In their recent study of the nature of high energy bonds, George et al.[11] concluded that solvation effects contributed very importantly, perhaps more than intramolecular effects, to the large negative enthalpy (and free energy)[12] of hydrolysis of "high energy" P-O-P bonds. The similarity in our calculated ΔE for reactions 1 and 2 would imply that the known high-energy nature of the former reaction is not entirely due to intramolecular electronic effects. Unfortunately, our minimal basis set calculations are probably not sufficiently accurate to allow one to place great confidence in differences of just a few kilocalories per mole.[13]

A comparison of the calculated hydrolysis energy of $^{-}HO_3POPO_3H^{-}$ with $H_2O_3POPO_3H_2$ indicates that, in the gas phase, electrostatic repulsions are important in determining the "high energy" nature of the former molecule. However, the similarity of the experimental enthalpies of hydrolysis of $H_2O_3POPO_3H_2$ and $^{-}HO_3POPO_3H^{-}$ in aqueous solution (−7.6 and −6.8 kcal/mol)[11] would imply that these electrostatic effects are diminished either by association with counterions or by the large dielectric constant of water. Our calculated gas phase energy of hydrolysis of $^{-}HO_3POPO_3H^{-}$ indicates that its solvation energy should be 209 rather than 134 kcal/mol as estimated by George et al.[14]

In contrast to the probable important contribution of solvation to high energy phosphate bonds, the "high energy" nature of carboxylic acid anhydrides is more clearly a result of intramolecular effects (described by George et al. as "opposing resonance" [15]). The precise role of solvation in other biologically important molecules with high group-transfer potentials and a further characterization of their electronic structure will be subjects of further studies. In addition, we hope that examination of reactions 1-6 with more extended basis sets[16] will yield a more precise measure of their hydrolysis energies.

Acknowledgments. Financial support from USPHS Grant AM 17323 (G.L.K.) and GM-20654 (P.A.K.) is gratefully acknowledged. P.A.K. and G.L.K. are grateful to the USPHS for Career Development Awards GM-70718 (P.A.K.) and AM-00014 (G.L.K.).

References and Notes

(1) P. D. Boyer, R. L. Cross, and W. Momsen, *Proc. Nat. Acad. Sci. U.S.A.* **70**, 2837 (1973).

(2) W. J. Hehre, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.*, **51**, 2657 (1969).

(3) We used the O–H bond length found to be the optimum in STO-3G calculations on H_2O (ref 5) and tetrahedral bond angles around the phosphorus. Based on known phosphate structures, (see *Chem. Soc. Spec. Publ.*, "Tables of Interatomic Distances", 1958 and 1965) these are reasonable approximations.

(4) In the case of $H_2O_3POPO_3H_2$, we considered three dihedral angle combinations. The first with all six dihedral angles (ϕ) = 0, leads to a very short $P{=}O\cdots O{=}P$ contact, $R(O\cdots O)$ = 1.9 Å, and consequent high energy; the second with all $\phi(H—O—P{=}O)$ = 0° and $\phi(P—O—P{=}O)$ = 180°, yielding a C_{2v} structure, was relatively unfavorable with a calculated energy 8.2 kcal/mol above the third structure of C_s symmetry, this structure retained all $\phi(H—O—P{=}O)$ = 0° but had one $\phi(P—O—P{=}O)$ angle equal to 0° and the other equal to 180°. The C_{2v} structure was probably relatively high in energy because of the unfavorable alignment of the phosphate dipoles, but studies to elucidate the conformational properties of $H_4P_2O_7$ are continuing.

(5) W. Lathan, L. Curtiss, W. Hehre, J. Lisle, and J. A. Pople, *Prog. Phys. Org. Chem.*, **11**, 175 (1974).

(6) M. D. Newton, *J. Am. Chem. Soc.*, **95**, 256 (1973).

(7) Since anions are poorly represented by single determinant wave functions, one has less confidence in the quantitative accuracy of these energies. However, a recent study by Radom (*Chem. Commun.*, 403 (1974); and L. Radom in "Modern Theoretical Chemistry II. Electronic Structure: *Ab Initio* Methods", H. F. Schaefer, Ed., Plenum Press, New York, N.Y., 1975) shows that isodesmic reacts may be reasonably represented for certain anions.

