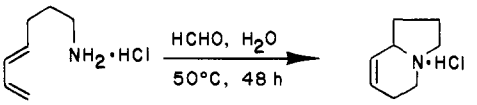
retarded relative to the formaldehyde case (16 h vs. 3 h) and the number of byproducts were significantly increased. Attempts to employ acetone in the aza Diels–Alder reaction led to no reaction whatsoever. Methylamine hydrochloride may be successfully substituted for benzylamine hydrochloride (Table I, entry 6). The yield is lower due only to the greater volatility of the product. Even ammonium chloride may be employed which provides access to the corresponding secondary amines (entries 7 and 8); however, a significant reduction in yield is observed.

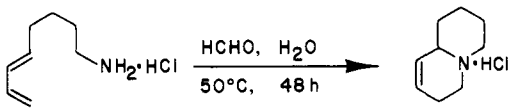
The intramolecular imino variation of the Diels–Alder reaction, like its intermolecular counterpart, has also received only limited attention. The first example of an intramolecular imino Diels–Alder reaction, in which an oximino dienophile was condensed with a highly reactive quinone methide, was reported by Oppolzer.[7] More recently Weinreb has relied on pyrolytically generated *N*-acyl imines as dienophiles.[8] To date no example of an iminium ion participating in an intramolecular Diels–Alder reaction has been recorded. We detail below the first example of such a reaction.

In order to examine the intramolecular iminium ion variation of the Diels–Alder reaction, we prepared substrates **7–9**. Treatment of a 0.2 M solution of (*E*)-4,6-heptadienylamine hydrochloride (**7**)[9a] with 37% aqueous formaldehyde (2.0 equiv) at 50 °C for 48 h gave rise to 95% yield of crystalline dehydro δ-coniciene hydrochloride (**10**).[5b] Similar exposure of **8**[9b] (0.2



7 10

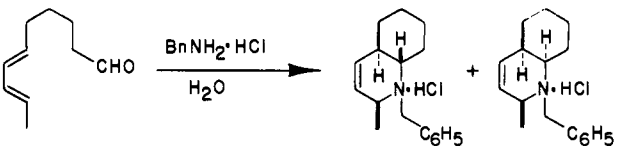
M in H_2O) to aqueous formaldehyde afforded a 65% yield of adduct **11**.[5b] The formation of **10** and **11** via the iminium



8 11

Diels–Alder strategy offers a mild and highly practical alternative to the pyrolytic conditions cited above. Moreover, the methodology should prove generally applicable to the synthesis of a number of alkaloids embodying a bridgehead nitrogen.

In order to expand the scope of this reaction we examined the cyclocondensation of dienyl aldehyde **9**[9c] with benzylamine hydrochloride. Slow addition of **9** over 20 h to a 1.0 M solution of benzylamine hydrochloride (5.0 equiv) in water/ethanol, 1:1, heated at ca. 70 °C provided[5c] a 63% yield (unoptimized) of adducts **12** and **13** in a ratio of 2.5:1. The extension of the



9 12 13

intramolecular reaction to iminium salts derived from aldehydes other than formaldehyde is very encouraging and may prove useful in alkaloid total synthesis.

Work is currently in progress to further expand the scope of the iminium Diels–Alder reaction and to examine its effectiveness in the construction of naturally occurring alkaloids.

Acknowledgment. This investigation was supported in part by a Public Health Service Research Grant (GM 33605) from the National Institute of General Medical Sciences. The 360-MHz NMR instrument (Nicolet) used in the above studies was purchased in part through funds provided by the National Science Foundation (Grant CHE-81-05004).

(5) (a) The reaction is diluted with an equal volume of water and is washed twice with ether. The aqueous phase is made basic with solid potassium hydroxide. The product is isolated by extraction with ether. (b) In cases where the amine hydrochlorides are isolated, the aqueous phase is evaporated to dryness after washing with ether. The product is isolated by extracting the residue with chloroform. (c) The reaction is diluted with an equal volume of water and is washed twice with an equal volume of ether–hexane (1:1). The products are isolated by extraction with chloroform.

(6) For a recent review, see: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876. Also see: Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261.

(7) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1031.

(8) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661 and references cited therein. Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240.

