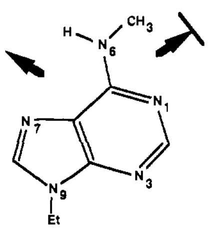
= 140 M^{-1}) to 9-ethyladenine (**3**) in THF-d_8.[13] For comparison, the binding of benzoic acid (K_a = 30 M^{-1}) and 2,6-diphenic acid (K_a = 20 M^{-1}) to **3** in THF-d_8 was also examined. The method of continuous variance (Job plot, Supplementary Material) revealed a 1:1 stoichiometry for the complex.[14-16] The results reveal that the binding of 9-ethyladenine is a unique feature of the orderly diacid. Support for the importance of simultaneous Watson–Crick and Hoogsteen interactions (Figure 2) is provided by the observed stoichiometry and especially by the relatively weak binding of 6-*N*-methyl-9-ethyladenine (**11**, K_a = 14 M^{-1}). This latter molecule cannot form four concurrent hydrogen bonds with the host.



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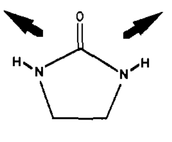
Tetrahydrofuran competes for H-bond sites, and association constants should be greater in chloroform than in THF. For example, the K_a for interaction of benzoic acid and 9-ethyladenine is 700 M^{-1} in $CDCl_3$ but only 30 M^{-1} in THF. Host **1** was poorly soluble in chloroform, and therefore host **2** was prepared and found to be easily dissolved in $CDCl_3$.

Host **2** in $CDCl_3$ is an outstanding new host for guests which present two H-bonding surfaces. Association constants for host **2** with several guests: 9-ethyladenine (**3**), 4.5 ± 1.7 × 10^4 M^{-1}; biotin methyl ester (**4**), 1.7 ± 0.3 × 10^4 M^{-1}; 2-imidazolidone (**12**), 2.1 ± 0.4 × 10^4 M^{-1}; trimethyleneurea (**13**), 3.3 ± 1.6 × 10^4 M^{-1}; 2-aminopyrimidine (**14**), 2.6 ± 0.5 × 10^3 M^{-1}.



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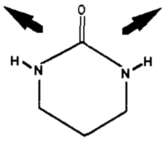

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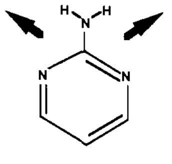

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To further explore solvent effects on host–guest interactions of this type, the affinity of these new hosts for 9-ethyladenine in polar and hydrogen bonding solvents (methanol-d_4 and deuterated aqueous methanol) was examined. In these solvents only proton transfer was observed, and there was no evidence for any association of the components of the resulting salt.[16]

This communication describes a practical approach to molecules that hold two functional groups in an orderly interrelationship. Hosts **1** and **2** contain two carboxylic acids so arranged as to support simultaneous formation of four hydrogen bonds with biotin or adenine derivatives and many similar substrates. This very simple synthesis provides multigram quantities of products and can be easily modified to afford new hosts in which various functional groups are brought into opposition or other orderly configurations. Further investigations of the binding properties and catalytic effects of host **2** and analogous functional group dyads are underway.

Acknowledgment. This work was made possible through funds provided by the National Institute of General Medical Sciences (GM-34846) and from the Alfred P. Sloan Foundation. X-ray structural analysis was carried out under the direction of Jaime E. Abola. Support for the x-ray diffraction laboratory is provided through PHS Grant No. 1-S10-RR02381-01.

Supplementary Material Available: Figure illustrating 300 MHz NMR ($CDCl_3$) spectra of tetraester **9** at 323, 310, and 233 K, Job plot[14] showing the change in concentration of the complex as a function of mole fraction of receptor, and partial crystallographic data including numbering scheme and positional parameters for all atoms of tetraester **9** (7 pages). Ordering information is given on any current masthead page.

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[13] Association constants were determined by direct analysis of NMR or UV/fluorescence titration data. The general procedure and the analytical process are described in ref 8d.

[14] Job, A. *Ann. Chim.* **1928**, *9*, 113. For an outstanding overview of techniques for measuring complex stoichiometry and stability, see: Connors, K. A. *Binding Constants*; Wiley: New York, 1987.

[15] Intermolecular hydrogen bonding of a carboxylic acid to N7/N6 of an adenine derivative has been observed (crystallographic data) to occur in the solid state without proton transfer: Narayanan, P.; Berman, H. M.; Rousseau, R. *J. Am. Chem. Soc.* **1976**, *98*, 8472.

