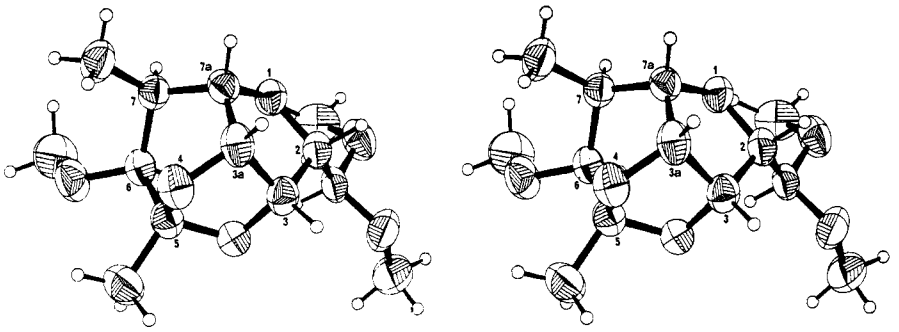


Figure 1.

side chain of **1** with the substituted tetrahydrofuran rings being related enantiomerically. Accordingly, **4a** and **4b** exhibit 7,7a-erythro and 7,7a-threo configurations, respectively, with the corresponding dihedral angles H–C(7a)–C(7)–H estimated to be 75 and 45°.

Although **4a** and **4b** fulfill the requirement of conformational stability, application of the Karplus equation did not permit a completely unequivocal choice between the two alternatives. Compounds **4a** and **4b** have no precedent as to Karplus constants, $J°$, but the selection of a $J°$ value for $0° \leqq \phi \leqq 90°$ considerably larger than 7.4 Hz appeared reasonable in view of available examples.[5] Equation $J = J° \cos^2 \phi - 0.3$ Hz, $J° = 12$ Hz, for example, led to $J_{7a,7,calcd} = 6$ Hz for $\phi = 45°$ (**4b**) and $J_{7a,7,calcd} = 0.5$ Hz for $\phi = 75°$ (**4a**). Consequently, the observed $J_{7a,7} = 1.8$ Hz suggested preference of **4a** implying a 7,7a-erythro configuration. In connection with the known chirality of C(7) in **4a** and the established relative configuration of the tetrahydrofuran ring, requiring all hydrogen substituents to be located on the same side of the ring,[4] all dissymmetric centers in **4a** would thus be defined. The inherent weakness of this analysis is due to the Karplus treatment. Although Karplus constants of $J° > 7.4$ Hz result in preference of **4a**, with $J° = 7.4$ Hz both alternatives become equiprobable whereas $J° < 7.4$ Hz tends to favor **4b**. This ambiguity is not completely unexpected and may be attributed to substituent effects and the presence of a strained ring system whereas the Karplus relationship is derived for truly tetrahedrally substituted systems.

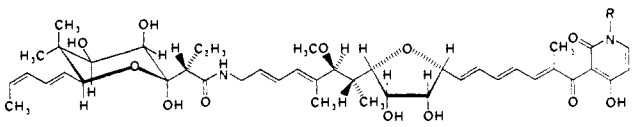
Compound **4a** was finally confirmed as the correct structure by single-crystal Roentgen analysis of **4a**, $C_{13}H_{22}O_6$, mp 98°, αD + 15° (*c* 1.0, dioxane), *m/e* (%) 274 (3), 75 (100), space group $P2_1$ with unit-cell dimensions $a = 7.503$ (4) Å, $b = 8.726$ (5) Å, $c = 11.268$ (7) Å, $\beta = 103.17$ (4)°, and $d_{calcd} = 1.268$ g cm^{-3} for $Z = 2$. Analysis was based on 1354 reflections with intensities significantly greater than background ($I > 2.5\ \sigma(I)$) which were part of 1604 accessible reflections with $\theta < 76°$.

The structure was elucidated by a multiple solution procedure.[6] Refinement of data was carried out by full-matrix least squares. Anisotropic thermal parameters were used for all atoms except hydrogen atoms. The final discrepancy index, *R*, is 0.039. A stereodrawing of **4a** is shown in Figure 1.

(5) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 280 ff.

(6) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970).

With the structure of **4a** established it is now possible to present the structure of antibiotic X-5108 in full stereochemical detail as shown in **5a**.



