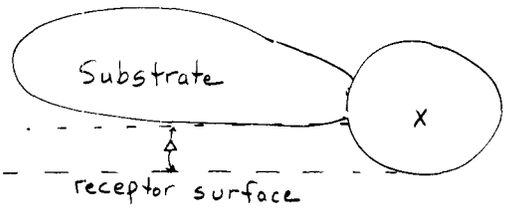


Figure 4. Cross section of the substrate–receptor complex.

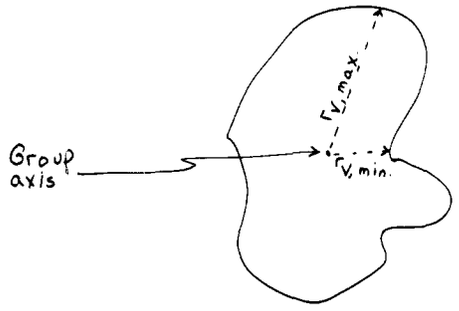


Figure 5. Cross section of the X group perpendicular to the group axis.

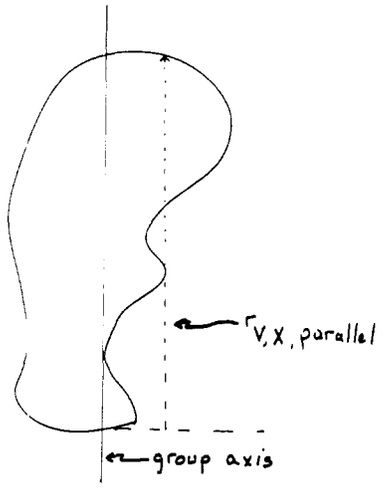


Figure 6. Cross section of the X group including the group axis.

involved and steric effects are not present.

It has been suggested that there may be "steric" effects in biological systems which are entirely different from those encountered in ordinary chemical reactions and that such effects may indeed be volume dependent. We would like to suggest that in biological systems two sources of steric effects are possible: those which are entirely analogous to the steric effects encountered in ordinary chemical reactions, and those which are due to the formation of a complex between the substrate and some receptor site. If the receptor site resembles a planar surface, the steric effect of a group attached to the substrate will depend on how far it extends beyond the rest of the substrate. Its steric effect will therefore be directional, as are the steric effects in ordinary chemical reactions (see Figure 4). If the receptor site is a hole or depression, the steric effect of the attached group X will be dependent on its minimum and maximum perpendicular van der Waals radii and its parallel van der Waals radius (see Figures 5 and 6). Unless the group has considerable symmetry, its appropriate van der Waals radii will not be a simple function of its volume. It follows then that even in a biological system a dependence of steric effects on group volume is not likely.

We suggest that the significance of volume or bulk parameters in QSAR is that they represent some kind of bonding interaction between the biologically active molecule and the receptor site contributing to the formation of a complex and that steric effects (in the sense normally used in physical organic chemistry) are *not* involved.

Acknowledgment. The senior author would like to acknowledge National Science Foundation Grant No. CHE 77-16421 for presentation of this paper at the IUPAC–IUPHARM Symposium, Biological Activity and Chemical Structure, Aug 30–Sept 2, 1977, at Noordwiukerhout, The Netherlands.

