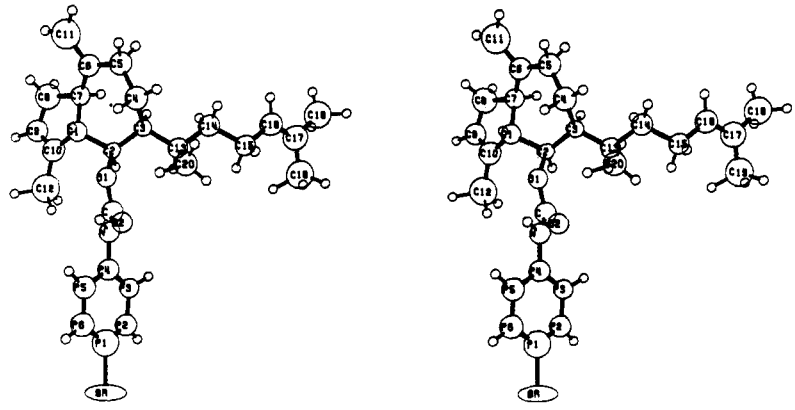


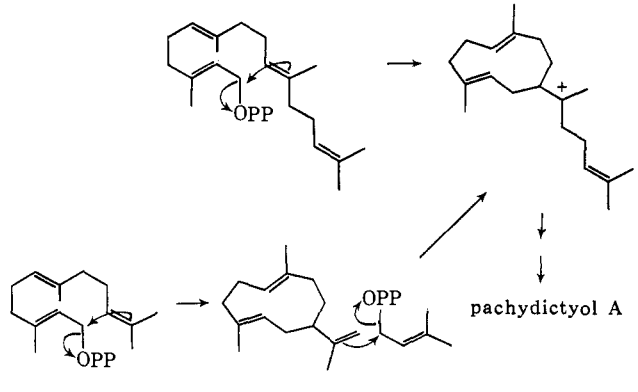
Figure 1. A stereo view of pachydictyol A *p*-bromophenylurethane.

bromine atom was treated anisotropically). After convergence to a weighted residue, $R_w$ (based on $|F|$), of 10.8% the absolute configuration was confirmed using the anomalous dispersion effect of the bromine atoms ($R_w$ = 11.3% for the enantiomer).[7] At this stage, all hydrogen atoms were located from a difference Fourier map. Hydrogen atoms were included in the structure factor calculation but not in a further refinement. The refinement converged to a final $R_w$ of 8.4%. The standard deviation of an observation of unit weight is 1.98.

An interesting question to consider is the biosynthesis of pachydictyol A. The perhydroazulene ring system of pachydictyol A is previously unknown among diterpenes. The ring system is well known in sesquiterpenes and one is tempted to consider pachydictyol A as a sequiterpene to which an isoprene unit has been added. Such a biogenesis is obvious for the many flavanoids to which one or more isoprene units have been added[8] but has not previously been proposed for any terpenoid.

The diterpenes are normally considered to be derived from geranylgeraniol. Pachydictyol A could be derived from this precursor by cyclization analogus to farnesol in sesquiterpene biosynthesis (Scheme I).

**Scheme I.** Possible Biosyntheses of Pachydictyol A




There are two other compounds among the diterpenes, artemisene and biflorin, which also resemble sesquiterpenes and for which this biosynthesis has been proposed.[9]

(7) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).
(8) T. A. Geissman and D. H. G. Crout, "Organic Chemistry of Secondary Plant Metabolism," Freeman, Cooper and Co., San Francisco, Calif., 1969, pp 242–246.
(9) T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds. Volume II. Terpenes," Academic Press, New York, N. Y., 1972.

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## Intrinsic Acidities of Carboxylic Acids from Gas-Phase Acid Equilibria

*Sir:*

Recently we reported[1,2] results for the gas-phase proton transfer equilibria ($B_1H^+ + B_2 = B_1 + B_2H^+$) measured with a pulsed electron beam high-pressure mass spectrometer.[2,3] The equilibrium constants and their temperature dependence allow the evaluation of free energy and enthalpy changes for the reactions and permit the measurement of the intrinsic basicity of the compounds in absence of a solvent.