(9) (a) Reduction ($LiAlH_4$, Et_2O) of (*E*)-3,5-hexadienoic acid[10] provided (100%) the corresponding alcohol which was converted (95%) [(a) TsCl, Et_3N, DMAP; (b) NaCN, Me_2SO] into 1-cyano-(*E*)-3,5-hexadiene. Reduction ($LiAlH_4$, Et_2O) and acidification (dry HCl, Et_2O, −44 °C) gave rise to amine hydrochloride **7**. (b) Reduction of 1-cyano-(*E*)-4,6-heptadiene,[11] followed by acidification as in 5a, provided an 82% overall yield of amine hydrochloride **8**. (c) Coupling (THF, Li_2CuCl_4) of the Grignard reagent derived from (4-chlorobutoxy)trimethylsilane with sorbyl acetate and subsequent treatment (reflux) with aqueous ethanol afforded (58% overall) (*E*,*E*)-6,8-decadienol, which upon PCC oxidation provided aldehyde **9**.

(10) Boeckman, R. K., Jr.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1789.

(11) Roush, W. R.; Ko, A. I.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4267.

Total Synthesis of (−)-Paspaline

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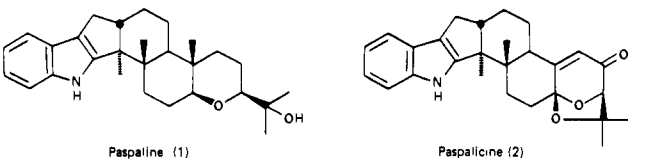
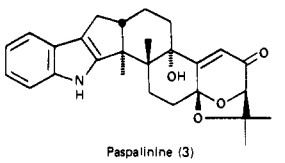
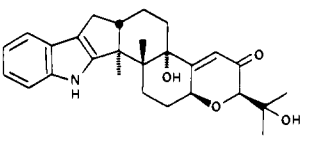
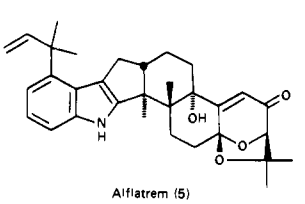
In this paper we disclose the *first* total synthesis of (−)-paspaline (**1**),[2,3] the simplest member of a rapidly growing class of indole

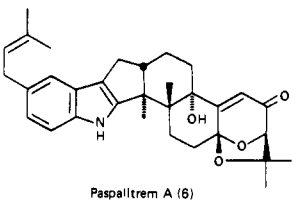

Paspaline (1)

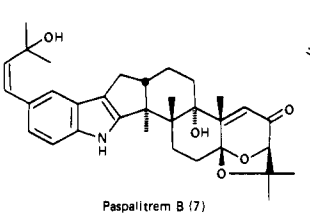
Paspalicine (2)

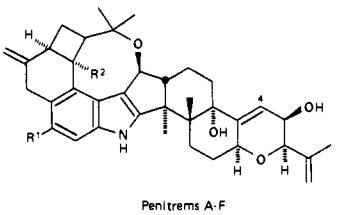

Paspalinine (3)


Paxilline (4)


Atlatrem (5)


Paspalitrem A (6)


Paspalitrem B (7)


Penitrems A-F

(8) A: R^1 = Cl, R^2 = OH; 4α, 4aα-epoxide
(9) B: R^1 = R^2 = H; 4α, 4aα-epoxide
(10) C: R^1 = Cl, R^2 = H
(11) D: R^1 = R^2 = H
(12) E: R^1 = H, R^2 = OH; 4α, 4aα-epoxide
(13) F: R^1 = Cl, R^2 = H; 4α, 4aα-epoxide

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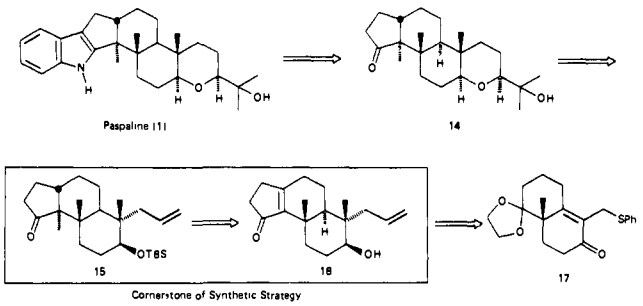
diterpene alkaloids, which now include paspalicine (**2**),[2] paspalinine (**3**),[4] paxilline (**4**),[5] aflatrem (**5**),[6] paspalitrem A and B (**6**, **7**)[4a] and penitrems A–F (**8**–**13**).[7] Paspaline (**1**) was first isolated by Arigoni and co-workers[2] in the mid 1960s from the ergot *Claviceps paspali*. The relative and absolute stereochemistry were deduced via a combination of chemical[2] and X-ray crystallographic[3] techniques.