Supplementary Material Available: Results of correlations with eq 1 (Table VI), 13 (Table VII), 28 (Table VIII), and 29 (Table IX) (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Quantitative structure–activity relationships (QSAR) are relationships between substituent constants or quantum chemical parameters and biological activities. Useful reviews of QSAR include W. P. Purcell, G. E. Bass, and J. M. Clayton, "Strategy of Drug Design", Wiley-Interscience, New York, 1973; M. S. Tute, *Adv. Drug Res.*, **6**, 1 (1971); A. Verloop, "Drug Design", Vol. 3, E. J. Ariens, Ed., Academic Press, New York, 1972; P. J. Goodford, *Adv. Pharmacol. Chemother.*, **11**, 52 (1973); K. C. James, *Prog. Med. Chem.*, **10**, 205 (1974); J. W. McFarland, *Prog. Drug Res.*, **15**, 124 (1971).
(2) A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).
(3) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).
(4) O. Exner, *Collect. Czech. Chem. Commun.*, **32**, 1 (1967).
(5) J. Traube, *Saml. Chem. Chem.-Techn. Vortr.*, **4**, 255 (1899); H. Holland, *Acta Chem. Scand.*, **27**, 2687 (1973).
(6) O. R. Quayle, *Chem. Rev.*, **53**, 439 (1953).
(7) M. Charton, *J. Am. Chem. Soc.*, **99**, 5687 (1977); Abstracts, 4th IUPAC Conference on Physical Organic Chemistry, York, England, Sept 1978.
(8) M. Charton, *J. Am. Chem. Soc.*, **97**, 1552 (1975).
(9) M. Charton, *J. Org. Chem.*, **41**, 2217 (1976).
(10) M. Charton *J. Am. Chem. Soc.*, **97**, 3694 (1975).
(11) M. Charton, *J. Org. Chem.*, **42**, 3531 (1977).
(12) M. Charton, *J. Org. Chem.*, **41**, 2906 (1976).
(13) M. Charton, *J. Org. Chem.*, **42**, 3535 (1977).
(14) M. Charton and B. I. Charton, *J. Org. Chem.*, **43**, 1161 (1978).
(15) M. Charton, *J. Am. Chem. Soc.*, **97**, 6159 (1975).
(16) M. Charton, "Design of Biopharmaceutical Properties Through Prodrugs and Analogs", E. B. Roche, Ed., American Pharmaceutical Society, Washington, D.C., 1977, p 228.
(17) M. Charton, Abstracts, 3rd IUPAC Conference on Physical Organic Chemistry, Montpellier, France, Sept 1976.
(18) M. Charton and B. I. Charton, 2nd International Symposium on Acetylenes, Allenes, and Cumulenes, Nottingham, England, Sept 1977.
(19) M. Charton, *Prog. Phys. Org. Chem.*, **10**, 81 (1973).

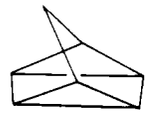
Cycloadditions with Quadricyclane. Synthesis of Fused-Ring 1,2-Diazetidines

Michael E. Landis* and John C. Mitchell

Department of Chemistry, Southern Illinois University, Edwardsville, Illinois 62026

Received November 13, 1978

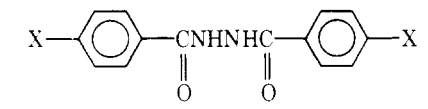
The unique chemical reactivity of molecules containing strained σ bonds has been of considerable experimental and theoretical interest to organic chemists. Most notable of these highly reactive compounds are bicyclo[2.1.0]pentane,[1] bicyclobutanes,[2] and tetracyclo[3.2.0.$0^{2,7}$.$0^{4,6}$]heptane[3] (quadricyclane, Q). The [$2_\pi + 2_\sigma + 2_\sigma$] cycloadditions of quadricyclane with a variety of dienophiles[3,4] suggest significant interaction



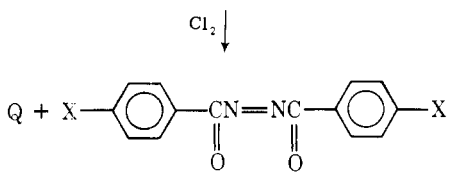
Q

between the two cyclopropane rings. Reactions with diastereomeric ethylenic dienophiles are both regio- and stereospecific,[3b] suggesting a concerted mechanism for the cycloaddition. Recent MINDO/2 calculations[5,6] have been interpreted in support of a concerted process.[6] We wish to report that the reaction of Q with diaroyldiazines **1**, as with diethyl azodicarboxylate,[3c] provides a general synthesis for fused-ring 1,2-diazetidines **2**. Substituent and solvent effects on reaction rates suggest the intermediacy of a charge-transfer complex in the cycloaddition.

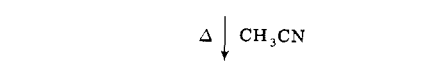
Diaroyldiazines **1** were synthesized by oxidation of the corresponding hydrazines **3** with 5% chlorine water. Refluxing **1** with excess Q produces 1,2-diazetidines **2**. ^{1}H NMR spectra of **2a–c** display singlets for diazetidine ring protons (H_2, H_5).

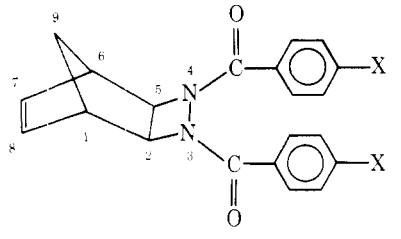


3



1





2

a, X = CF_3; b, X = H; c, X = OCH_3

The absence of significant coupling between protons at C-2 (C-5) and bridgehead protons at C-1 (C-6) supports the assigned exo stereochemistry[3a,b,7] for **2a–c**.