Similar measurements, but at much lower pressure and constant temperature, have been made by several groups,[4–6] using ion cyclotron spectrometers.

The present communication represents an extension of the proton transfer work to equilibria involving the acids HA.

$$A_1^- + A_2H = A_1H + A_2^- \quad (1)$$

The results, measured with the same instrument,[2,3] are given in Table I.

The data were obtained by passing through the ion source a carrier gas ($O_2$, $N_2$, or Ar) at 4 Torr, typically containing the weaker acid HA at some 100 mTorr and

(1) J. P. Briggs, R. Yamdagni, and P. Kebarle, *J. Amer. Chem. Soc.*, **94**, 5128 (1972).
(2) R. Yamdagni and P. Kebarle, to be submitted for publication.
(3) A. J. Cunningham, J. D. Payzant, and P. Kebarle, *J. Amer. Chem. Soc.*, **94**, 7627 (1972).
(4) E. M. Arnett, F. M. Jones, III, M. Taagepera, W. G. Henderson, D. Holtz, J. L. Beauchamp, and R. W. Taft, *ibid.*, **94**, 4724 (1972).
(5) D. H. Aue, H. M. Webb, and M. T. Bowers, *ibid.*, **94**, 4726 (1972).
(6) W. G. Henderson, M. Taagepera, D. Holtz, R. T. McIver, Jr., J. L. Beauchamp, and R. W. Taft, *ibid.*, **94**, 471 (1972).

Table I[a]

| (a) Acid Equilibria Measured $A_1^- + A_2H = A_1H + A_2^-$ | | | | | (b) Acidities of AH (acidity increases from HF to HI) | | |
|---|---|---|---|---|---|---|---|
| $A_1H$ | $A_2H$ | $K$ | $T$, °K | $-\Delta G°$ | AH | $D$(A–H) − $EA$(A) | $EA$(A) |
| $CH_3COOH$ | HCOOH | 18.0 | 562 | 3.2 | HF | 56.3[b] | 79.5[b] |
| $CH_3COOH$ | $CH_3CH_2COOH$ | 3.0 | 562 | 1.2 | $CH_3COOH$ | 31.8 | (78.2)[c] |
| $CH_3COOH$ | $n$-$C_3H_7COOH$ | 6.2 | 562 | 2.0 | $C_2H_5COOH$ | 30.6 | (79.4)[c] |
| $C_2H_5COOH$ | HCOOH | 6.5 | 562 | 2.1 | $n$-$C_3H_7COOH$ | 29.7 | (80.3)[c] |
| $n$-$C_3H_7COOH$ | HCOOH | 2.8 | 562 | 1.2 | HCOOH | 28.6 | (81.4)[c] |
| HCOOH | HCl | 1300 | 600 | 8.5 | HCl | 20.0[b] | 83.3[b] |
| $CH_2ClCOOH$ | $CHCl_2COOH$ | 1380 | 490 | 7.0 | $CH_2ClCOOH$ | 19.0 | (91.0)[c] |
| HCl | $CH_2ClCOOH$ | 2.4 | 600 | 1.0 | $CHCl_2COOH$ | 12.0 | (98.0)[c] |
| | | | | | HBr | 10.0[b] | 77.5[b] |
| | | | | | HI | 0.7[b] | 70.6[b] |

[a] All energy values in kcal/mol. [b] From ref 10. [c] Estimated on basis of $D$(A–H) = 110 kcal/mol: V. I. Vedeneyev, *et al.*, "Bond Energies, Ionization Potentials and Electron Affinities," Edward Arnold Publishers, London, 1966.