[16] NMR chemical shift changes induced by dilution of an equimolar mixture of **1** and **2** in (deuterated) aqueous methanol were very small and linear, as required for proton transfer phenomena and not association. In contrast, the same experiment in THF-d_8 revealed both large changes in chemical shift and saturation binding characteristics.

[17] The molecule crystallized from ethanol–water as an internal salt. A proton has been transferred from one acid to a diazocine nitrogen. The resulting ammonium group is hydrogen bonded to the carboxylate of a nearby molecule (not shown). This proton transfer does not occur in THF or chloroform.

Thermal Generation of α,3-Dehydrotoluene from (*Z*)-1,2,4-Heptatrien-6-yne

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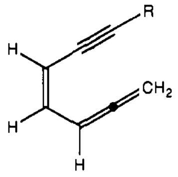
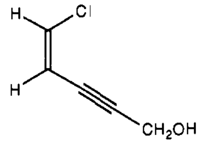
(*Z*)-1,2,4-Heptatrien-6-yne (**1**) undergoes a first-order thermal reaction to produce an intermediate or intermediates whose reactivity is consistent with that of a species designated α,3-dehydrotoluene.



1 R = H
5 R = TMS



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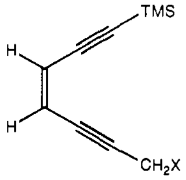
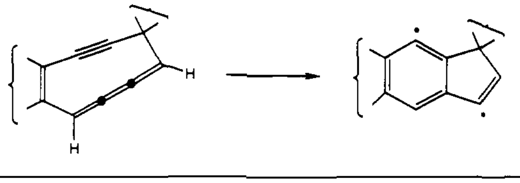


3 X = OH
4 X = $NHNH_2$

Recently, a new class of antitumor antibiotics has been defined on the basis of their proposed transformation to highly reactive, DNA-bound biradical intermediates. In the case of the antibiotics calichemicin and esperamicin, the reactive intermediate is proposed to be a 1,4-dehydrobenzene derivative and is suggested to arise thermally from a (*Z*)-enediyne in a cyclic version of the Bergman reaction.[1,2] Neocarzinostatin chromophore has been proposed to produce a 3,7-dehydroindene derivative through the cyclization reaction depicted in eq 1.[3] The lack of precedent in the latter



(1)

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[1] (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466. (c) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (d) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.

[2] (a) Bergman, R. G.; Jones, R. R. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082. (c) Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091. (d) For a definition and discussion of the term "dehydroaromatic", see: Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25.

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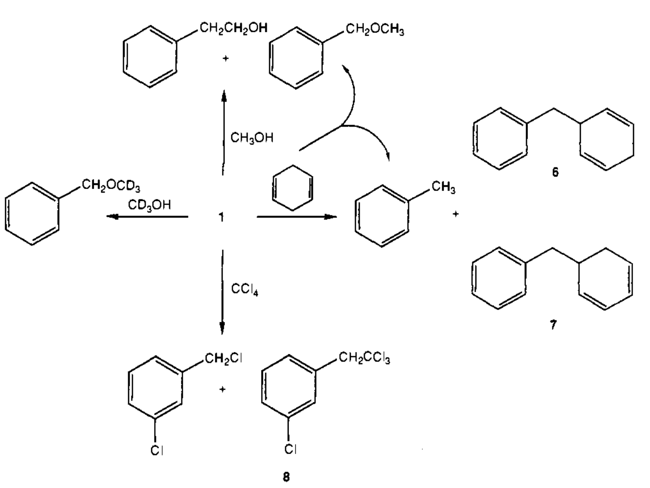


Figure 1. Products of thermolysis of (*Z*)-1,2,4-heptatrien-6-yne (**1**) in various solvents.

transformation and a desire to gain a greater understanding of these processes in general have led us to explore the thermal chemistry of the hydrocarbon **1**.[4]

