07657), the University of Wisconsin Graduate School, and the Research Corporation.

Marion H. O'Leary,* Michael D. Kluetz
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

Received September 16, 1971

Bis(1,3,5,7-tetramethylcyclooctatetraene)uranium(IV) and Bis(1,3,5,7-tetramethylcyclooctatetraene)neptunium(IV). Proton Magnetic Resonance Spectrum and the Question of f-Orbital Covalency[1]

Sir:

Our previously published[2] analysis of the observed large upfield shift for bis(cyclooctatetraene)uranium(IV), $(COT)_2U$, uranocene, indicated a large positive net contact shift that suggests some form of covalency; however, in the absence of data relating to the type of ligand MO (σ or π) containing the delocalized spin, no attempt was made to evaluate the possible role of f orbitals in such covalency. Methyl substitution provides a useful technique for characterizing the spin-containing ligand. For spin in π orbitals it is well known that an attached ring proton and methyl proton exhibit contact shifts of comparable magnitude but of opposite sign; for spin in in-plane or σ orbitals, these shifts are of the same sign with the ring-proton shift three–five times larger than the methyl shifts.[3] To apply this approach to the uranocene case we have prepared and characterized bis(1,3,5,7-tetramethylcyclooctatetraene)uranium(IV) and -neptunium(IV), $(TMCOT)_2U$ and $(TMCOT)_2Np$. These compounds were prepared in a similar fashion to the parent compounds,[4,5] using the TMCOT prepared as described by de Mayo and Yip.[6] The TMCOT compounds had similar properties to the COT compounds except for greater solubility in organic solvents. An attempt was made to prepare $(TMCOT)_2Pu$ but Pu(IV) was reduced by $(TMCOT)^{2-}$ to Pu(III).

The proton nmr spectrum of a THF-d_8 solution of $(TMCOT)_2U$ was recorded as a function of temperature on a Varian HA-100 operating in the HR mode with variable-frequency modulation. Two peaks with intensities of 3:1 were observed and can be assigned to the methyl and ring protons, respectively. The observed shifts at room temperature, referenced against $TMCOT^{2-}$, are given in Table I together with that observed for $(COT)_2U$. The ring-proton shifts and their temperature dependences are virtually the same for both complexes.[7] The proton nmr spectrum of a toluene-d_8 solution of $(TMCOT)_2Np$ was recorded at 37°. The corresponding proton peaks of the methyl group (line width ~300 Hz) and ring (line width ~2000 Hz) were much broader than for the U complex. The shifts are listed in Table I.

Table I. Chemical Shifts and Hyperfine Coupling Constants for $(TMCOT)_2U$, $(COT)_2U$ in THF, and (TMCOT)Np in Toluene

	$(TMCOT)_2U$		$(COT)_2U$	$(TMCOT)_2Np$	
	Ring-H	Methyl-H	Ring-H	Ring-H	Methyl-H
Shifts[a]					
Observed	+41.3	+6.0	+42.6	+41.5 ± 2	−9.9
Dipolar	+7.9	+23.6	+7.9	+5.2	+13.2
Contact	+33.4	−17.6	+34.7	+36.3 ± 2	−23.1
A_F[b]	+0.98	−0.52	+1.02	+0.95	−0.61

[a] Shifts in parts per million, referenced against uncomplexed diamagnetic $TMCOT^{2-}$ and COT^{2-}. U data given at 298°K, Np data at 307°K. [b] Hyperfine coupling constants in megahertz; estimated accuracy, ±25%.

The known structure[8] of $(COT)_2U$ and an extrapolated structure based upon ionic radii for $(TMCOT)_2Np$ plus the assumption of a freely rotating methyl group were used to calculate the geometric factors.[9] The calculated dipolar shifts of the various protons were subtracted from the experimental shifts to give the net contact shifts listed in Table I. The hyperfine coupling constants A_F are also given.[10] The derived contact shifts are of opposite sign for the methyl and ring protons and their ratios [−0.5 for (TMCOT)U and −0.6 for (TMCOT)Np] are indicative of systems having considerable π spin density.[11] These results strongly suggest that the spin density in our ligands is primarily in π MO's; indeed, application of the McConnell equation, $A = Q\rho/2S$, with $Q = -63$ MHz, indicates in excess of 0.1 unpaired electron per ligand ring. Although the coupling constants are approximately the same for $U(TMCOT)_2$ and $Np(TMCOT)_2$, the U complex has only two unpaired electrons whereas the Np complex has three and suggests stronger covalency for $U(TMCOT)_2$.[12] The high magnitude of this delocalized spin density compared with that observed in more ionic lanthanide and actinide complexes implies a high degree of covalency and raises the question of f-orbital involvement in such covalency.