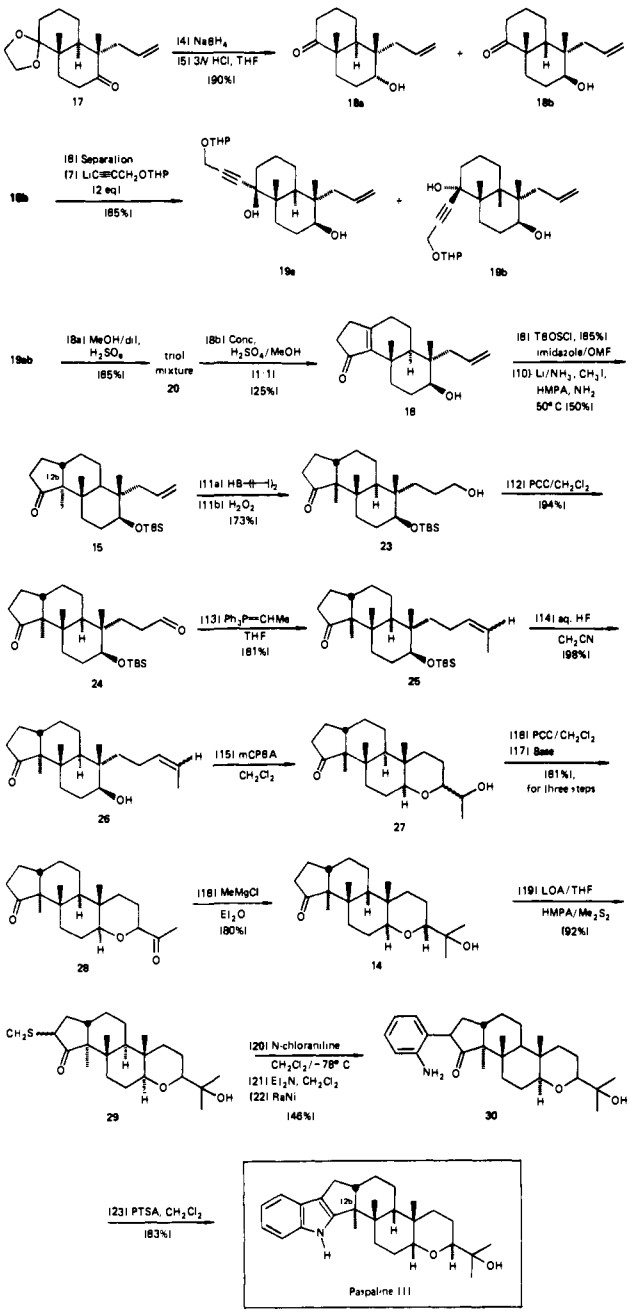
As a class these alkaloids are of interest not only because of their novel architecture but also because they display potent tremorgenic activity,[3,4b,5a,6] the symptoms of which are similar to a number of human disorders.[8] Structurally they are distinct, even remote from the more commonly encountered ergot alkaloids of the lysergic acid and clavine type, as well as from other naturally occurring tremorgenic alkaloids such as fumitremorgen and verruculogen.[9] Despite their novel structural features, no reports directed at the synthesis of members of this class have appeared.

The cornerstone of our synthetic strategy was envisioned to be the reductive alkylation of enone **16** to **15**. Given the precedent



found in the Trost aphidicolin synthesis,[10] such a transformation was anticipated to establish not only the required trans C/D ring fusion but also to introduce the quaternary methyl substituent at C(12b) trans to the vicinal methyl at C(12c), the key architectural features of this class of alkaloids. Elaboration of ring F and the indole system would then afford paspaline (**1**).