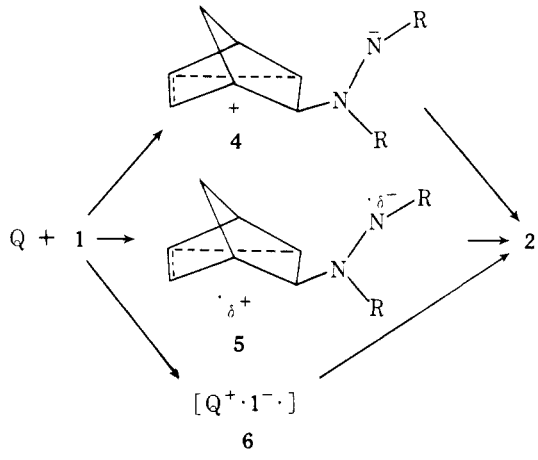
Rates of reaction were determined by monitoring the disappearance of azo compound by visible spectroscopy. Rates for **1a–c** in the presence of a tenfold excess of Q were of the first order through three half-lives in both carbon tetrachloride and acetonitrile. Second-order rate constants k determined at 60 °C are listed in Table I. Two trends are readily discernible from Table I: (1) reaction rate is accelerated as the azo substituent becomes more electron withdrawing, a factor of 220 for **1a** vs. **1c** in acetonitrile; and (2) a small rate enhancement is observed as solvent polarity increases, factors of 6, 14, and 24 for **1c**, **1b**, and **1a**, respectively, on changing from carbon tetrachloride to acetonitrile.

These results indicate that an intermediate of polar character precedes product formation. A fully developed dipolar ion **4** is unlikely since rate enhancements in polar solvents are small. Mechanisms with polarized biradical **5** or charge-transfer complex **6** as intermediates are reasonable alternatives. The stereospecificity observed[3b] in other cycloadditions involving Q renders unlikely the involvement of a biradical long lived enough to undergo rotational equilibration.[8] Charge-transfer complexes of Q with a variety of dienophiles have been reported,[3a,4] and the involvement of an analogous complex **6** in this cycloaddition is consistent with the observed polar solvent and substituent effects. Attempts to observe

Table I. Second-Order Rate Constants for the Reaction of Quadricyclane with Diaroyldiazines at 60 °C

compd[a]	solvent	10^4k, M^{-1} s^{-1}	λ, nm[b]
1a	CCl_4	9.6	465
	CH_3CN	229	485
1b	CCl_4	0.51	455
	CH_3CN	7.5	465
1c	CCl_4	0.16	465
	CH_3CN	1.04	500

[a] $[1]_0$ = 0.01 M; $[Q]_0$ = 0.10 M. [b] Wavelength at which disappearance of **1** was monitored.



4

5

$[Q^+ \cdot 1^- \cdot]$

6

complexes **6** by visible spectroscopy have been unsuccessful, perhaps attributable to an unfavorable equilibrium for formation and/or rapid collapse to product.[4]

Experimental Section

^{1}H NMR spectra were recorded on a Varian T-60 or a Hatachi Perkin-Elmer R-24B spectrometer; chemical shifts (δ) are expressed in parts per million relative to tetramethylsilane. ^{19}F NMR spectra were recorded on a Varian T-60 spectrometer with chemical shifts in parts per million relative to $CFCl_3$; IR spectra were recorded on a Perkin-Elmer 710B spectrometer. Melting points are uncorrected. All solvents were freshly distilled before use.

Preparation of Diaroylhydrazines 3a–c. Hydrazine hydrate (1.4 g, 43.1 mmol) was added dropwise over a 30-min interval to an ice-cold solution of 86.2 mmol of the appropriate para-substituted benzoyl chloride in 100 mL of pyridine. The solution was stirred for an additional 1 h at room temperature and diluted with 1 L of water. The resulting precipitate was filtered and dried in vacuo. Analytically pure samples can be obtained by recrystallization from acetone or ethanol.