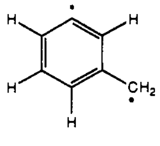
(*Z*)-1,2,4-Heptatrien-6-yne (**1**) was synthesized as follows. Propargyl alcohol and (*Z*)-1,2-dichloroethylene (1.1 equiv) were coupled at 0 °C with tetrakis(triphenylphosphine)palladium (0.05 equiv)–cuprous iodide (0.20 equiv) in ether containing *n*-propylamine (4.0 equiv) to provide the (*Z*)-vinyl chloride **2** in 54% yield after chromatographic purification.[5] A second stereospecific coupling reaction with (trimethylsilyl)acetylene (1.4 equiv) under identical conditions then transformed **2** into the (*Z*)-enediyne **3** (83%). Sequential addition of triethylamine (3.0 equiv) and methanesulfonyl chloride (2.0 equiv) to a solution of **3** in methylene chloride at 0 °C[6] followed by direct addition of this reaction mixture to excess dry hydrazine (10 M, 100 equiv) in methanol, also at 0 °C, afforded, after extractive isolation, the propargylhydrazine **4**.[7] Treatment of an ethereal solution of crude **4** with diethyl azodicarboxylate (DEAD, 1.1 equiv) at 0 °C led to spontaneous evolution of dinitrogen with formation of the allene **5** (62% from **3**, after chromatographic purification).[8] Clean desilylation of **5** was achieved with potassium fluoride dihydrate in methanol (23 °C, ca. 60%) producing, after extraction into pentane and preparative gas chromatography, the hydrocarbon **1** as a colorless, volatile liquid. Alternatively, solutions of **1** could be prepared by direct extraction of the desilylation reaction mixture with an appropriate solvent (e.g., 1,4-cyclohexadiene) and were stored at −100 °C to avoid polymerization.

Mild thermolysis of **1** (0.003 M) in deoxygenated 1,4-cyclohexadiene produced toluene (60%) and combination products **6** and **7** (1:1, 40%) quantitatively (Figure 1). The disappearance of **1** was readily monitored by gas chromatography and exhibited clean first-order behavior at five reaction temperatures over a 60-deg range (39–100 °C) with the following activation parameters: $\Delta H^{\ddagger} = 21.8 \pm 0.5$ kcal/mol, $\Delta S^{\ddagger} = -11.6 \pm 1.5$ eu ($E_a = 22.5$ kcal/mol, $\log A = 10.7$).

Heating of **1** in carbon tetrachloride solution at 100 °C produced the adduct **8** and 3-chlorobenzyl chloride as the only detectable products in a combined yield of 15–25%. The low yield of volatile products in these experiments is believed to be due to less efficient trapping of radical intermediates by carbon tetrachloride (as compared to 1,4-cyclohexadiene) leading to competitive radical-induced polymerization of **1**. In support of this theory, the yield of 3-chlorobenzyl chloride was observed to increase as the initial concentration of **1** was lowered: 0.08 M, 1%; 0.008 M, 5%; 0.0008 M, 8%.

Pyrolysis experiments in methanol (0.003 M **1**, 100 °C, 30 min) led to the formation of products consistent with both polar (methyl benzyl ether, 35%) and free-radical (2-phenylethanol, 10%; bibenzyl, 2%) reaction pathways. This product distribution was found to be reproducible and was insensitive to acidic or basic preconditioning of the reaction glassware. Heating solutions of **1** (0.003 M) in methanol containing 1,4-cyclohexadiene (0.2 M) produced toluene (19%), **6** and **7** (1:1, 9%), methyl benzyl ether (25%), and only traces of 2-phenylethanol and bibenzyl. Increasing the concentration of 1,4-cyclohexadiene to 1.0 M led to an increase in the yield of toluene (32%) and **6** and **7** (1:1, 19%) with a concomitant decrease in the formation of methyl benzyl ether (12%). Bibenzyl and 2-phenylethanol were not detected in this experiment. When **1** was heated in CD_3OH (0.003 M), methyl-d_3 benzyl ether was formed exclusively, in 70% yield. The kinetics of decomposition of **1** in the latter experiment were first-order ($k = 4.0 \pm 0.2 \times 10^{-4}\ s^{-1}$ at 75 °C) and, importantly, were indistinguishable from those obtained in 1,4-cyclohexadiene ($k = 3.8 \times 10^{-4}\ s^{-1}$). Together, these results are consistent with a mechanism in which **1** undergoes rate-limiting, first-order transformation to an intermediate or intermediates, here designated as α,3-dehydrotoluene,[2d] whose partitioning between polar and free-radical reaction pathways reflects the homolytic bond dissociation energy of the trapping agent.[9]

A fundamental distinction between the 3,7-dehydroindene intermediate of eq 1 and the putative α,3-dehydrotoluene species described herein is the fact that the former is almost certainly constrained as a σ-radical pair, while the latter can, at least in concept, exist as a σ,π-biradical (represented as **9**) capable of full



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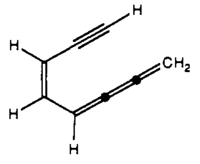

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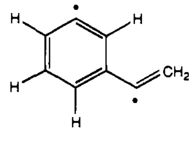

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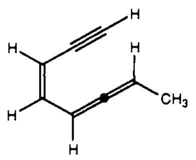

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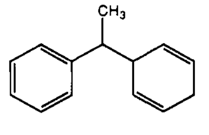

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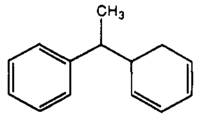

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benzylic resonance. A significant thermodynamic consequence of this description is that **9** is calculated to lie ~15 kcal/mol below **1** in energy.[10] By contrast, the hypothetical cyclization of **10** to

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[3] (a) Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493. (b) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212. (c) Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146.