Scheme I



Our synthesis (Scheme I) begins with ketone **17**[11] available in high enantiomeric purity from (+)-Wieland–Miescher ketone[12] via an efficient three-step protocol recently introduced by our laboratory.[13] Carbonyl reduction ($NaBH_4$/MeOH, 95%) followed by deketalization (3 N HCl/THF, 95%) afforded a 4:1 mixture of alcohols **18a** and **18b**,[11] readily separable by flash chromatography.[14] Construction of ring C was initiated by reaction of ketone **18b** with the lithium anion derived from the tetrahydropyranyl ether of propargyl alcohol (2.2 equiv, THF, 0 °C, 95%)[15]

(1) (a) Camille and Henry Dreyfus Teacher Scholar, 1978–1983; National Institutes of Health (National Cancer Institute) Career Development Award 1980–1985. (b) Dean's Fellow, University of Pennsylvania, 1983 and 1984.

(2) (a) Fehr, T.; Acklin, W. *Helv. Chim. Acta* **1966**, *49*, 1907. (b) Gysi, R. P. Ph.D. Dissertation, Eidgenossiche Technische Hochschule, Zürich, Switzerland, 1973, No. 4990. (c) Leutwiler, A. Dissertation No. 5163, Eidgenossiche Technische Hochschule, Zürich, Switzerland, 1973.

(3) Springer, J. P.; Clardy, J. *Tetrahedron Lett.* **1980**, 231 and references therein.

(4) (a) Cole, R. J.; Dorner, J. W.; Lansden, J. A.; Cox, R. H.; Pape, C.; Cunfer, B.; Nicholson, S. S.; Bedell, D. M. *J. Agric. Food Chem.* **1977**, *25*, 1197. (b) Cole, R. J.; Dorner, J. W.; Springer, J. P.; Cox, R. H. *Ibid.* **1981**, *29*, 293. (c) Gallagher, R. T.; Finer, J.; Clardy, J. *Tetrahedron Lett.* **1980**, *235*.

(5) (a) Cole, R. J.; Kirksey, J. W.; Wells, J. M. *Can. J. Microbiol.* **1974**, *20*, 1159. (b) Springer, J. P.; Clardy, J.; Wells, J. M. *Tetrahedron Lett.* **1975**, 2531.

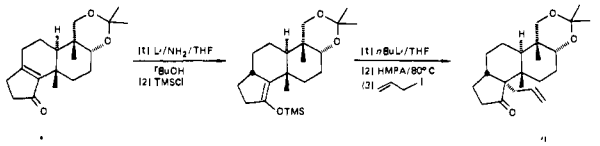
(6) (a) Wilson, B. J.; Wilson, C. H. *Science (Washington, D.C.)* **1964**, *144*, 177. (b) Gallagher, R. T.; Clardy, J.; Wilson, B. J. *Tetrahedron Lett.* **1980**, 239.

(7) (a) De Jesus, A. E.; Steyn, P. S.; Van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Chem. Commun.* **1981**, 289. (b) Wilson, B. J.; Wilson, C. H.; Hayes, A. W. *Nature (London)* **1968**, *220*, 77. (c) Hou, C. T.; Ciegler, A.; Hesseltine, C. W. *Can. J. Microbiol.* **1971**, *17*, 599.

(8) Brimbelcombe, R. W.; Prinder, R. M. "Tremors and Tremorgenic Agents, Scientechnia"; Bristol, UK, 1972; pp 14–15.

(9) Cysewski, S. J. "Mycotoxic Fungi, Mycotoxins, Mycotoxicoses"; Wyllic, T. D., Morehouse, L. G., Eds.; Marcel Dekker: New York, 1977; Vol. I, pp 357–64.

(10) In the Trost aphidicolin synthesis reductive alkylation of i afforded



ii: Trost, B. M.; Nishimura, Y.; Yamamoto, K. *J. Am. Chem. Soc.* **1979**, *101*, 1328.

(11) All new compounds gave 250-MHz ^1H NMR, IR, high-resolution mass spectra, and/or satisfactory C,H combustion analysis in accord with the structure given. All yields recorded are based upon isolated material which was >97% pure.

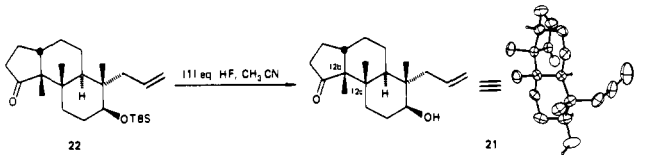
(12) (a) German Offenlegungsschrift (DOS) 21 102 623, priority Jan 21, 1970. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) German Offenlegungsschrift (DOS) 2 014 757, priority March 20, 1970. Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem.* **1971**, *83*, 492; *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (c) Gutzwiller, J.; Buchschacher, P.; Furst, A. *Synthesis* **1977**, 167.