(8) The geometrical parameters for $^{-}HO_3POPO_3H_2$ were chosen as follows: (1) for the negative end of the molecule optimum values for H_2PO_4— were used; (2) for the neutral end, the optimum values for H_3PO_4 were used; (3) for the POP linkage, one P–O bond length was taken from $H_4P_2O_7$ and the other from $H_2P_2O_7^{2-}$. The POP angle was taken from $H_4P_2O_7$.

(9) J. D. Cox and G. Pilcher, "Thermochemistry of Organic and Organo-Metalic Compounds", Academic Press, London and New York, 1970.

(10) We used the acetic acid geometry deduced from microwave spectra (W. J. Tabor, *J. Chem. Phys.*, **27**, 974 (1957) except for R(O–H) = 0.99 Å to be consistent with the water O–H bond. We then optimized the C–OH bond lengths in acetic acid and C–O–C bond length and COC angle in acetic anhydride.

(11) P. George, R. J. Witonsky, M. Trachtman, C. Wu, W. Donvart, L. Richman, F. Shurayh, and B. Lentz, *Biochim. Biophys. Acta*, **223**, 1 (1970).

(12) Reference 11 has found that *both* the solution phase free energy and enthalpy of hydrolysis are more negative for the P–O–P compounds than P–O–C by about 4 kcal/mol.

(13) W. J. Hehre, R. Ditchfield, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.*, **92**, 4796 (1970). These authors have studied a series of bond separation reactions involving molecules containing only C, N, O, F, and H and have found that although most chemical trends are correctly reproduced, the mean error in the energies relative to known experimental values at the STO-3G level is 5.8 kcal/mol. We know of no comparable study involving second-row atoms.

(14) It should be pointed out that George et al. emphasized that their entries in Table V were lower bounds for the solvation energy and our calculations show this is most clearly the case when the products have more charge separation than the reactants. Even though a minimal basis set will exaggerate the exothermicity of this reaction, we feel its magnitude is correctly represented.

(15) "Opposing resonance" means the products have a larger number of contributing resonance structures than the reactants.

(16) All of the reactions studied here are examples of isodesmic reactions which should be well-treated at the single determinant level.

(17) *Chem. Soc., Spec. Publ.*, "Tables of Interatomic Distances", 1958 and 1965.

David M. Hayes, George L. Kenyon, Peter A. Kollman*
Department of Pharmaceutical Chemistry
School of Pharmacy, University of California
San Francisco, California 94143

Received March 27, 1975

9-Isocyanopupukeanane, a Marine Invertebrate Allomone with a New Sesquiterpene Skeleton[1]

Sir:

An observation by Johannes,[2] that the nudibranch *Phyllidia varicosa* Lamarck, 1801 secretes a strong and unusually smelling, heat-stable, volatile substance, lethal to fish and crustaceans, has led us to the isolation of this metabolite from *P. varicosa* and also from its prey, a sponge, *Hymeniacidon* sp. This secretion, which protects the delicate, shell-less, brightly colored opisthobranch mollusk from its predators, and which at the same time is the allomone of the browser-prey relationship, has the structure of a tricyclic sesquiterpene isocyanide with a new, rearranged isoprenoid skeleton (**1**).

Locating and netting the relatively rare *P. varicosa* by SCUBA and maintaining the mollusks in aquaria proved to be difficult. By gently squeezing and rinsing 20 animals with sea water we gradually accumulated sufficient mucus for purification by vacuum distillation of the wet salty secretion, followed by extraction of the distillate with methylene chloride, TLC on alumina (methylene chloride-hexane, 15:85, R_f 0.6), thus yielding 20 mg of a mobile oil with the typical odor of the animal and lethal to fish. We characterized this metabolite as an isocyanide (ν_{max} 2120 cm^{-1}; thermal isomerization to nitrile, ν_{max} 2250 cm^{-1}; acid hydrolysis to formamide, ν_{max} 1685 cm^{-1}) possessing a sesquiterpenoid ($C_{16}H_{25}N$; highest m/e 205, prominent losses of Me_2CH, Me; isopropyl doublet of doublets and tertiary methyls in NMR) skeleton, which clearly differed from a sponge-derived bicyclic isocyanosesquiterpene which we were studying.[3]