5a: R = CH_3 (Antibiotic X-5108)
5b: R = H (Mocimycin)

We have previously demonstrated that mocimycin can be regarded as des-*N*-methyl antibiotic X-5108 (**5b**); the evidence of chiral identities of the two antibiotics was elaborated by establishing identity of essential degradation products.[2] As additional proof of chiral parity of **5a** and **5b**, we now obtained **4a** from mocimycin *via* **2** and **3**. Compound **4a** derived from mocimycin exhibited melting point, optical rotation, and ir and nmr spectra identical with those of **4a** derived from **5a**. The structure of mocimycin is thus established as **5b**.

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Substituent Effects on the Intrinsic Acidities of Benzoic Acids Determined by Gas Phase Proton Transfer Equilibria Measurements

Sir:

Quantitative correlations of reaction rates and equilibria, particularly in the form of linear free energy relationships, have played a central role in physical organic chemistry. These studies were initiated by the Hammett acidity plot in which the free energy changes for proton transfer from benzoic to substituted benzoic acids in aqueous solution were used as a standard scale. Hammett's work was followed by very substantial experimental and interpretative development. However, some problems have remained. Many of these are connected with the difficulty of assessing the effect of the solvent. Therefore it is of importance to obtain substituent energy differences for the isolated molecules. The present work describes such measurements. The proton transfer equilibria (1) were ob-

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

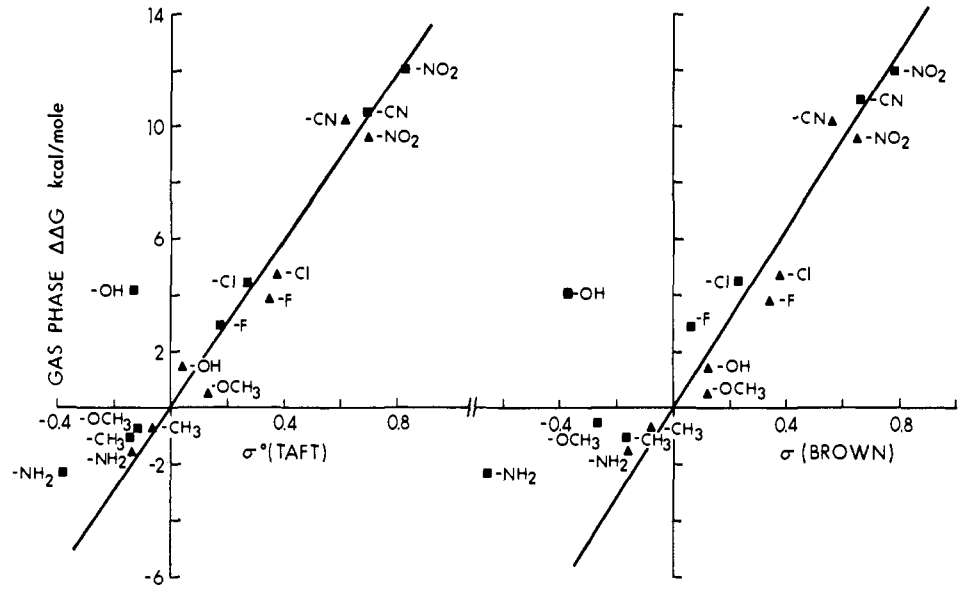


Figure 1. Correlation of gas phase acidities of meta (▲) and para (■) substituted acids with σ and σ°. $\Delta\Delta G$ gas phase corresponds to free energy change for proton transfer from the substituted acid to benzoic acid.

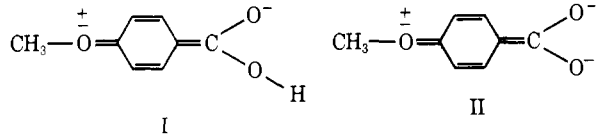
Table I. Gas Phase Acidities of Benzoic Acids HA[a]

Substituent	H	CH_3	COH_3	OH	F	Cl	NH_2	NO_2	CN
Ortho	23.1	22.3	22.55	9.8	20.8	19.3	20.4	14.3	
Meta	23.1	23.8	22.6	21.75	19.25	18.4	24.65	14.1	13.5
Para	23.1	24.15	23.85	19.05	20.2	18.65	25.4	12.0	12.8