the stronger $HA_2$ at 5–20 mTorr. Efficient negative ion production was obtained by capture of near thermal secondary electrons with $NF_3$ added at some 50 mTorr. Dissociative electron capture, $e^- + NF_3 = NF_2 + F^-$, is exothermic with this compound but endothermic with the acids (HA) used. Since HF is a much weaker acid than the HA compounds, rapid proton transfer from the $HA_1$, present in excess, occurs, $F^- + HA_1 = HF + A_1^-$. Proton transfer *via* (1) and the establishment of the equilibrium 1 could be then observed some 50–100 μsec after the electron pulse. The equilibrium constant $K_1$ was determined by measuring the intensities of $A_1^-$ and $A_2^-$ after equilibrium was established. The concentration of $HA_1$ and $HA_2$ was determined by weight loss measurements[2] and by ionization of neutrals escaping from the ion source,[2] by an auxiliary electron beam. The principle source of error is believed to be determination of the HA concentration ratio since the acids are rather difficult to handle in the gas phase.[7]

The equilibria 1 were measured above 560°K since at lower temperatures the dimers $(AHA)^-$ become the dominant ionic species. Temperatures considerably higher than 600°K led to thermal decomposition of the neutral acids. This decomposition could be observed with the auxiliary filament.

Calculation of the concentration of the neutral acid dimers $(HA)_2$ based on the data of Bernstein[8] showed that the $(HA)_2$ species concentration is negligible for the conditions used.

The temperature dependence of $K_1$ was examined for some of the reactions and found to be small.[9] This means $\Delta S_1°$ is small and $\Delta G_1° \approx \Delta H_1°$ and $\Delta G_1°$ (600°) $\approx \Delta G_1°$ (300°). A very small entropy change is expected for proton transfer reactions and was observed for the amines.[1,2]

The enthalpy change is related to the bond energies and electron affinities by eq 2

$$\Delta H_1 = D(A_2\text{–H}) - D(A_1\text{–H}) + EA(A_1) - EA(A_2) \quad (2)$$

Since $D$(H–Cl) − $EA$(Cl) = 103 − 83 = 20 kcal/mol,[10] the $D$(A–H) − $EA$(A) for the other acids can be evaluated. The results are shown in Table Ib where the acids are arranged in order of increasing gas-phase acidity.

The acidity increases in the order acetic, propionic, and butyric acid. This increase follows changes observed by Brauman[11] for the alcohols, $CH_3O^- + C_2H_5OH = CH_3OH + C_2H_5O^-$ etc., where the acidity was found to increase with increasing size and thus polarizability of the alkyl group. In aqueous solution acidity decreases from acetic to butyric acid. This reversal is probably due to a decrease in anion hydration energy with increasing size of the alkyl group.[4]

Interestingly the formic acid does not fit in the above gas-phase order and is stronger than butyric acid (Table I). This result is in agreement with an earlier study[12] of the hydrogen bonds $D(Cl^-\text{–HA})$ which were found to increase with acidity of HA and predicted a higher gas-phase acidity for formic acid. Brauman[13] has observed an analogous first member anomaly in the acetylenes whose acidity was found[13] to increase in the order $CH_3C{=}CH$, $C_2H_5C{\equiv}CH$, and $HC{\equiv}CH$. The explanation of this effect in terms of permanent dipole moments in $sp^2$ and sp hybridized systems given by Brauman should apply also to the present observations.

The effect of the chlorine substituent is seen to be very strong. Thus $\Delta G_1°$ is −12.8 (acetic → chloroacetic) and −7.0 kcal/mol (chloroacetic → dichloroacetic). The corresponding $\Delta G°$ values in aqueous solution are only −2.6 and −2.2 kcal/mol.[14] Attenuations of substituent stabilizing effects from gas phase to aqueous solutions have been observed previously.[15,16]

Accurate $D$(RCOO–H) values do not seem to be available. The bond energy should be close to 110 kcal/mol[17] and not strongly dependent on the nature of

(7) A more detailed description of the experimental procedure, temperature dependence of $K_1$, and a larger variety of acids will be published later.

