(1) the differences between the pK_a's of the phosphonylphosphinyl analogue and the normal diphosphate substrates and (2) small geometric differences between C-P and O-P bonds.[1,15]

Analogue **2** has the unusual property of being a substrate for the 1'-4-condensation, thereby generating a phosphonylphosphinyl product that is a nonreactive inhibitor for subsequent reactions in the pathway. When a solution (4.5 mM, 2.7 μmol) in **2** was incubated at 37 °C with 11.9 mM (7.1 μmol) **10** and 0.14 mg (2.1 μmol min^{-1} mg^{-1}) of avian liver farnesyl diphosphate synthetase,[16] the AB pattern at δ −13.2 and −10.2 ppm in the ^{1}H-decoupled ^{31}P NMR spectrum of the allylic substrate disappeared and was replaced by a singlet at −1.3 ppm, characteristic of inorganic pyrophosphate.[17] In a related experiment, **2** (40 μg, 0.14 μmol) was incubated at 37 °C with [1-^{3}H]**10** (4.7 μg, 0.013 μmol, 70 μCi/μmol). The sample was lyophilized, and the residue was analyzed by TLC[18] with use of authentic samples of **2**, **10**, and farnesyl diphosphate (**11**) as standards. A new radioactive component was identified, $R_f = 0.75$ ($R_{f(10)} = 0.55$, $R_{f(11)} = 0.70$), whose mobility was consistent with the phosphonylphosphinyl analogue **12** of farnesyl diphosphate (**11**). Similar experiments using [1-^{3}H]**5** (23 μCi/μmol) as the allylic substrate gave a radioactive product, $R_f = 0.58$, whose mobility was consistent with formation of a geranyl phosphonylphosphinyl derivative.

Phosphonylphosphinyl analogues **2** and **3** are both good inhibitors of the 1'-4-condensation reaction. In addition, homoallylic analogue **2** has the unusual property of functioning as a substrate for 1'-4-condensation and generating a product that can presumably inhibit the next step in the pathway. When dimethylallyl diphosphate (**5**) is the allylic substrate, the next step is the second prenyl transfer catalyzed by farnesyl diphosphate synthetase. When geranyl diphosphate (**10**) is the allylic substrate, the putative phosphonylphosphinyl farnesyl product (**12**) is also a potential inhibitor for all of the normal isoprenoid reactions that utilize farnesyl diphosphate as a substrate, including squalene synthetase (sterols), geranylgeranyl diphosphate synthetase (carotenoids), dehydrodolichol synthetase (dolichols), and decaprenyl diphosphate synthetase (ubiquinones). A related phosphonylphosphate metabolic block at the farnesyl stage was synthesized by Corey and Volante.[19] The major difference between their inhibitor and the phosphonylphosphinyl class is that the latter compounds cannot be hydrolyzed enzymatically or chemically to less potent phosphonate analogues. The accumulation of nonhydrolyzable allylic analogues should be particularly devastating to higher polyprenyl diphosphate synthetases which catalyze multiple 1'-4-condensations.

The synthetic approach described here can be applied to other systems to give P-C-P-C analogues of diphosphates or higher phosphate anhydrides. Work in that direction is continuing in our (R.W.M.) laboratory.

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Supplementary Material Available: Details of the syntheses of **2**, **3**, and **6** (2 pages). Ordering information is given on any current masthead page.

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[15] (a) Blackburn, G. M.; England, D. A.; Kolkmann, F. *J. Chem. Soc., Chem. Commun.* **1981**, 930. (b) Blackburn, G. M. *Chem. Ind.* (*London*) **1981**, 134.

[16] Enzymatic experiments were done in a standard buffer containing 20 mM *endo*-bicyclo[2.2.1]heptane dicarboxylate, 1 mM magnesium chloride, pH 7.00.

[17] Spectra are referenced to external H_3PO_4.

[18] Mixtures were cospotted with authentic samples (cellulose TLC, tetrahydrofuran: 100 mM ammonium bicarbonate, 75:25, $R_{f(11)} = 0.70$, $R_{f(10)} = 0.55$, $R_{f(2)} = 0.26$, $R_{f(6)} = 0.17$).

[19] Corey, E. J.; Volante, R. P. *J. Am. Chem. Soc.* **1976**, *98*, 1291.