[a] Values given correspond to the difference between the bond dissociation energy D(A–H) and the electron affinity of A for the acid HA. The higher D(A–H) − EA(A), the weaker is the acid. Acid standards used: formic 28.6, fluoroacetic 21.0, chloroacetic 19.0, difluoroacetic 13.8, dichloroacetic 12.0, trifluoroacetic 6.6 kcal/mol.[2-6] Measurements involving standard acids and benzoic acids led to numerous cross-checks which will be reported in a more detailed publication. (T. B. McMahon, R. Yamdagni, and P. Kebarle, *J. Amer. Chem. Soc.* to be submitted for publication.)

served with a "high" pressure mass spectrometer.[1] The ions are produced by an electron pulse, and the establishment of the equilibrium is observed some 100 μsec after the pulse. The neutral acids AH were present at some 0.05–0.3 Torr. CH_4 at 2–5 Torr was present to ensure thermal equilibrium. Measurements were done at 327° (600°K) since at lower temperatures partially solvated ions $A^-(AH)_n$ became dominant. The free energy $\Delta G_1^\circ = -RT \ln K_1$ is obtained from the measured equilibrium constant. Since ΔS_1° is generally small for proton transfer reactions,[2,3] ΔG° (T = 600°) $\approx \Delta G^\circ$ (T = 300°) and $\Delta G^\circ \approx \Delta H^\circ$. Table I summarizes the results obtained for nearly 30 substituted benzoic acids. Some other acids measured in related work[3-6] are included for comparison.

A quick comparison between the substituent effects on the gas phase and aqueous acidities can be obtained on the basis of Hammett type plots. Figure 1 shows the gas phase free energies for proton transfer from meta- and para-substituted benzoic acids to benzoic acid plotted *vs.* the σ values (McDaniel and Brown).[7] A fair correlation is observed. Shown also in Figure 1 is a plot *vs.* σ^0 (Taft).[8] The correlation is noticeably better. As will be recalled, Taft[8] and van Bekkum[9] independently showed that π donating substituents like CH_3O and NH_2 in the para position can stabilize the free acid because of the resonance structure I. Since the equivalent resonance II in the anion should not be



I II

important, a decrease of acidity should result. The σ^0 values were obtained with compounds (phenyl acetic acids) where the direct conjugation as in I is not possible.

The structure (I) being charge separated should be most important in polar solvents. Therefore I cannot be contributing significantly in the gas phase, the "ultimate" least polar solvent. This explains the better correlation of σ^0 with the gas phase data.

It is interesting to note that the slope ρ of the lines in Figure 1 (when the σ's are converted to ΔG° values) is

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(2) J. P. Briggs, R. Yamdagni, and P. Kebarle, *J. Amer. Chem. Soc.*, 94, 5128 (1972).
(3) R. Yamdagni and P. Kebarle, *J. Amer. Chem. Soc.*, 95, 4050 (1973).
(4) K. Hiraoka, R. Yamdagni, and P. Kebarle, *J. Amer. Chem. Soc.*, 95, 6833 (1973).
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(7) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 23, 420 (1958).
(8) R. W. Taft, Jr., *J. Phys. Chem.*, 64, 1805 (1960).
(9) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, 78, 815 (1959).

around ten. Thus the effect of the substituents in the gas phase is ten times larger. While attenuation in aqueous solution is always observed, the ρ factor is normally around four, *i.e.*, considerably smaller.[4,5,10]

The largest deviation between gaseous and aqueous values is observed for *p*-OH benzoic acid which is much stronger in the gas phase. (See Figure 1.) In a study of the gas phase acidity of substituted phenols[6] plots similar to those shown in Figure 1 but involving the phenols were made. Taking $\sigma^- = 0.728$ for the *p*-CO_2H substituent (Jaffé[11]) it could be estimated with help of these plots that the acidity of the *hydroxy* proton in *p*-OH benzoic acid should be higher than that of the *carboxy* proton and close to that observed for *p*-OH benzoic acid. This explains why this acid does not fit in the benzoic series.