[4] (a) An isoelectronic rearrangement (wherein the allene of **1** is replaced by a ketene) has been proposed to occur in the thermolysis of 4-alkynyl-4-alkoxycyclobutenones: Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc*. **1989**, *111*, 975. (b) Cyclization reactions of bisallene precursors of formula $(H_2C{=}C{=}CH)_2X$ are known. X = *cis*-HC=CH: Ben-Efraim, D. A.; Sondheimer, F. *Tetrahedron Lett.* **1963**, 313. X = O and S: Greenberg, M. M.; Blackstock, S. C.; Berson, J. A. *Tetrahedron Lett.* **1987**, *28*, 4263 and references therein.

[5] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313. (c) Use of *cis*-dichloroethylene in coupling reactions: Vollhardt, K. P. C.; Winn, L. S. *Tetrahedron Lett.* **1985**, *26*, 709. (d) Differential coupling of *cis*-dichloroethylene: Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631.

[6] Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

[7] Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717.

[8] (a) Myers, A. G.; Finney, N. S.; Kuo, E. Y. *Tetrahedron Lett.*, in press. (b) Oxidative rearrangement of an allylic hydrazine has been accomplished with molecular oxygen; see ref 7. (c) For the oxidation of 1,1- and 1,2-dialkylhydrazines, respectively, with diethyl azodicarboxylate, see: Fahr, E.; Koch, K.-H. *Liebigs Ann. Chem.* **1980**, 219. Stone, K. J.; Greenberg, M. M.; Blackstock, S. C.; Berson, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 3659.

[9] While our data do not allow further description of the reactive intermediate(s), we note that our results are inconsistent with a cascade pathway in which a short-lived "polar" species decays irreversibly to an intermediate with radical reactivity. A cascade mechanism with the inverse ordering of reactive intermediates is not ruled out.

(planar) **11** is calculated to be exothermic by only 1 kcal/mol[11] and the cyclization of (*Z*)-3-hexene-1,5-diyne to 1,4-dehydrobenzene is inherently endothermic ($\Delta H_0 = +14$ kcal/mol).[2a] This potential ground-state stabilization may be reflected in the transition state for cyclization of **1**, perhaps by twisting of the allenic methylene group toward the plane of conjugation.

Alkyl substitution of the allene terminus of **1**, and thereby the benzylic carbon of the corresponding dehydroaromatic intermediate, is found to accelerate the cyclization reaction. (*Z*)-3,5,6-Octatrien-1-yne (**12**), synthesized in analogy to **1**, produces ethylbenzene (45%) and combination products **13** and **14** (1:1, 55%) in quantitative yield upon thermolysis in 1,4-cyclohexadiene (0.001 M, 100 °C, 30 min). Kinetic analysis shows the loss of **12** to be first-order and approximately 6-fold faster than loss of **1** under the same conditions ($k = 3.24 \pm 0.75 \times 10^{-3}$ s^{-1} at 78 °C). The facility of both cyclizations is striking ($t_{1/2}$ of **1** at 37 °C ~ 24 h) and raises the intriguing possibility that these simple structures may themselves form the basis for the design of new antibiotics.

Acknowledgment. We gratefully acknowledge financial assistance from the National Science Foundation and a Kodak fellowship to E.Y.K. We are indebted to our colleagues Professors Dennis Dougherty and Robert Grubbs for many helpful discussions.

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(10) ΔH_f (**1**) is calculated to be 117.9 kcal/mol by using group additivities (Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1976). The ΔH_f of the planar, biradical form of α,3-dehydrotoluene is estimated to be 103 kcal/mol by subtraction of the bond dissociation energy of molecular hydrogen (104.2 kcal/mol: Herzberg, G. *J. Mol. Spectrosc.* **1970**, *33*, 147) from the sum of ΔH_f (toluene) (11.95 kcal/mol: Stull, D. R.; Westrum, E. F., Jr.; Sinke, G. C. *The Chemical Thermodynamics of Organic Compounds*; Wiley: New York, 1969) and the two relevant CH bond dissociation energies (85 and 110 kcal/mol).

