{10} \frac{{}^2K_a^2}{{}^1K_a^2} \dots \dots \dots \text{(viii)}$$

so that it becomes equal to

$${}^1K_a^2 \cdot {}^2K_a^2 \cdot e^{-N_0 e^2 / R T D_{E'}}$$

from which  $p\omega$  may be calculated provided that  ${}^1K_a^2$  or  ${}^2K_a^2$  is known. Measurements on (say) monomethyl esters readily provide this information.

Before proceeding further with application of (vi) it is of interest to see how far  $K_a^n$  values are in agreement with those calculated from the dissociation constants of the appropriate methyl esters in the case of the tricarboxylic acid (II;  $R_1 = R_2 = R_3 = \text{H}$ ) and its derivatives. It will be seen from Table II that agreement is satisfactory, the carboxyl group having an apparently more powerful " inductive effect " than the carbomethoxyl group, an observation in full accord with the data for comparable acids (see Greenspan, *Chem. Reviews*, 1933, 12, 339).

\* Thus the left-hand superscript refers to the ions, numbered in order, produced by the dissociation, the left-hand subscript to the dissociating molecules or ions numbered in order, the right-hand superscript to the number of dissociatable carboxyl groups in the initial polybasic acid, and the right-hand subscript to the stage of dissociation—first stage, one dash; second stage, two dashes, and so on. The subscript  $a$  indicates that reference is made to thermodynamic partial dissociation constants. For the first dissociation the left-hand subscript may be omitted, since it is unity for all  $n$  values of the left-hand superscript. Similarly for the last dissociation the left-hand superscript may be omitted without ambiguity.

TABLE II.\*

| Substance.                             | $K_a^3 \times 10^6$ . |                                                |
|----------------------------------------|-----------------------|------------------------------------------------|
|                                        | Obs.                  | Calc. from dimethyl esters (see Experimental). |
| (II; $R_1 = R_2 = R_3 = H$ ).....      | 14.0                  | 11.8                                           |
| (II; $R_1 = Me, R_2 = R_3 = H$ ) ..... | 10.3                  | 8.8                                            |
| (II; $R_2 = Me, R_1 = R_3 = H$ ) ..... | 6.54                  | 6.04                                           |

\* All data are for aqueous solutions.

The asymmetric monomethyl ester (II;  $R_1 = Me, R_2 = R_3 = H$ ) of the tricarboxylic acid being considered, application of equations (vii) and (viii) should enable a  $p\omega_{1,2}$  value to be obtained for comparison with those given in Table I. A *cis*-dicarboxylic acid should have a  $p\omega_{1,2}$  value of about 1.85, a *trans*-acid a value of about 1.13. In practice a value of  $p\omega_{1,2} = 1.11$  was found, which is proof that the  $C_2$  carboxyl in the tricarboxylic acid has the *trans*-configuration with respect to the  $C_1$  and  $C_3$  carboxyls.

Now it is easily seen that the  $n$ th measured thermodynamic dissociation constant of an  $n$ -basic acid is related to the corresponding partial dissociation constants by the equation

$$\frac{1}{K_{a^n}^n} = \sum_{i=1}^{n-1} \frac{1}{K_{a_i}^i} \quad \dots \quad (ix)$$

For the tricarboxylic acid (II;  $R_1 = R_2 = R_3 = H$ ) it is clear, having regard to symmetry conditions, that the equation

$$\frac{1}{K_{a^3}^3} = \frac{2}{1K_{a^2}^2} + \frac{1}{2K_{a^1}^1} \quad \dots \quad (x)$$

must hold. Since  $1K_{a^2}^2$  and  $2K_{a^1}^1$  can be calculated from the  $K_a^1$  values of the appropriate dimethyl esters (see Tables IV and V) and the appropriate  $p\omega$  values (see Exptl.), calculated values of  $pK_{a^n}^n$  may be compared with those observed experimentally. This information is presented in Table III. It will be seen that the observed values are in satisfactory agreement for a *cis*-structure in the tricarboxylic acid, a result in apparent conflict with the evidence given above. In actual fact there is no disagreement, for the following reasons.