For 1,2-bis[*p*-trifluoromethyl)benzoyl]hydrazine (**3a**, 75%): mp 265–267 °C; ^{1}H NMR (pyridine-d_5) δ 8.18 (d, 4 H, J = 9 Hz), 7.70 (d, 4 H, J = 9 Hz); ^{19}F NMR (pyridine-d_5) ϕ 38.92 (s); IR (KBr) 3200 (NH), 1603 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{10}F_6N_2O_2$: C, 51.08; H, 2.68; N, 7.45. Found: C, 50.74; H, 2.44; N, 7.45.

For 1,2-dibenzoylhydrazine (**3b**, 90%): mp 241–243 °C (lit.[10] 240–242 °C).

For 1,2-bis(*p*-methoxybenzoyl)hydrazine (**3c**, 89%): mp 228–229 °C (lit.[11] 228 °C).

Preparation of Diaroyldiazines 1a–c. A mixture of 13.3 mmol of hydrazine, 125 mL of dichloromethane, and 200 mL of 5% chlorine water was stirred at room temperature. Upon complete extraction of the water-insoluble diazine into dichloromethane, the organic phase was separated, washed with 10% aqueous sodium bicarbonate, and dried over magnesium sulfate. Solvent was removed at reduced pressure; of the resulting crude azo compounds, only **1a** required recrystallization from petroleum ether.

For bis[*p*-(trifluoromethyl)benzoyl]diazine (**1a**, 54%): mp 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, 4 H, J = 8 Hz), 7.85 (d, 4 H, J = 8 Hz); ^{19}F NMR ($CDCl_3$) ϕ 37.08 (s); IR (KBr) 1718 cm^{-1} (C=O), no NH; UV (CCl_4) λ_{max} 465 nm (ϵ 61). Anal. Calcd for $C_{16}H_8F_6N_2O_2$: C, 51.35; H, 2.15; N, 7.49. Found: C, 51.29; H, 1.97; N, 7.51.

For dibenzoyldiazine (**1b**, 73%): mp 117–119 °C (lit.[12] 119.5–121.5 °C).

For bis-(*p*-methoxybenzoyl)diazine (**1c**, 96%): mp 133–134 °C (lit.[11] 132 °C).

Preparation of 1,2-Diazetidines 2a–c. A solution of 4.6 g (50.0 mmol) of quadricyclane and 16.8 mmol of the appropriate diaroyldiazine **1a–c** in 200 mL of acetonitrile was refluxed for the following periods of time: 1.5 h for **1a**, 3 h for **1b**, and 24 h for **1c**. Removal of solvent and excess quadricyclane at reduced pressure afforded crude 1,2-diazetidines **2a–c** in yields in excess of 90%. Recrystallization from carbon tetrachloride afforded analytically pure 1,2-diazetidines in 90, 65, and 60% yields for **2a, 2b,** and **2c,** respectively.

For 3,4-bis[*p*-(trifluoromethyl)benzoyl]-3,4-diazatricyclo-[4.2.1.$0^{2,5}$]non-7-ene (**2a**): mp 220–221 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, 4 H, J = 9 Hz), 7.37 (d, 4 H, J = 9 Hz), 5.95 (broad s, 2 H), 4.42 (s, 2 H), 2.98 (broad s, 2 H), 2.25 (d, 1 H, J = 9 Hz), 1.77 (d, 1 H, J = 9 Hz); ^{19}F NMR ($CDCl_3$) ϕ 36.81 (s); IR (KBr) 1685 cm^{-1} (C=O), no NH. Anal. Calcd for $C_{23}H_{16}F_6N_2O_2$: C, 59.23; H, 3.46; N, 6.01. Found: C, 59.28; H, 3.24; N, 5.90.

For 3,4-dibenzoyl-3,4-diazatricyclo[4.2.1.$0^{2,5}$]non-7-ene (**2b**): mp 211–212 °C; ^{1}H NMR ($CDCl_3$) δ 7.57–8.09 (m, 10 H), 6.10 (broad s, 2 H), 4.49 (s, 2 H), 3.08 (broad s, 2 H), 2.38 (d, 1 H, J = 11 Hz), 1.78 (d, 1 H, J = 11 Hz); IR (KBr) 1680 cm^{-1} (C=O), no NH. Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.01; H, 5.22; N, 8.16.