(13) Smith, A. B., III; Mewshaw, R. *J. Org. Chem.* **1984**, *49*, 3685.

(14) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

followed by methanolysis (MeOH, H_2SO_4). Triols **20a,b** (6:1) were then subjected to a 1:1 mixture (v/v) of H_2SO_4(conc)–MeOH (0 °C, 20 min) to afford enone **16** [$[\alpha]^{25}D$ + 46° (*c* 1.6, $CHCl_3$)][11] in modest but useful yield.[16]

With enone **16** in hand, we turned to the reductive alkylation sequence, the cornerstone of our synthetic strategy. Toward this end, enone **16** protected as the *tert*-butyldimethylsilyl ether (TBSCl, imidazole, DMAP, DMF, 95%) was dissolved in THF containing 0.9 equiv of H_2O and added to a lithium–ammonia solution (0.25 M) held at −78 °C.[17] Alkylation of the derived lithium enolate at −78 °C with MeI afforded a single product in 50% yield. To our surprise, single-crystal X-ray analysis of alcohol **21**,[11] derived from **22**[11] by deprotection (aqueous, HF, CH_3CN;



22 21

mp 113.5–114.5 °C), indicated that the crucial reductive alkylation had afforded **22** in which the C(12b), C(12c) vicinal methyl groups were disposed cis, not trans as required for paspaline (**1**). Fortunately for the paspaline synthetic venture, modification of the reductive alkylation process, in particular execution of the alkylation under conditions that more closely resembled those of Trost (i.e., inverse addition of the enolate to a solution of MeI–HMPA held at +50 °C) led in 50% yield to a 2:1 mixture of **22** and **15**,[11] respectively, in addition to a small amount (10–15%) of unalkylated material. All attempts to enhance further the ratio of **15** relative to **22** proved unsuccessful. Separation was achieved via flash chromatography[14] after selective reduction ($NaBH_4$, CH_3OH, O °C) of the unalkylated material.

Our attention next focused on annulation of the pyranyl ring system. First, a two-carbon chain extension led to olefins **26** (*Z*:*E* = 85.15);[11] the overall yield of this four-step sequence was 54%. Ring formation was then accomplished via treatment of **26** with an unbuffered solution of MCPBA in CH_2Cl_2 to afford a mixture of pyranyl alcohols **27**. Without separation the latter were oxidized (PCC, CH_2Cl_2, 4 Å molecular sieves)[18] and equilibrated (K_2CO_3, MeOH) to provide diketones **28a** and **28b** (85:15, respectively)[11] in 81% yield. Recrystallization (hexane–ether) improved this ratio to 95:5. Finally, introduction of the methyl group (MeMgCl, THF) proceeded without event to afford **14** (80%, mp 149–150.5 °C).[11] The chemoselectivity observed here is attributed to the steric encumberance of the cyclopentyl carbonyl group.

With construction of the diterpenoid portion of paspaline complete, there remained only introduction of the indole nucleus. We selected the Gassman procedure.[19] Treatment of **14** with LDA [3 equiv, THF–HMPA (1:1)] followed by addition of dimethyl disulfide (4 equiv) led to 1:1 mixture of thiomethyl ketones (**29a,b**,[11,20] 92%), shown by NMR (250 MHz) to be epimeric only at C(7a). Reaction of the latter with *N*-chloroaniline (aniline, CH_2Cl_2, *tert*-butyl hypochlorite, −78 °C) followed by addition of triethylamine and reduction with Raney Ni (EtOH) resulted in efficient [2,3]-sigmatropic rearrangement, rearomatization, and reductive removal of the thiomethyl substituent to provide **30** [$[\alpha]^{24}_D$ +122° (*c* 0.5, $CHCl_3$)][11] as a single compound (250-MHz NMR). It is interesting to note that **30** and its immediate precursor preferred to exist in the ketoaniline form rather than undergo spontaneous dehydration. Dehydration (PTSA, CH_2Cl_2, Δ), however, proved straightforward to afford (−)-paspaline (**1**) [$[\alpha]^{24}_D$ −42° (*c* 0.6, benzene); natural paspaline $[\alpha]^{24}_D$ −38.5° (*c* 0.47, benzene)][21] in 83% yield. That in fact (−)-paspaline was in hand derived from careful comparison of the physical and spectral properties with those of an authentic sample kindly provided by Professor Arigoni.[22]

In summary, the first total synthesis of (−)-paspaline (**1**) has been achieved. The synthesis proceeded in 23 steps from Wieland–Miescher ketone, afforded (−)-paspaline in high enantiomeric purity, and for the most part was highly stereocontrolled.