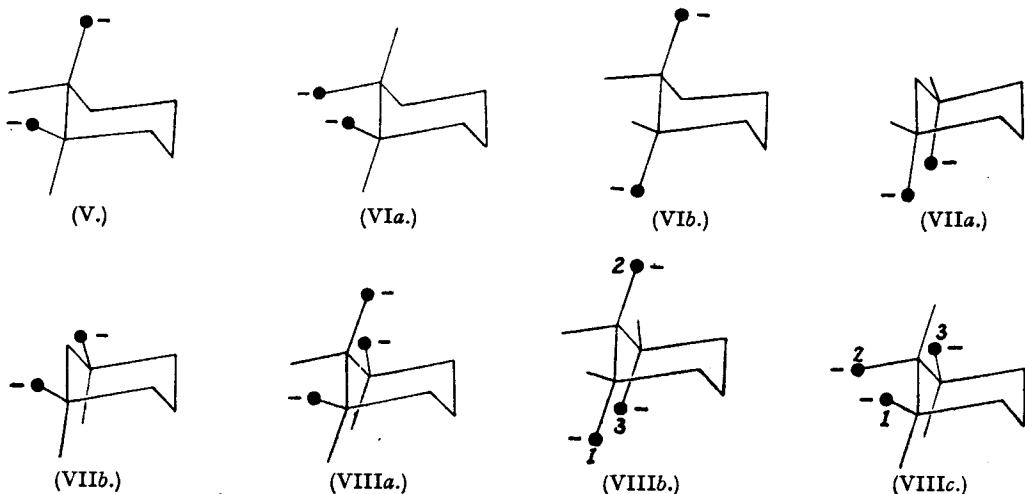
TABLE III.

| Solvent.                                | $pK_{a^n}^n$ . |                |      | Remarks.                                                                                    |
|-----------------------------------------|----------------|----------------|------|---------------------------------------------------------------------------------------------|
|                                         | <i>cis</i> .   | <i>trans</i> . | Obs. |                                                                                             |
| H <sub>2</sub> O .....                  | 8.03           | 7.09           | 7.83 | Determined potentiometrically                                                               |
| 50 : 50-MeOH-H <sub>2</sub> O (by vol.) | 10.23          | 8.86           | ~9.6 | This observed value is only an approximate one for $pK_{a^n}^n$ determined colorimetrically |

It is now generally accepted that the chair configuration of *cyclohexane* is appreciably more stable than the boat configuration (compare Barton, *loc. cit.*). In the former all arrangements of the valency directions about the carbon atoms correspond to the staggered configuration in ethane, in which there are two distances between hydrogen atoms not bonded to the same carbon atom, a "short" distance and a "long" distance. In the chair configuration of *cis-cyclohexane-1:2*-dicarboxylic acid the negative charges of the bivalent anion must be separated by the "short" distance [as in (V)] whilst in the *trans*-acid the distance may be either "short" or "long" [as in (VIa) and (VIb) respectively]. The fact that *cis*- and *trans*-acids have greatly different  $p\omega_{1,2}$  values is, on the assumption that  $D_B$  is roughly the same for both, a proof that the configuration of the bivalent anion of the *trans*-acid must be as in (VIb) (compare Speakman, *J.*, 1941, 490), which is, of course, energetically more stable on electrostatic reasoning than (VIa). Now the  $p\omega_{1,3}$  value for *cis-cyclohexane-1:3*-dicarboxylic acid in water from Table I is 0.76, whilst that for the symmetrical monomethyl ester (II;  $R_2 = Me, R_1 = R_3 = H$ ) (see Exptl.) is in fair agreement at 0.96. The discrepancy is doubtless due to the lower value of  $D_B$  in (II;  $R_2 = Me, R_1 = R_3 = H$ ) because here more of the lines of force in the bivalent anion travel through the bulky carbomethoxyl group of low dielectric constant than through the relatively small hydrogen atom in the reference compound. The bivalent anions of such *cyclohexane-1:3*-dicarboxylic acids can adopt two configurations shown in (VIIa) and (VIIb). In (VIIa) the charges (assumed to lie 1 A. beyond the C atom of the COO<sup>-</sup> group and on the line of the terminal C-C bond: compare Gane and Ingold, *loc. cit.*) are 2.51 A. apart, whilst in (VIIb) they are 6.66 A. apart, so that (VIIb) is clearly the configuration to be expected. The relative

$\rho_{\omega_{1,2}}$  and  $\rho_{\omega_{1,3}}$  values confirm this. The calculations of Table III have been made assuming that the *cis*-tervalent anion would have the configuration (VIIIa) and the *trans*-anion that in (VIIIb), both configurations being logical extensions of (V) and (VIb) respectively.