Luckily one of us (B.J.B.), while diving off Pupukea on the north shore of Oahu, observed *P. varicosa* feeding on an

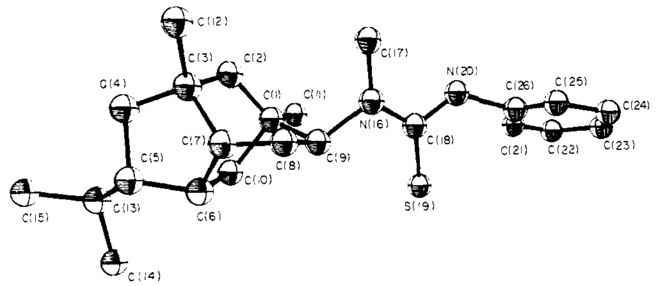
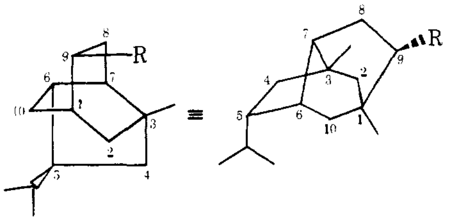


Figure 1. A computer generated drawing of the phenylthiourea derivative of 9-isocyanopupukeanane. Both molecules in the asymmetric unit are identical within experimental error, and only one is shown. Hydrogens are omitted for clarity, and no absolute configuration is implied.

off-white sponge, *Hymeniacidon* sp. Ethanol extraction of 240 g (dry) of sponge yielded 6 g of an oily mixture, from which we isolated 2 g of isocyanide by TLC (silica gel, hexane, short wavelength uv detection, R_f 0.3), identical with the *Phyllidia* isocyanide (ir, NMR, small negative rotation $[\alpha]_D$ −5° or −9° (*c* 3.0, 3.7 CCl_4)). We confirmed the tricyclic nature of the isocyanide by converting it (Li, $EtNH_2$)[4] to its parent hydrocarbon (**2**), $[\alpha]_D$ −17° (*c* 3.6, CCl_4) which exhibited 15 ^{13}C NMR signals between 18.6 and 54.0 ppm (TMS = 0) and which resisted Pd–C or Se dehydrogenation.



1, R = $\overset{+}{N}\overset{-}{C}$
2, R = H
3, R = NH_2
4, R = O
5, R = $N(CH_3)C(S)NHC_6H_5$

We attempted to relate the isocyanide to a known sesquiterpenoid by successive transformation (6 *N* HCl, 4 hr reflux, N_2) to amine **3** (*m/e* 221, 100%); hence without purification of intermediates to the chloramine (*N*-chlorosuccinimide in C_6H_6, 1 hr reflux), to the imine (0.9 *M* NaOEt in EtOH), and finally (10% H_2SO_4, reflux 1 hr) to the ketone **4**, which was purified by TLC (silica gel, hexane–benzene, 9:1, uv, R_f 0.3) to an oil, $[\alpha]_D$ −48° (*c* 0.54, CCl_4), ν_{max} 1720 cm^{-1}. We had hoped that this ketone might be identical with a known tricyclic sesquiterpene ketone, either copacamphor,[5] $[\alpha]_D$ +98.7°, ν_{max} 1738 cm^{-1},[6] or ylangocamphor,[7] $[\alpha]_D$ −57.7°, ν_{max} 1733 cm^{-1}, but ir and rotation data, reinforced by direct spectral comparison[8] with both compounds, proved that our isocyanide was unrelated to any known sesquiterpene.