For 3,4-bis(*p*-methoxybenzoyl)-3,4-diazatricyclo[4.2.1.$0^{2,5}$]non-7-ene (**2c**): mp 190–191 °C; ^{1}H NMR ($CDCl_3$ (δ 7.97 (d, 4 H, J = 9 Hz), 7.05 (d, 4 H, J = 9 Hz), 6.10 (broad s, 2 H), 4.47 (s, 2 H), 3.95 (s, 6 H), 2.38 (d, 1 H, J = 10 Hz), 1.85 (d, 1 H, J = 10 Hz); IR (KBr) 1670 cm^{-1} (C=O), no NH. Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.71. Found: C, 70.52; H, 5.56; N, 7.53.

Kinetic Measurements. Solutions of 0.01 M in **1a–c** and 0.1 M in quadricyclane in acetonitrile or carbon tetrachloride were tightly stoppered in round-bottom flasks and heated at 60 ± 1 °C in a thermostatically controlled water bath. Aliquots were withdrawn at various intervals and immediately quenched at −78 °C. Analyses for unreacted **1a–c** were performed by visible spectroscopy on a Cary-14 ultraviolet–visible spectrometer at the wavelengths shown in Table I. Pseudo-first-order rate constants were determined graphically over at least three half-lives for the disappearance of **1a–c**. Second-order rate constants k (shown in Table I) were determined by dividing the observed pseudo-first-order rate constants by initial quadricyclane concentration and represent the average of at least two runs. First-order rate constants at 60 °C for the unimolecular decomposition of **1a–c** in the absence of quadricyclane account for less than 5% of the observed pseudo-first-order rate constant in the presence of the hydrocarbon.

Acknowledgment. The authors wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Office of Research and Projects at Southern Illinois University at Edwardsville for support of this research.

Registry No.—**1a,** 69780-57-0; **1b,** 959-31-9; **1c,** 38192-16-4; **2a,** 69780-58-1; **2b,** 69780-59-2; **2c,** 69780-60-5; **3a,** 69780-61-6; **3b,** 787-84-8; **3c,** 849-82-1; *p*-(trifluoromethyl)benzoyl chloride, 329-15-7; benzoyl chloride, 98-88-4; *p*-methoxybenzoyl chloride, 100-07-2; hydrazine, 302-01-2; quadricyclane, 278-06-8.

References and Notes

(1) See, for example, (a) P. G. Gassman and K. Mansfield, *Chem. Commun.*, 391 (1965); (b) *J. Am. Chem. Soc.*, **90,** 1517, 1524 (1968); (c) R. Noyori, T. Suzuki, Y. Kumagai, and H. Takaya, *ibid.*, **93,** 5896 (1971); (d) N. A. Porter and D. W. Gilmore, *ibid.*, **99,** 3503 (1977).
(2) See, for example, (a) A. Cairncross and E. P. Blanchard, *J. Am. Chem. Soc.*, **88,** 496 (1966); (b) R. Noyori, T. Suzuki, Y. Kumagai, and H. Takaya, *ibid.*, **93,** 5894 (1971); (c) P. G. Gassman and T. Nakai, *ibid.*, **93,** 5897 (1971); (d) E. Lee-Ruff and G. Just, *Can. J. Chem.*, **46,** 1887 (1968); (e) M. Pomerantz, R. N. Wilke, G. W. Gruber, and U. Roy, *J. Am. Chem. Soc.*, **94,** 2752 (1972).
(3) See, for example, (a) C. D. Smith, *J. Am. Chem. Soc.*, **88,** 4273 (1966); (b) I. Tabushi, K. Yamamura, and Z. Yashida, *ibid.*, **94,** 1787 (1972); (c) D. M. Lemal, *ibid.*, **91,** 5688 (1969); (d) H. Prinzbach and J. Rivier, *Angew. Chem., Int. Ed. Engl.*, **6,** 1069 (1967); (e) H. Prinzbach, *Pure Appl. Chem.*, **16,** 17 (1968); (f) G. Kaupp and H. Prinzbach, *Chem. Ber.*, **104,** 182 (1971).
(4) I. Tabushi and K. Yamamura, *Tetrahedron*, **31,** 1827 (1975).
(5) (a) M. J. S. Dewar and E. Haselbach, *J. Am. Chem. Soc.*, **92,** 590 (1970); (b) N. Bodor, M. J. S. Dewar, A. Harget, and E. Haselbach, *ibid.*, **92,** 3854 (1970).
(6) (a) H.-D. Martin, C. Heller, E. Haselbach, and Z. Lanyjova, *Helv. Chim. Acta*, **57,** 465 (1974); (b) E. Haselbach and H.-D. Martin, *ibid.*, **57,** 472 (1974).
(7) See, for example, (a) P. Laszlo and P. Von R. Schleyer, *J. Am. Chem. Soc.*, **86,** 1171 (1964); (b) E. I. Snyder and B. Franzua, *ibid.*, **86,** 11166 (1964); (c) W. D. Kumler, J. N. Shoolery, and F. Brutcher, Jr., *ibid.*, **83,** 1657 (1961).
(8) Determination of the stereospecificity in 1,2-diazetidine products **2** is impossible since rapid consecutive nitrogen inversions equilibrate all possible cis and trans diasteriomers.[9]
(9) J. C. Mitchell, M. S. Thesis, Southern Illinois University, Edwardsville, Ill.
(10) H. H. Hatt, "Organic Syntheses", Collect. Vol. 2, A. H. Blatt, Ed., Wiley, New York, 1943, p 208.
(11) L. Horner and W. Naumann, *Justus Liebigs Ann. Chem.*, **587,** 93 (1954).
(12) J. E. Leffler and W. B. Bond, *J. Am. Chem. Soc.*, **78,** 335 (1956).