It is, however, possible for the *trans*-anion to adopt the configuration (VIIIc), in which the distance between the negative charges 1 and 2 and 2 and 3 (4.02 Å.) corresponds to the "short" distance and not the "long" distance (5.78 Å.) as in (VIIIb). In this case the  $pK_a^{3,4}$  value for the tricarboxylic acid would approximate to that required by the *cis*-anion (VIIIa), as is experimentally observed. Using the  $\rho_{\omega}$  values of Table I for the evaluation of electrostatic energy differences



and making the necessary extrapolation to obtain  $D_E$  for  $r = 2.51$  Å., we can readily show that (VIIIc) is about 1 kilocal. more stable than (VIIIb). It is possible to reconcile therefore the data of Table III with the *trans*-configuration of the tricarboxylic acid (II;  $R_1 = R_2 = R_3 = H$ ) without undue difficulty.

Finally, one can evaluate  $\rho_{\omega_{1,2}}$  for the tricarboxylic acid by the application of equation (vi) to the first two-thirds of its titration curve. As before, a  $\rho_{\omega_{1,2}}$  value of about 1.85 would indicate a *cis*-acid and a value of about 1.13 a *trans*-acid. Experimentally a value of about 1.37 was observed. This may be taken as being in fair agreement with the requirement for a *trans*-acid because the constant term in (vi), from which  $\rho_{\omega_{1,2}}$  is evaluated, is sensitive to errors in the determination of the second measured dissociation constant of (II;  $R_2 = Me$ ,  $R_1 = R_3 = H$ ).

From these experiments it is to be concluded that the ring fusion between rings A and C in abietic acid is *trans*-. The same conclusion must apply to levopimaric acid, *isobietic* acid, *neobietic* acid, and *dextrosapinic* acid, and also to *dextropimaric* acid and *iso-dextropimaric* acid. (The inter-relationship of these acids is fully dealt with in "The Terpenes", Vol. III, by Simonsen and Barton, Cambridge Univ. Press.)

#### EXPERIMENTAL.

All m. p.s of acids which decomposed at the temperature of fusion were taken in the manner described by Ruzicka *et al.* (*Helv. Chim. Acta*, 1931, 14, 545). Under these conditions reproducible results were obtainable.

The expression "light petroleum" refers to the fraction of b. p. 40—60°.

*Tricarboxylic Acid* (II;  $R_1 = R_2 = R_3 = H$ ).—Abietic acid was prepared from colophony by Dupont's method (*Bull. Soc. chim.*, 1924, 35, 394), which was found to be superior to that of Steele (*J. Amer. Chem. Soc.*, 1922, 44, 1333). The abietic acid was oxidised by nitric acid according to the second procedure described by Levy (*Ber.*, 1929, 62, 2497) except that addition, as catalyst, of 0.2% by weight of the abietic acid of vanadium pentoxide was found to be beneficial (compare Lombard, *Bull. Soc. chim.*, 1942, 9, 833; Thesis, Paris, 1943, p. 40). A preliminary oxidation of the abietic acid by potassium permanganate was not required. The tricarboxylic acid was isolated by evaporation of the nitric acid solution at 50—60° and then readily crystallised out in a nearly pure form. It was purified by recrystallisation from acetone; m. p. 218° (decomp.) (Found: equiv., 81.0. Calc. for  $C_{11}H_{16}O_6$ : equiv., 81.3); yield about 7%.

*Trimethyl Ester* (II;  $R_1 = R_2 = R_3 = Me$ ).—The tricarboxylic acid, suspended in ether, was esterified with diazomethane in the usual way. After removal of the ether in a vacuum and recrystallisation from aqueous methanol, an almost quantitative yield of the trimethyl ester, m.p. 73.5—74.5°, was obtained.