Direct delocalization of f electrons into a vacant ligand π MO would give proton shifts of opposite sign to those observed.[2] A more plausible mechanism is charge transfer from filled ligand π MO's to vacant f orbitals; because of exchange interaction the transfer of spin parallel to the spin on the metal ion is energetically more favorable and would leave net posi-

---

[1] This research was supported in part by Grant No. 13369 of the National Science Foundation. Part of this work was performed under the auspices of the U. S. Atomic Energy Commission.

[2] N. Edelstein, G. N. La Mar, F. Mares, and A. Streitwieser, Jr., *Chem. Phys. Lett.*, **8**, 399 (1971).

[3] (a) A. Forman, J. N. Murrell, and L. E. Orgel, *J. Chem. Phys.*, **31**, 1129 (1959); (b) J. A. Happe and R. L. Ward, *ibid.*, **39**, 1211 (1963); (c) however, *cf.* W. D. Horrocks, Jr., and D. L. Johnston, *Inorg. Chem.*, **10**, 1835 (1971); note that the symmetry of the present complexes precludes application of their arguments.

[4] A. Streitwieser, Jr., and U. Muller-Westerhoff, *J. Amer. Chem. Soc.*, **90**, 7364 (1968).

[5] D. G. Karraker, J. A. Stone, E. R. Jones, Jr., and N. Edelstein, *ibid.*, **92**, 4841 (1970).

[6] P. de Mayo and R. W. Yip, *Proc. Chem. Soc.*, 84 (1964).

[7] At $1/T = 0$ the methyl proton shift extrapolates to a nonzero intercept greater than that for the ring-proton shift. At present we have no explanation for this observation.

[8] (a) A. Zalkin and K. N. Raymond, *J. Amer. Chem. Soc.*, **91**, 5667 (1969); (b) A. Avdeef, K. N. Raymond, K. O. Hodgson, and A. Zalkin, *Inorg. Chem.*, in press; use of the refined structure of $U(COT)_2$ greatly reduces the geometric uncertainty in the calculation of the dipolar shifts. For this reason the numbers given in Table I differ from those given in ref 2.

[9] The geometric factors of the ring H and methyl H for $(TMCOT)_2U$ are -0.0020×10^{24} cm^{-3} and -0.0059×10^{24} cm^{-3}, respectively; for the ring H and methyl H of $(TMCOT)_2Np$ the factors are -0.0024×10^{24} cm^{-3} and -0.0061×10^{24} cm^{-3}, respectively. Small variations of the $C-CH_3$ distances have little effect on the results.

[10] Similar assumptions as discussed in ref 2 were used to calculate the $(TMCOT)_2Np$ coupling constants.

[11] D. R. Eaton and W. D. Phillips, *Advan. Magn. Resonance*, **1**, 103 (1965).

[12] G. N. La Mar, *Inorg. Chem.*, **10**, 2633 (1971).

tive spin density on the ligand as observed.[13] Donation of ligand electrons into empty 7s, 7p, or 6d orbitals will also produce the correct sign but is less likely because of their relatively high energies. Exchange polarization of filled metal orbitals will also give the correct sign but the magnitudes calculated and observed for other lanthanide and actinide compounds[14] appear to be much smaller than observed in the present COT complexes. This interpretation is consistent with the Mössbauer isomer shift in $(COT)_2Np$[5] and does not disagree with the simple MO formulation presented earlier.[4,15] We hope that a more detailed model will result from further experimental and theoretical studies in progress.

Acknowledgment. We thank R. G. Hayes for helpful discussions and advice.

[13] J. Owen and J. H. M. Thornley, *Rep. Progr. Phys.*, **29**, 675 (1966).

[14] R. E. Watson and A. J. Freeman, *Phys. Rev. Lett.*, **6**, 277 (1961); J. M. Baker and W. B. J. Blake, *Phys. Lett. A*, **31**, 61 (1970); W. Kolbe and N. Edelstein, *Phys. Rev. B*, **4**, 2869 (1971); M. T. Eastman, H. G. Hecht, and W. B. Lewis, *J. Chem. Phys.*, **54**, 4141 (1971).

[15] The one-electron MO description in ref 4 should be regarded as one of the several configurations because of the mixing of f orbitals resulting from spin-orbit coupling.

[16] Address correspondence to this author at: Department of Chemistry, University of California, Davis, California 95616.

A. Streitwieser, Jr.,* D. Dempf, G. N. La Mar*[16]
Department of Chemistry, University of California
Berkeley, California 94720

D. G. Karraker*
E. I. du Pont de Nemours and Company
Savannah River Laboratory
Aiken, South Carolina 29801

N. Edelstein*
Lawrence Berkeley Laboratory, University of California
Berkeley, California 94720

Received June 1, 1971

The Structure of Saxitoxin[1]

Sir:

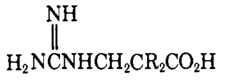
Saxitoxin, the powerful neurotoxin produced by the dinoflagellate *G. catenella*, has been degraded to a pyrimido[2,1-*b*]purine containing nine of the ten carbons and six of the seven nitrogens of the original toxin. Establishment of structure **1** for this key degradation product,[2] together with additional data now to be presented, allows us to formulate a complete structure for saxitoxin.