Transition State Structure Variation in the Diels-Alder Reaction from Secondary Deuterium Kinetic Isotope Effects: The Reaction of a Nearly Symmetrical Diene and Dienophile Is Nearly Synchronous

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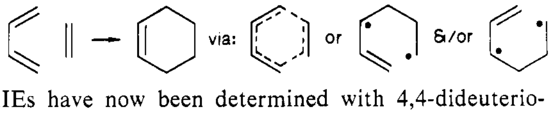
Diels-Alder transition states are of concern.[1] There is little doubt but that the reaction of unsymmetrical dienophiles proceeds via an unsymmetrical transition state[2] (and is not synchronous[3]), but the question of concert still remains in these cases, and in the case of symmetrical addends the question of synchrony is paramount. Dewar has calculated that the reaction involves a highly unsymmetrical transition state if not a biradical.[3] Previous work with secondary deuterium kinetic isotope effects (KIEs),[4] the most appropriate probe for these questions, has been criticized for not distinguishing between the alternatives particularly with symmetrical addends.



KIEs have now been determined with 4,4-dideuterio- and 1,1,4,4-tetradeuterioisoprene, *4,4-d_2* and *-d_4*, respectively, in their reaction with the acrylonitrile, fumaronitrile, vinylidene cyanide, and methyl *trans*-β-cyanoacrylate in benzene solvent (Table I). Isoprene is a diene of choice because its methyl group might not affect the symmetry of a near-synchronous path, but because the methyl strongly affects the regiochemistry with highly unsymmetrical dienophiles the methyl must strongly perturb the relative energies of the potential biradical pathways *even with symmetrical dienophiles*. The KIEs were determined by competition, reacting the dienophile with excess (>10-fold) of a mixture of d_0 and d_n isoprene and observing the d_0/d_n ratio in each adduct by either GCMS in CI mode[5] or by capillary GC.[6] The d_0/d_n ratio in starting isoprene was found by using an excess of the dienophile.[5] KIEs from d_4 when divided by those from *4,4-d_2* give the KIEs for 1,1-dideuterioisoprene, *1,1-d_2*. Also listed in Table I are the maximum kinetic isotope effects expected for two deuteriums, which are derived from the equilibrium constants for fractionation of deuterium between exomethylene carbon and secondary saturated allylic carbon in degenerate thermal 1,3- and 3,3-shifts over nearly a 200 °C range.[7]

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[1] For a review, see: Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779. For the most recent work on the stereochemistry of the reaction and a summary of theoretical work, see: Houk, K. N.; Lin, Y.-T.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554.

[2] Woodward, R. B.; Katz, T. J. *Tetrahedron* **1959**, *5*, 70. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley; London, 1976, Chapter 4.

[3] (a) Dewar, M. J. S.; Olivella, S.; Rzepa, H. J. *J. Am. Chem. Soc.* **1978**, *100*, 5650. (b) Dewar, M. J. S.; Pierini, A. B. *Ibid.* **1984**, *106*, 203. (c) Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *Ibid.* **1986**, *108*, 5771.

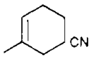
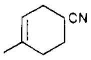
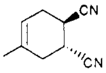
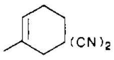
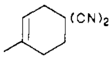
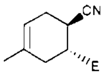
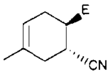
[4] (a) van Sickle, D. W. *Tetrahedron Lett.* **1961**, *687*. van Sickle, D. W.; Rodin, J. O. *J. Am. Chem. Soc.* **1964**, *86*, 3091. (b) Seltzer, S. *Ibid.* **1963**, *85*, 1360; **1965**, *87*, 1534. (c) Brown, P.; Cookson, R. C. *Tetrahedron* **1965**, *21*, 1973. (d) Taagepera, M.; Thornton, E. R. *J. Am. Chem. Soc.* **1972**, *94*, 1168.

[5] GCMS in CI mode was performed on a Hewlett-Packard Model 5985 equipped with a 30-m DB-5 capillary column. GCMS analyses of the excess vinylidene cyanide reactions were irreproducible so the value of the d_0/d_2 ratio in the standard is that from the excess acrylonitrile runs.