*s*-Dimethyl Ester (II;  $R_1 = R_2 = \text{Me}$ ,  $R_3 = \text{H}$ ).—Prepared by esterification of the tricarboxylic acid with methanolic hydrogen chloride according to directions given by Ruzicka *et al.* (*loc. cit.*), and recrystallised from ether—light petroleum, this had m. p. 120—120.5° (Found: equiv., 272. Calc. for  $\text{C}_{13}\text{H}_{20}\text{O}_6$ : equiv., 272).

*as*-Dimethyl Ester (II;  $R_1 = R_2 = \text{Me}$ ,  $R_3 = \text{H}$ ).—1.49 G. of the trimethyl ester (II;  $R_1 = R_2 = R_3 = \text{Me}$ ) in methanol solution were refluxed for 18 hours with the theoretical amount of methanolic potassium hydroxide required for the hydrolysis of one carbomethoxyl group. The methanol was removed by evaporation in a vacuum, and the crystalline residue separated by addition of ether and a little water into acid and neutral fractions. The latter furnished 1.17 g. of unchanged trimethyl ester, whilst the former, after acidification, afforded a total of 210 mg. of *as*-dimethyl ester; recrystallised from benzene—light petroleum, this had m. p. 119—121°. There was a large depression in m. p. on admixture with the *s*-dimethyl ester described above (Found: C, 57.4; H, 7.6; equiv., 273.  $\text{C}_{13}\text{H}_{20}\text{O}_6$  requires C, 57.4; H, 7.4%; equiv., 272).

*as*-Monomethyl Ester (II;  $R_1 = \text{Me}$ ,  $R_2 = R_3 = \text{H}$ ).—The tricarboxylic acid was esterified with methanolic hydrogen chloride according to Ruzicka *et al.* (*loc. cit.*), but working up of the product according to their directions afforded various preparations of m. p.s between 152° and 160°. Those of lower m. p. had equivalents that were too high, and those of higher m. p. equivalents that were too low. These products could be crystallised with difficulty from ethyl acetate—benzene on long standing. After such treatment the m. p.s were usually about 156°; Ruzicka *et al.* (*loc. cit.*) give m. p. 154—156° for a preparation described as a fine powder. It was finally found that the *as*-monomethyl ester crystallised well from water to give a product, m. p. ca. 163° (decomp.) (Found: equiv., 133. Calc. for  $\text{C}_{12}\text{H}_{18}\text{O}_6$ : equiv., 129). Repeated crystallisation from water did not change the m. p. significantly and did not greatly alter the equivalent (Found: equiv., 129, 130, 129). It is to be concluded that the preparation described here was pure *as*-monomethyl ester.

*s*-Monomethyl Ester (II;  $R_2 = \text{Me}$ ,  $R_1 = R_3 = \text{H}$ ).—Prepared by vigorous alkaline hydrolysis of the trimethyl ester (II;  $R_1 = R_2 = R_3 = \text{Me}$ ) (see above) following the directions of Ruzicka *et al.* (*loc. cit.*), and recrystallised from water, this had m. p. 188—190° (decomp.) (Found: equiv., 130. Calc. for  $\text{C}_{12}\text{H}_{18}\text{O}_6$ : equiv., 129).

*Determination of Dissociation Constants.*—Thermodynamic dissociation constants in water were determined by potentiometric titration following, in general, Speakman's procedure (*J.*, 1940, 855). The measurements were made at room temperature which varied over the range  $23^\circ \pm 2^\circ$ . All solutions were made up in carbon dioxide-free distilled water.

A saturated calomel electrode was used as source of constant potential and was joined by means of a glass capillary containing potassium chloride solution, suitably gelled by the addition of agar-agar, to the titration cup of 10—20 ml. capacity. This cup contained a glass electrode and the drawn out tip of a mercury-operated 1-ml. micro-burette (reading to 0.001 ml.).