(11) Calculated as in ref 10: ΔH_f (**10**) = 152.13, ΔH_f (**11**) = 151 kcal/mol [35 (ΔH_f of styrene) + 2 × 110 (BDE of ArH) − 104.2 (BDE of H_2)].

The Role of d Functions in Sulfur Oxide Molecules

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An empirical observation that has provoked much debate and interest is the important role that higher angular momentum basis functions play in predicting accurate bond lengths and angles for *some* molecules containing second-row atoms. Associated with this observation is an anomalously large lowering of the calculated total energy when, for example, d functions are included in the basis set as compared to the total energy calculated when only an sp basis set is employed. In this communication we provide new insight regarding these observations by considering the kinds of bonding found for sulfur in sulfur oxides and hydrogen sulfide.

In a recent paper we presented a new description of the bonding in sulfur dioxide and other sulfur oxide molecules.[1] For these molecules it was found that there are six valence orbitals on the sulfur atom arranged in a trigonal prism which form covalent bonds to oxygen atoms or, if unbonded, combine as lone pairs. This is illustrated schematically at the top of Figure 1. Results of generalized valence bond (GVB) calculations on sulfur dioxide using a double-ζ sp basis set and the same basis set augmented by single-ζ d basis functions on each atom are shown in Figures

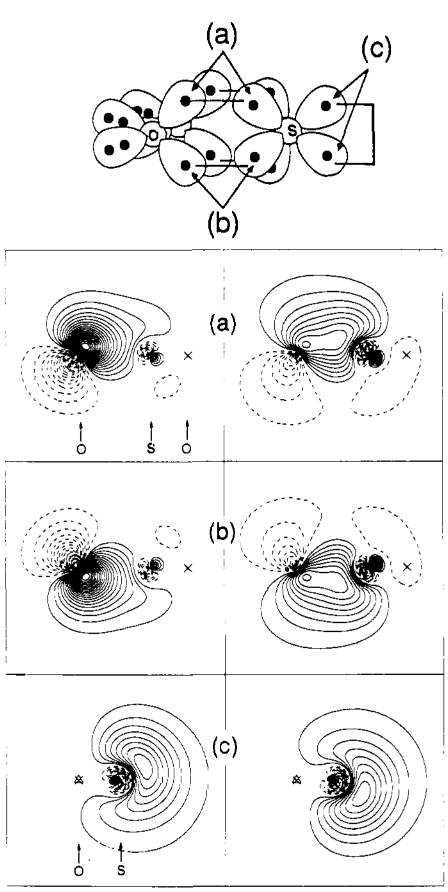

Figure 1. GVB orbitals for SO_2 using a DZ+d(O,S) basis set. (a, b) Orbitals representing the S=O double bond. (c) Angularly correlated S lone pair. Contours are separated by 0.04 au in both figures.

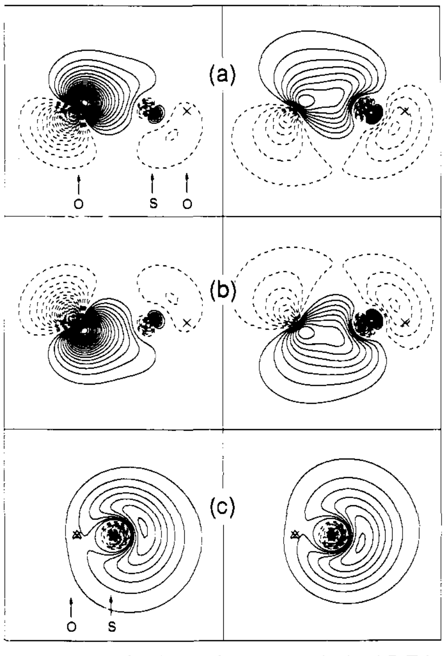

Figure 2. GVB orbitals for SO_2 using an unpolarized DZ basis set. (a, b) Orbitals representing the S=O double bond. (c) Angularly correlated S lone pair.

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* Address correspondence to this author at General Electric Co.

(1) Patterson, C. H.; Messmer, R. P. *J. Am. Chem. Soc.* Submitted. Calculations were performed within the strong orthogonality and perfect pairing (SOPP) approximations to the GVB wave function. The form of this wave function is described in the following: Bobrowicz, F. W.; Goddard, W. A., III *Modern Theoretical Chemistry*; Schaefer, H. F., III, Ed.; Plenum Press: New York, 1977; Vol. 3, Chapter 4.

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