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (Institute of Neurology and Commication Disorders and Stroke) through Grant 18254. In addition, we thank Drs. George Furst and Patrick Carroll of the University of Pennsylvania Spectroscopic Facilities for aid in obtaining the high-field NMR and X-ray spectral data, respectively.

(15) (a) Islam, A. M.; Raphael, R. A. *J. Chem. Soc.* **1953**, 2247. (b) Baumann, M.; Hoffman, W.; Muller, N. *Tetrahedron Lett.* **1976**, 3585. (c) Hiyama, T.; Shinoda, M.; Saimoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2747. (d) MacAlpine, G. A.; Raphael, R. A.; Shaw, A.; Taylor, A. W.; Wild, H.-J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 410.

(16) Several minor products were also isolated. Structural identification of these products will be reported in our full account of this work.

(17) For best results, the concentration of the lithium–ammonia solution should be 0.25 M or greater, in order that the radical anion can compete effectively for the limited amount of water.

(18) Herscovici, J.; Egron, M.-J.; Antonakis, K. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1962.

(19) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5495 and references therein.

(20) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

(21) Reference 2a reports a rotation of $[\alpha]_D$ −23° (*c* 0.36, chloroform).

(22) We thank Professor D. Arigoni of the Eidgenossiche Technische Hochschule Zürich, for providing a very generous sample of (−)-paspaline (**1**) as well as for copies of the spectra.

Structure of a Heteropoly Blue. The Four-Electron Reduced β-12-Molybdophosphate Anion

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Received November 26, 1984

Despite wide analytical applications involving "molybdenum blues"[1] and current interest in mixed-valence chemistry,[2] definitive evidence concerning the electronic and molecular structures of heteropoly blues[3] is scarce. Contributions from the Université Pierre et Marie in Paris and from our laboratory have established, via ESR, that one-electron reduced heteropolymolybdates and -tungstates are class II mixed-valence species with weakly trapped (thermally mobile) Mo^{5+} or W^{5+} centers.[4] More highly reduced heteropolyanions are ESR silent and the extent or nature of the delocalization is unclear.[5]

Fruchart and Souchay have shown that reduction of the Keggin-structure anion α-$[PMo_{12}O_{40}]^{3-}$ leads, in aqueous acidic solutions, to stable heteropoly blues derived from an isomeric (β) anion.[6] It has generally been assumed[7] that the β-12-molybdates

(1) See, for example: Murphy, J.; Riley, J. P. *Anal. Chim. Acta* **1962**, *27*, 31.

(2) Brown, D. B., Ed. "Mixed Valence Compounds"; Reidel: Dordrecht, 1980. Day, P. *Int. Rev. Phys. Chem.* **1981**, *1*, 149.

(3) Pope, M. T. "Heteropoly and Isopoly Oxometalates"; Springer-Verlag: New York, 1983; Chapter 6.

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(5) It has, however, been inferred from ^{17}O NMR that the extra electrons in the two-electron blue of $[P_2Mo_{18}O_{62}]^{6-}$ are localized on Mo atoms in the two equatorial belts of the Dawson structure (Kazansky, L. P.; Fedotov, M. A. *J. Chem. Soc., Chem. Commun.* **1980**, 644).

(6) Fruchart, J. M.; Souchay, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1968**, *266*, 1571. This anion (λ_{max} 830 nm; ε ca. 28 000 M^{-1} cm^{-1}) appears to be the complex formed in a widely used "molybdenum blue" spectrophotometric determination of phosphorus.[1]

(7) Thouvenot, R.; Fournier, M.; Franck, R.; Rocchiccioli-Deltcheff, C. *Inorg. Chem.* **1984**, *23*, 598.

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