Ortho substituents have long been known to have specific or "anomalous" effects in solution. Thus the aqueous acidities of ortho-substituted benzoic acids are generally much higher than those of the para compounds. Some of these effects have been partially explained. Thus the direct conjugation by π donating substituents as illustrated in resonance structure I, which weakens the para-substituted benzoic acids, is assumed to be ineffective in ortho position since steric hindrance causes the carboxy group to twist out of the phenyl ring plane. The lack of resonance stabilization in the neutral ortho acid results in increased acidity relative to the para-substituted isomer. As was pointed out earlier in the gas phase resonance, structure I does not make a marked contribution and the benzoic acids with π donating ortho and para substituents should have more similar gaseous acidities. That this is the case is easily verified from Table I. The *o*-OH benzoic acid, or, as was established above, the *o*-COOH phenol, is an exception and has a much larger gaseous acidity than the para isomer. This must be due to stabilization of the ortho anion by strong intermolecular hydrogen bonding involving the remaining acidic proton and the negative center.

The very much higher aqueous acidity of *o*-NO_2 and *o*-CN substituted acids relative to the para isomers seems less well understood. It is interesting to note (Figure 1) that in the gas phase *p*-NO_2 and *o*-NO_2 benzoic acids have roughly similar acidities, the para isomer being the stronger acid.

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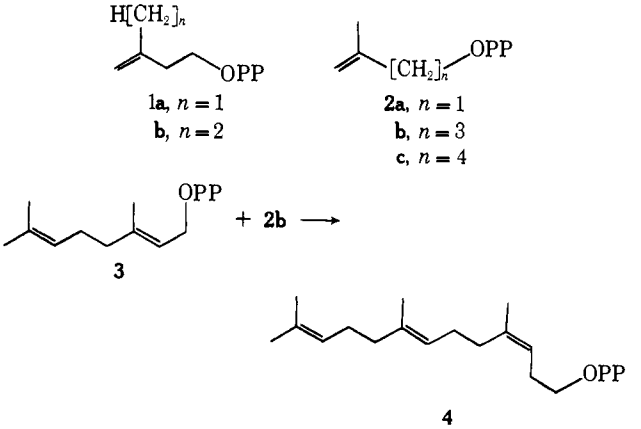
A Novel Substrate for Prenyltransferase. Formation of a Nonallylic *cis*-Homofarnesyl Pyrophosphate

Sir:

The substrate specificity of prenyltransferase (farnesyl pyrophosphate synthetase EC 2.5.1.1) is relatively low with respect to the structure of the allylic pyrophosphate, and a number of allylic pyrophosphates have been found to act as substrates to react with isopentenyl pyrophosphate (3-methylbut-3-enyl pyrophosphate, **1a**) in the reaction catalyzed by either liver or pumpkin enzyme.[1-7] However, the structural requirement for the condensing partner has been shown to be so stringent that in a series of homologs of **1** only 3-ethylbut-3-enyl pyrophosphate (**1b**) can act as an artificial substrate in place of the genuine substrate **1a**.[8,9] This fact has stimulated us to explore other artificial substrates of the isopentenyl pyrophosphate type, and we have examined the substrate specificity of this enzyme with respect to homologs of **2**. In this paper we report the finding that among **2a**, **2b**, and **2c** only **2b** is reactive and that the enzymatic reaction of 4-methylpent-4-enyl pyrophosphate (**2b**) with geranyl pyrophosphate (**3**) results in an exclusive formation of the cis isomer of a nonallylic homofarnesyl pyrophosphate (**4**).



Compounds **2a**, **2b**, and **2c** were prepared from the corresponding alcohols by phosphorylation as usual and were purified by selective crystallization from a solvent system of *n*-propyl alcohol–ammonia–water (6:3:1).[10] The incubation mixture for the enzymatic reaction contained, in a final volume of 5 ml, 125 μmol of Tris–HCl buffer, pH 7.5, 25 μmol of $MgCl_2$, 125 nmol of [^{3}H]-geranyl pyrophosphate (**3**), 500 nmol of a homolog to be examined, and 0.5 mg of prenyltransferase purified from pig liver according to the method of Holloway and Popják.[1] The mixture was kept at 37° for 5 hr and was then treated with alkaline phosphatase, and the radioactive materials were extracted with light petroleum and analyzed by radio-glpc with a 1-m column of Silicon OV-17 1.5% at linear programmed temperature at a rate of 4°/min from 100 to 200°.

The material thus derived from the incubation of [^{3}H]-**3** with either **2a** or **2c** showed no radioactivity peak other than that for geraniol recovered from the starting substrate, but the material from the reaction of [^{3}H]-**3** with **2b** gave a radioactivity peak at a retention time of

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