During titration the solution in the cup was stirred by passage of a stream of nitrogen previously saturated with water vapour. When using 0.0263*N*-sodium hydroxide solution delivered from the micro-burette and an acid molarity of about 0.0003 it is not necessary to correct for the change in volume during the titration. The pH scale was standardised by the buffers suggested by Hitchcock and Taylor (*J. Amer. Chem. Soc.*, 1937, 59, 1812), and activity coefficients, *f*, were calculated from the Debye-Hückel equation  $\log_{10} f = -0.5z^2\sqrt{\mu}$ , where *z* = valency of the ion and  $\mu$  = the ionic strength. In view of the very dilute solutions employed in the experiments in this paper, the use of this equation is fully justified.

The results obtained are summarised in Table IV, the symbolism being that defined above. It is also fully explained in the text how the results of a potentiometric titration are converted into the linear equations required for the evaluation of the thermodynamic dissociation constants.

TABLE IV.

| Substance.                                            | Molarity. | $K_a$ values.                                                                              |
|-------------------------------------------------------|-----------|--------------------------------------------------------------------------------------------|
| (II; $R_1 = R_2 = R_3 = \text{H}$ )                   | 0.000460  | $K_a^3 = 13.3 \times 10^{-5}$ ; $p\omega_{1:2} = 1.32^*$                                   |
|                                                       | 0.000223  | $K_a^3 = 14.0 \times 10^{-5}$ ; $p\omega_{1:2} = 1.42^*$                                   |
|                                                       |           | $K_a^{3''} = 1.48 \times 10^{-6}$ † or $1.61 \times 10^{-6}$ ‡                             |
| (II; $R_1 = R_3 = \text{Me}$ , $R_2 = \text{H}$ ) ... | 0.000293  | $K_a^1 = 5.75 \times 10^{-5}$                                                              |
| (II; $R_1 = R_2 = \text{Me}$ , $R_3 = \text{H}$ ) ... | 0.000416  | $K_a^1 = 3.02 \times 10^{-5}$                                                              |
| (II; $R_1 = \text{Me}$ , $R_2 = R_3 = \text{H}$ ) ... | 0.000570  | $K_a^2 = 10.3 \times 10^{-5}$ ; $p\omega_{1:2} = 1.11^*$                                   |
| (II; $R_2 = \text{Me}$ , $R_1 = R_3 = \text{H}$ ) ... | 0.000500  | $K_a^2 = 6.54 \times 10^{-5}$ ; $K_a^{2''} = 1.84 \times 10^{-6}$ ; $p\omega_{1:3} = 0.96$ |

\* Values of  $p\omega$  are calculated by using the result  $K_a^1 = 3.27 \times 10^{-5}$  obtained in the titration of (II;  $R_2 = \text{Me}$ ,  $R_1 = R_3 = \text{H}$ ). This is then used to obtain the other necessary figures by subtraction from  $K_a^2$  values.

† The Henderson equation being assumed to apply to the last third of the titration curve.

‡ On the assumption that the last two thirds of the titration curve can be analysed by the use of equation (vii) (see text).

(With C. J. W. BROOKS.) Concentration dissociation constants in 50:50 (by vol.) methanol-water were determined by colorimetry, approximately 0.01*M*-solutions, one-half neutralised with respect to the appropriate dissociation constant, being used. The match points were determined against partly neutralised solutions of benzoic acid and phenol or *p*-chlorophenol depending on the approximate pH. Reference data for these substances were taken from Bright and Briscoe (*J. Physical Chem.*, 1933, 37, 787) and from Kuhn and Wassermann (*Helv. Chim. Acta*, 1928, 11, 1). Table V summarises the results of the experiments.

TABLE V.

| Substance.                                                           | Indicator.       | Reference acid.        | pK <sub>a</sub> values. |
|----------------------------------------------------------------------|------------------|------------------------|-------------------------|
| (II; R <sub>1</sub> = R <sub>2</sub> = R <sub>3</sub> = H) .....     | Thymol-blue      | Phenol                 | ~9.6                    |
|                                                                      | Thymol-blue      | <i>p</i> -Chlorophenol | ~9.6                    |
|                                                                      | Bromothymol-blue | <i>p</i> -Chlorophenol | ~9.6                    |
| (II; R <sub>1</sub> = R <sub>3</sub> = Me, R <sub>2</sub> = H) ..... | Methyl-red       | Benzoic acid           | ~5.45                   |
| (II; R <sub>1</sub> = R <sub>2</sub> = Me, R <sub>3</sub> = H) ..... | —                | —                      | ~5.73 *                 |

\* This value was assigned from consideration of that for (II; R<sub>1</sub> = R<sub>3</sub> = Me, R<sub>2</sub> = H). It cannot be seriously in error.