(8) A. D. Claque and H. J. Bernstein, *Spectrochim. Acta, Part A*, **25**, 593 (1969).

(9) The available temperature range was restricted due to thermal decomposition, generally decarboxylation, of the acids at high temperature.

(10) Selected Values of Chemical Thermodynamic Properties: National Bureau of Standards (U. S.), Technical Note 270-3; R. S. Berry and C. W. Reimann, *J. Chem. Phys.*, **38**, 1540 (1963).

(11) J. I. Brauman and L. K. Blair, *J. Amer. Chem. Soc.*, **90**, 6561 (1968).

(12) R. Yamdagni and P. Kebarle, *ibid.*, **93**, 7139 (1971).

(13) J. I. Brauman and L. K. Blair, *ibid.*, **93**, 4315 (1971).

(14) Obtained from standard acid dissociation constants at room temperature.

(15) A. G. Harrison, P. Kebarle, and F. P. Lossing, *J. Amer. Chem. Soc.*, **83**, 777 (1961).

(16) M. Taagepera, W. G. Henderson, R. T. C. Brownlee, J. L. Beauchamp, D. Holtz, and R. W. Taft, *ibid.*, **95**, 1369 (1972).

(17) V. I. Vedeneyev, *et al.*, "Bond Energies, Ionization Potentials and Electron Affinities," Edward Arnold Publishers, London, 1966.

R. Taking a constant value of 110 for all the acids one obtains the estimates for the electron affinities shown in Table Ib. All values are quite high and lead one to expect an affinity of over 100 kcal for $CF_3COO$. Measurements involving fluoroacetic and other organic acids are presently in progress.

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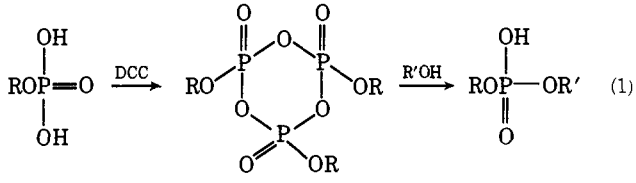
## An Improved Method for the Study of Reaction Intermediates. The Mechanism of Peptide Synthesis Mediated by Carbodiimides

*Sir:*

Carbodiimides continue to be the most versatile dehydrating agents for the synthesis of peptides and nucleotides, yet their mechanism of action remains incompletely understood. During phosphodiester synthesis with *N,N*-dicyclohexylcarbodiimide (DCC) an exceedingly complex reaction occurs in which Khorana[1] was able to identify the trimetaphosphate (**1**) as the initial phosphorylating agent (eq 1). The structure of the corresponding (acylating) agent during peptide synthesis with DCC (eq 2) has yet to be established despite considerable research.[2]



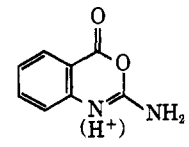

(1)