[6] Capillary GC analyses were performed on a 100-m SPB-5 column with a 60-m SP2330 column connected in series. Under conditions of 3-h retention times, all four peaks for d_0 and d_2 (and d_0 and d_4) regioisomers from methyl *trans*-β-cyanoacrylate were separated sufficiently (valley 30% above base line in the worse case). Any inaccuracy in the absolute values of the ratios is offset by the cancellation of errors because of identical analytical techniques for the standard.

[7] Calculated from the equation $\log K^{D}2/K^{H} = (291.6/2.303RT) - 0.0818$ ($r = 0.977$). Conrad, N. D. Ph.D. Thesis, Indiana University, 1978. For a discussion of the use of this equation in other pericyclic reactions, see: Gajewski, J. J. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, The Netherlands, Vol 7, Chapter 3, p 1987. Note that the equilibrium IEs reported in Appendix B Vol 7, should be inverted.

Table I. Secondary Deuterium KIEs in Isoprene 4 + 2 Cycloadditions[f]

acrylonitrile +				maximum[c]
$d_0/4,4\text{-}d_2$	at 100 °C[a]	1/1.105 (0.007)	1/0.99 (0.002)	1/1.22
$d_0/1,1\text{-}d_2$[e]	at 100 °C[a]	1/1.020 (0.030)	1/1.13 (0.04)	1/1.22
fumaronitrile +				maximum[c]
$d_0/4,4\text{-}d_2$	at 100 °C[a]	1/1.05 (0.022)		1/1.22
$d_0/1,1\text{-}d_2$[e]	at 100 °C[a]	1/1.05 (0.03)		1/1.22
vinylidene cyanide +				maximum[c]
$d_0/4,4\text{-}d_2$	at 25 °C[a]	1/1.26 (0.07)	1/0.98 (0.06)	1/1.35
$d_0/1,1\text{-}d_2$[e]	at 25 °C[b]	1/1.02 (0.10)	1/1.28 (0.07)	1/1.35
methyl *trans*-β-cyanoacrylate +		 regioisomer 1[d]	 regioisomer 2[d]	maximum[c]
$d_0/4,4\text{-}d_2$	at 25 °C[b]	1/1.14 (0.04)	1/1.125 (0.025)	1/1.35
$d_0/1,1\text{-}d_2$[e]	at 25 °C[b]	1/1.09 (0.05)	1/1.11 (0.04)	1/1.35

[a] Analyses by GCMS in CI mode—see footnote 5. [b] Analyses by capillary GC—see footnote 6. [c] Calculated for two deuteriums at the reaction temperature—see footnote 7. [d] The regiochemistry could not be assigned due to the inseparability of the diastereomers on a preparative scale. [e] Determined from KIE for $1,1,4,4\text{-}d_4$/KIE for $4,4\text{-}d_2$. [f] Standard deviations are in parentheses.

All reactions in Table I reveal either no KIE or an inverse KIE which is expected if the site in transition state becomes tetravalent. The "meta" adduct from reaction of $4,4\text{-}d_2$ with acrylonitrile has a KIE which must be related to the extent of bond making at the β site of acrylonitrile; the "para" adduct has but a very small KIE suggesting little bond making to the α site of acrylonitrile (the gross para/meta ratio is 7:3). The effects with $1,1\text{-}d_2$ reveal the same unsymmetrical transition state. Significant is the fact that the inverse KIE observed at the β site of acrylonitrile in both experiments is only half of the maximum value expected indicating an early, unsymmetrical transition state—not one with a single bond fully formed. If the reaction involved biradicals, the obvious cyano-bearing diradical species leading to each of the regioisomers would dominate, and the maximum value for the KIE should have been observed at the site of bonding to the β carbon of acrylonitrile in both experiments. With the more unsymmetrical dienophile, vinylidene cyanide, a more unsymmetrical transition state is observed since the para/meta ratio is 7:1 and the KIE at the bond forming to the β site of the dienophile is half to three-quarters of the maximum value and there is little if any KIE in bond making to the α site.[5,8]