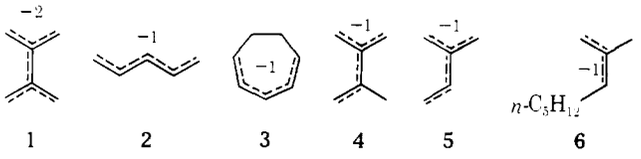
2,3-Dimethylenebutadiene Dianion: Convenient Procedure for Allylic Metalation of Conjugated Dienes

Joseph J. Bahl, Robert B. Bates,* and Bernard Gordon III

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

Received January 22, 1979

While 2,3-dimethylenebutadiene dianion (**1**) has been formally present as a ligand of iron in a complex,[1] efforts to prepare alkali metal salts of it by metalation of 2,3-dimethylbutadiene with base–solvent systems such as *n*-butyllithium–tetramethylethylenediamine have failed due to faster addition to its conjugated diene system. This rapid addition to 1,3-dienes has made the much less accessible 1,4-dienes the usual precursors of pentadienyl carbanions,[2] though 1,3-dienes can be used with KNH_2/NH_3 with its temperature and pressure limitations.[3] We wish to report that Lochmann's base mixture *n*-butyllithium–KO-*t*-Bu[4] metalates 2,3-dimethylbutadiene smoothly to dianion **1** and in addition gives pentadienyl anions **2** and **3** in good yield from the corresponding 1,3-dienes.



1 **2** **3** **4** **5** **6**

After efforts to prepare **1** by dimetalation/ring opening of isopropenylcyclopropane failed,[5] direct dimetalation of 2,3-dimethylbutadiene using Lochmann's base was found to work well. The dianion salt dissolved in tetrahydrofuran (THF) to give a ^{1}H NMR spectrum consisting of a broad singlet at δ 1.05. It reacted with D_2O to give a 73% yield of dideuterio-2,3-dimethylbutadiene and with diethyl sulfate to give a 71% yield of 2,3-dipropyl-1,3-butadiene.

This same metalation procedure gave a quantitative yield of pentadienyl anion (**2**, ^{1}H NMR in THF-d_8,[6] expected products from D_2O quench[2]) from a mixture of (*Z*)- and (*E*)-piperylenes but went to a mixture of di- and trianion[7] from 1,3-cycloheptadiene. Monanion **3**[8] was prepared virtually free of di- and trianion using 1 equiv each of KO-*t*-Bu and *n*-butyllithium and *inverse* addition.

As monoanion **4** is no doubt an intermediate in the above metalation which produces dianion **1**, it was expected that isoprene could be metalated by this system to the elusive 2-vinylallyl anion **5**,[9] isomeric with **2**. However, in this case addition of *n*-butyllithium to give allyl anion **6** predominates (H_2O quench products: 2-methyl-1-octene and 2-methyl-2-octene). The formation of an allyl anion with a primary and a *secondary* charge-bearing carbon in the latter case (primary and *tertiary* in the 2,3-dimethylbutadiene case) presumably tips the balance in favor of addition.

This metalating system can no doubt be used for the

0022-3263/79/1944-2290$01.00/0