We therefore converted the isocyanide to its formamide (HOAc), hence by LAH to the methylamine (*m/e* 235 (63), 204 (100%)), which reacted with phenylisothiocyanate to yield a crystalline phenylthiourea, **5**, mp 149–151°, from EtOH, the structure of which was secured by X-ray diffraction. The phenylthiourea derivative (**5**) crystallizes as very thin plates in the uniquely determined space group $P2_1$ with a = 13.837 (3) Å, b = 9.989 (2) Å, c = 16.803 (3) Å and β = 110.27 (1)°. A calculated (for Z = 4) and measured density of 1.13 g/cm^3 indicated two molecules per asymmetric unit.

All unique data were collected using an ω-scan technique and graphite monochromated Cu Kα (1.5418 Å) radiation. Only 1709 of the 3487 reflections with $\theta \leq 114°$ were judged observed ($F_o > 3\sigma(F_o)$) after correction for Lorentz, polarization, and background effects. The structure was solved routinely using a weighted tangent formula approach.[9] Full-matrix least-squares refinement with anisotropic temperature factors for all non-hydrogen atoms and fixed temperature factors for hydrogens has reduced the conventional discrepancy index to its present value of 8.99.[10]

A computer generated drawing of the X-ray model is presented in Figure 1. Both molecules in the asymmetric unit are identical within experimental error. We propose to name this new, rearranged sesquiterpene ring system pupukeanane (1,3-dimethyl-5-isopropyl[4.3.1.0^{3,7}]decane) after the place where the mollusk and sponge were collected. See paragraph at end of paper regarding supplementary material.

Acknowledgment. We thank Dr. Ole Tendal for sponge identification and the National Science Foundation (MPS 74-21575) for support.

Supplementary Material Available. The fractional coordinates (Table I), bond distances (Table II), bond angles (Table III), and calculated and observed structure factors (Table IV) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for \$4.50 for photocopy or \$2.50 for microfiche, referring to code number JACS-75-4763.

References and Notes

(1) A preliminary account was presented at the Western Regional Meeting, San Diego, Calif., Nov 1973, Abstract 69.
(2) R. E. Johannes, *Veliger*, **5**, 104–105 (1963).
(3) B. J. Burreson, C. Christophersen, and P. J. Scheuer, *J. Am. Chem. Soc.*, **97**, 201–202 (1975).
(4) I. Ugi and F. Bodesheim, *Chem. Ber.*, **94**, 1157–1158 (1961); W. Büchner and R. Dufaux, *Helv. Chim. Acta*, **49**, 1145–1150 (1966).
(5) E. Piers, R. W. Britton, R. J. Keziere, and R. D. Smillie, *Can. J. Chem.*, **49**, 1620–1622 (1971).
(6) M. Kolbe-Haugwitz and L. Westfelt, *Acta Chem. Scand.*, **24**, 1623–1630 (1970).
(7) E. Piers, M. B. Geraghty, F. Kido, and M. Soucy, *Synth. Commun.*, **3**, 39–43 (1973).
(8) We thank Professor T. Money for the spectra.
(9) P. Main, M. Woolfson, and G. Germain, MULTAN, Department of Physics, University of York, York, England, 1971.
(10) The following library of crystallographic programs was used: C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, "The Fast Fourier Algorithm and the Programs ALFF, ALFFDP, ALFFT and Friedel", USAEC Report IS-2625, Iowa State University-Institute for Atomic Research, Ames, Iowa, 1971; W. R. Busing, K. O. Martin, and H. A. Levy, "ORFLS, A Fortran Crystallographic Least Squares Program", USAEC Report ORNL-TM-305, *Oak Ridge National Laboratory, Oak Ridge, Tenn.*, 1965; C. Johnson, "ORTEP, A Fortran Thermal-Ellipsoid Plot Program", U.S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(11) NIH Special Fellow, 1972–1974.
(12) Camille and Henry Dreyfus Teacher-Scholar Grant Awardee, 1972–1977 and Fellow of the Alfred P. Sloan Foundation, 1973–1975.

B. Jay Burreson,[11] Paul J. Scheuer*
Department of Chemistry, University of Hawaii at Manoa
Honolulu, Hawaii 96822

Janet Finer, Jon Clardy*[12]
Ames Laboratory-USERDA and Department of Chemistry
Iowa State University
Ames, Iowa 50010

Received April 28, 1975