The reaction of fumaronitrile provides only one adduct, but it is significant that the KIEs at C1 and C4 of the diene are roughly equal and one-quarter of the maximum value. If biradicals were involved, the one with a bond to C-1 of isoprene should dominate by at least a factor of 7 over the one with a bond to C-4 judging by the regiochemistry with highly unsymmetrical dienophiles.[8] This would require the KIE at C-1 to be near the maximum value and that at C-4 to be very small.[9] In the reaction of $4,4\text{-}d_2$ (and $1,1\text{-}d_2$) with methyl *trans*-β-cyanoacrylate,[10] both regioisomers[11] show the same inverse KIE (within experimental error) at each site, and it is roughly one-third of the maximum value. If the reaction were stepwise, then the two biradicals giving each regioisomer should be involved in a ratio of ca. 7:1, assuming that α cyano radical stabilization is equivalent to α carbomethoxy radical stabilization (since the regiopreference is unity, the assumption must be true). Under this circumstance, the KIE for $4,4\text{-}d_2$ should be roughly $^1/_8$ the maximum value, and the KIE for $1,1\text{-}d_2$ should be roughly $^7/_8$ the maximum value in each regioisomer. Thus, the KIEs with fumaronitrile and the nearly symmetrical–unsymmetrical dienophile are consistent with a nearly synchronous, concerted pathway with an early transition state.

Acknowledgment. We thank the National Science Foundation for support, and we thank Professor Ronald A. Hites and Dr. William Simonsick for providing the GCMS-CI instrument and help in its use, respectively.

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[8] The Diels–Alder reaction of 1,1-dichloro-2,2-difluoroethylene with isoprene gives almost an identical regiopreference: Bartlett, P. D.; Wallibillich, E. H.; Wingrove, A. S.; Swenton, J. S.; Montgomery, L. K.; Kramer, B. D. *J. Am. Chem. Soc.* **1968**, *90*, 2049. In a 2 + 2 and in a 4 + 4 cycloaddition which probably proceed via biradicals, the KIEs at the obvious bond-forming site are near the maximum values of Holder et al. (Holder, R. W.; Graf, N. A.; Duesler, E.; Moss, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2926) and Chou et al. (Chou, C. H.; Trahanovsky, W. S. *J. Am. Chem. Soc.* **1986**, *108*, 4138.), respectively; in the 2 + 2 cycloaddition, the SDKIE at a radical site is unity.

[9] the same analysis can be applied to Seltzer's results.[4b]

[10] Sauers, C. K.; Cotter, R. J. *J. Org. Chem.* **1961**, *26*, 6.

[11] The ratio of regioisomers from methyl *trans*-β-cyanoacrylate is 1:1. PMR of the mixture (360 MHz, $CDCl_3$): δ 5.45 (s, 1 H); 5.36 (s, 1 H); 3.75 (s, 6 H); 3.05 (m, 2 H); 2.85 (m, 2 H); 2.4 (m, 8 H); 1.65 (s, 6 H).

A New Structural Form of Tin in a Cubic Cluster

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We have reported new forms of tin comprised of oligomeric oxotin carboxylates that are based on the compositions $[R'Sn(O)O_2CR]_6$[1-5] and $[(R'Sn(O)O_2CR)_2R'Sn(O_2CR)_3]_2$.[2-5] These have "drum" and "ladder" structures, respectively. We also reported the oxygen-capped cluster, $[(n\text{-}BuSn(OH)O_2PPh_2)_3O][Ph_2PO_2]$,[6] which has tin in a partial cubic array surrounded by chelating phosphinate groups. In all of these forms, tin generally is octahedrally coordinated. One useful synthetic route for their formation employs the interaction of an alkyl or aryl stannoic acid with either a carboxylic acid or a phosphorus-containing acid.

The number of tin atoms in these oligomers is either three or six. We now have obtained an additional form containing four tin atoms. The present report concerns the synthesis and structural

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[1] Chandrasekhar, V.; Day, R.O.; Holmes, R. R. *Inorg. Chem.* **1985**, *24*, 1970–1971.

[2] Holmes, R. R.; Schmid, C. G.; Chandrasekhar, V.; Day, R. O.; Holmes, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 1408–1414.

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[5] Chandrasekhar, V.; Schmid, C. G.; Shafeizad, S.; Johnson, S. E.; Holmes, J. M.; Day, R. O.; Holmes, R. R. *Abstracts of Papers*, 191st National Meeting of the American Chemical Society, New York, NY; American Chemical Society: Washington, DC, 1986; INOR 179.

[6] Day, R. O.; Holmes, J. M.; Chandrasekhar, V.; Holmes, R. R. *J. Am. Chem. Soc.* **1987**, *109*, 940–941.

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