We are indebted to the Government Grants Committee of the Royal Society for financial assistance in the purchase of a pH meter. This work was carried out during the tenure of an I.C.I. Fellowship by one of us (D. H. R. B.).

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,  
LONDON, S.W. 7.

[Received, September 9th, 1947.]

## 237. Isomers of 2-Chlorovinyl-dichloroarsine.

By C. L. HEWETT.

Two isomeric forms of 2-chlorovinyl-dichloroarsine have been prepared from the mixture obtained by the interaction of acetylene and arsenic trichloride in the presence of catalysts. The pure arsonic acids have also been prepared.

THE possibility that 2-chlorovinylarsonic acid and the derived dichloroarsine ("lewisite") could exist in *cis*- and *trans*-forms has been mentioned in the literature (cf. Gibson and Gibson, *J.*, 1931, 753), but no attempt had been made to prepare the two forms in a pure state.

The mixture known as "lewisite", prepared by interaction of acetylene and arsenic trichloride in the presence of aluminium chloride (Green and Price, *J.*, 1921, 119, 448) was reported to be highly active as a vesicant, its activity being due to the 2-chlorovinyl-dichloroarsine. When, however, 2-chlorovinyl-dichloroarsine was prepared by using mercuric chloride or cuprous chloride as a catalyst (Jones *et al.*, *Ind. Eng. Chem.*, in the press), it appeared to be somewhat less vesicant and it seemed possible that this difference might be due to different amounts of the two isomers being present. Since aluminium chloride usually favours the formation of the *trans*-compound (Zelinsky and Turowa-Pollak, *Ber.*, 1929, 62, 1618; 1932, 65, 1299) and since acetylene normally gives rise to *trans*-addition products (Garner, *Chem. News*, 1919, 119, 16), it seemed probable that the aluminium chloride product would have the *trans* configuration. Backe and Beute (*Rec. Trav. chim.*, 1935, 54, 167), however, have shown that under certain conditions propiolic acid gives rise to *cis*-addition products, and it seemed possible that mercuric chloride and cuprous chloride might give rise to more *cis*-2-chlorovinyl-dichloroarsine than would aluminium chloride.

2-Chlorovinyl-dichloroarsine prepared by all three methods was shown to consist in the main of the same isomer by oxidation, by means of hydrogen peroxide, to the same arsonic acid, m. p. 130—131°, which is presumed to have the *trans*-configuration. In each case the liquors of this acid contained a second acid which was extremely soluble in water and in all aqueous solvents and difficult to isolate.

Attempts to separate *cis*- and *trans*-2-chlorovinyl-dichloroarsine by fractional distillation indicated that the isomer presumed to have the *cis*-configuration had a lower b. p. than the other, since the lower-boiling fractions yielded less arsonic acid, m. p. 130—131°, than did the higher-boiling fractions. However, since no clear cut could be observed between the first and last fractions without a slow distillation rate, this method of separation was abandoned, since prolonged heating of the dichloroarsine causes disproportionation to arsenic trichloride and the 2 : 2'-dichlorodivinylchloroarsine.

Pure *trans*-chlorovinyl-dichloroarsine, prepared from the arsonic acid, liberates two molecules of hydrochloric acid with water with formation of chlorovinylarsine oxide; on treatment with cold sodium hydroxide solution a third molecule of hydrochloric acid is liberated with the formation of sodium arsenite and evolution of one molecule of acetylene. This gives a useful method of estimating the purity of *trans*-2-chlorovinyl-dichloroarsine; when, however, it was applied to redistilled 2-chlorovinyl-dichloroarsine prepared by using cuprous chloride as catalyst, it gave results of only 90%. This suggested that the other constituent, presumably the *cis*-compound, was present to the extent of 10% and had different properties.