**1**

$$RCO_2H \xrightarrow{DCC} ? \xrightarrow{R'NH_2} RCONHR' \quad (2)$$

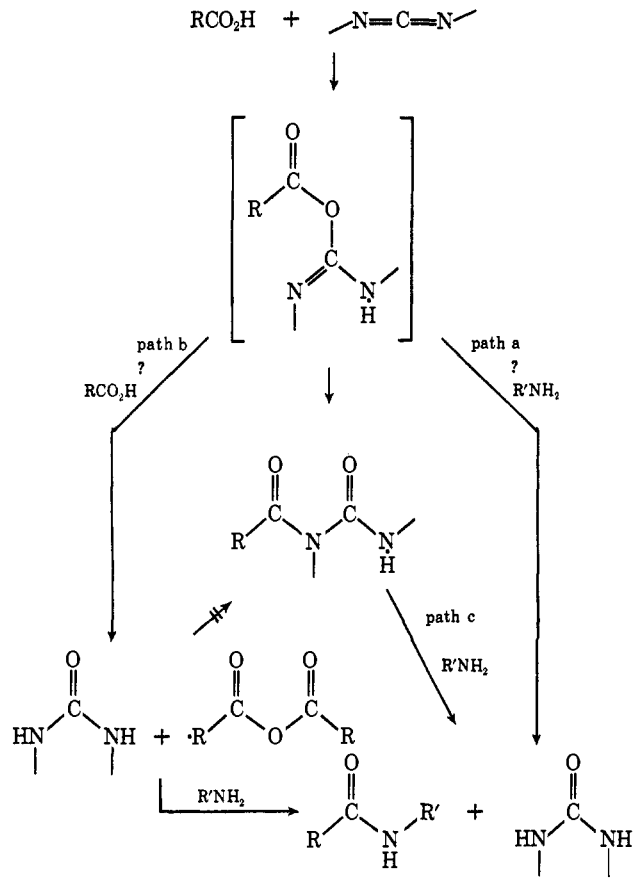
Scheme I formulates the mechanistic question, does amide formation proceed directly from the *O*-acylisourea (path a) or *via* the symmetrical anhydride (path b)? The *N*-acylurea (path c) has already been excluded as the acylating agent.[3]

Evidence for the two paths may be summarized as follows. In the absence of amine nucleophiles DCC smoothly converts carboxylic acids to their anhydrides; subsequent aminolysis occurs at a rate compatible with the anhydride's intermediacy during peptide synthesis.[3-5] Evidence supporting the *O*-acylisourea was first obtained by Weetall[6] through the DCC-mediated acylation of amines by polymer-bound carboxylic acids, a system which virtually precludes anhydride formation. More recently, Bruice[7] has shown that the model compound **2** (and its protonated form) readily acylates amines in the absence of carboxylic acids. Since each path has been demonstrated only in systems which



**2**

**Scheme I**




physically exclude the other, the evidence for either path is necessary but not sufficient, and the mechanism during the actual conditions of peptide synthesis remains unknown.

Similar mechanistic problems are posed by a variety of existing peptide reagents such as ethoxyacetylene,[8] isonitriles,[9] and redox systems,[10] which share with DCC the ability to convert carboxylic acids to their anhydrides. The mechanistic distinction is an important one since peptide synthesis is more likely to benefit from new acylating agents than from new methods of generating symmetrical anhydrides. Herein we report evidence that bears on this question for DCC-mediated peptide synthesis and propose an improved technique which appears applicable to the study of a variety of reaction intermediates.

We have determined the product distributions for the reaction of three amines with the anhydride, $(Z\text{-}Gly)_2O$, of benzyloxycarbonylglycine *and* with the Z-Gly-OH-DCC intermediate *under identical reaction conditions*. The results, tabulated in Table I for two reaction temperatures, indicate that the anhydride cannot entirely account for behavior of the initial acylating

(1) G. Weimann and H. G. Khorana, *J. Amer. Chem. Soc.*, **84**, 4329 (1962).
(2) A summary may be found in E. Schröder and K. Lübke, "The Peptides," Vol. I, Academic Press, New York, N. Y., 1965, p 108.
(3) D. F. DeTar and R. Silverstein, *J. Amer. Chem. Soc.*, **88**, 1013 (1966); also ref 2.
(4) H. Schüssler and H. Zahn, *Chem. Ber.*, **95**, 1076 (1962).
(5) D. F. DeTar and R. Silverstein, *J. Amer. Chem. Soc.*, **88**, 1020, 1024 (1966).
(6) H. H. Weetall and N. Weliky, *Nature (London)*, **204**, 896 (1964).
(7) A. F. Hegarty and T. C. Bruice, *J. Amer. Chem. Soc.*, **92**, 6568 (1970).
(8) H. Panneman, A. Marx and J. Arens, *Recl. Trav. Chim. Pays-Bas*, **78**, 487 (1959).
(9) J. V. Nef, *Justus Liebigs Ann. Chem.*, **270**, 267 (1892).
(10) T. Mukaiyama, *Syn. Commun.*, **2**, 243 (1972).