Determination of the molecular formula of saxitoxin has been difficult because of its noncrystalline, highly polar, nonvolatile nature.[3] Characterization of the pure toxin as the dihydrochloride, $C_{10}H_{17}N_7O_4 \cdot 2HCl$, has been reported;[4] however, we found that combustion analyses of saxitoxin, dried to constant weight at 110° (10^{-5} mm) (with no loss of biological activity) were consistent with $C_{10}H_{15}N_7O_3 \cdot 2HCl$. That 1 mol of water of solvation reconciles the difference in the two formulas was indicated by exchange with $H_2{}^{18}O$. Upon dissolution of saxitoxin in $H_2{}^{18}O$ followed by drying at room temperature, ^{18}O analysis[5] showed that one (98%) of the four oxygens was ^{18}O. Subjecting this sample to the more vigorous drying conditions left the molecule containing three oxygens and no ^{18}O. Also, since Dumas and Kjeldahl nitrogen determinations were identical, the toxin contains no N–N or N–O bonds.

Oxidation of saxitoxin with 15% hydrogen peroxide at pH 4.6 yielded guanidine (0.8 mol), the pyrimidopurine **1** (0.15 mol), and 3-guanidinopropionic acid (**2**) (0.3 mol). Formation of 140 mol % of guanidine residues under these oxidizing conditions established the presence of two guanidine residues in the toxin and confirmed the absence of any N–N bonding.

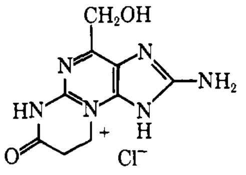
Isotopic labeling was used to investigate the origin of the propionyl residue of **2**. Two methylene hydrogens (δ 2.37, m)[6] of saxitoxin underwent slow, reversible isotopic exchange in water at room temperature. When deuterium-exchanged toxin (no signal at 2.37) was oxidized using protium reagents as above, 3-guanidinopropionic-*2-d*$_2$ acid (**2a**) (δ 3.66, s) was obtained. Oxidation of nonexchanged saxitoxin with D_2O_2[7] generated **2** containing no deuterium. Thus, the propionyl moiety of **2** maintains its integrity throughout the oxidation of saxitoxin and must be present as such and bonded to the same guanidino group in the toxin.

Further structurally definitive conclusions follow from the exchangeability of the α-CH_2 protons in the propionyl residue. Model compounds of the type $H_2NC(=NH)NHCH_2CH_2COR$ (R = aryl, alkyl) also showed exchange of the α-CH_2 protons in D_2O. However, the corresponding acids, esters, amides, and guanidides [R = OH, alkoxyl, NH_2, $NHC(=NH)NH_2$] failed to undergo H–D exchange even at elevated temperatures. The presence of a 2-guanidinoethyl alkyl ketone in saxitoxin thus is assured. The keto group accounts for the ir absorption in saxitoxin at 5.7 μ which disappeared upon reduction (H_2, PtO_2, or $NaBH_4$) to dihydrosaxitoxin. In dihydrosaxitoxin the methylene hydrogens were no longer exchangeable, and the Baeyer–Villiger type peroxide degradation (see below) did not occur.

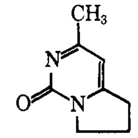


$H_2N\overset{\overset{NH}{\|}}{C}NHCH_2CR_2CO_2H$

2, R = H
a, R = D



1



3

[1] Supported in part by the U.S. Army Research Office, Durham, N. C.

[2] J. L. Wong, M. S. Brown, K. Matsumoto, R. Oesterlin, and H. Rapoport, *J. Amer. Chem. Soc.*, **93**, 4633 (1971).

[3] These properties precluded the use of mass spectrometry and X-ray crystallography. Also, suitable derivatives (salts or acyl, alkyl, or silyl derivatives) with properties amenable to these physical methods could not be prepared despite herculean efforts.

[4] E. J. Schantz, J. M. Lynch, G. Vayvada, K. Matsumoto, and H. Rapoport, *Biochemistry*, **5**, 1191 (1966).

[5] C. D. Snyder and H. Rapoport, *ibid.*, 7, 2318 (1968).

[6] Nmr spectra were taken in D_2O using sodium trimethylpropanesulfonate as internal standard (δ 0) at 100 and 220 HMz.

[7] Procedure of P. Askenasy and R. Rose, *Z. Anorg. Allg. Chem.*, **189**, 27 (1930), using deuterium oxide.