mixed and 1-2 μL of the resultant clean light yellow to dark red-brown liquid was subjected to GC analysis.

Acknowledgment. We thank W. B. Studabaker and D. Moynihan for their technical assistance, Dr. R. Jasinski and Prof. M. Baizer for many helpful discussions, and Occidental Research for releasing this work for publication.

Registry No. *m*-phenoxytoluene, 3586-14-9; ceric trifluoroacetate, 70236-93-0.

Dynamic Nuclear Magnetic Resonance and Empirical Force Field Studies of Podophyllotoxin

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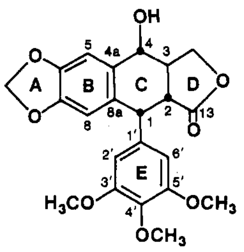
Proton dynamic nuclear magnetic resonance (DNMR) spectra (250 MHz) of the biologically active podophyllotoxin (1) at low temperatures reveal long sought evidence for hindered rotation of the pendant E ring. Under conditions of slow E-ring rotation on the NMR time scale at 137 K, the 2′- and 6′-protons of the E ring show two different NMR singlets of equal area separated by a substantial chemical shift difference ($\Delta\delta = 1.08$ ppm). Simulation of the DNMR spectrum at 156 K gives a barrier ($\Delta G^{\ddagger}$) to E-ring rotation of 7.0 ± 0.2 kcal/mol. The NMR data suggest that in the stable conformation of 1, the E ring is essentially perpendicular to the rigid framework of the remainder of the molecule. Empirical force field calculations presented here are in qualitative agreement with the NMR data. Decoalescence of the 3′- and 5′-methoxyl proton resonances is also assigned to restricted E-ring rotation, but it is apparent that another lower barrier rate process (i.e., rotation about the phenyl–oxygen bonds of the E ring) contributes to additional broadening of the DNMR spectra especially at the lower temperatures employed in this study.

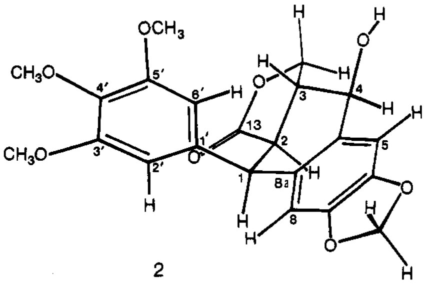
Podophyllotoxin (1) and most of the other members of the podophyllotoxin family are constituted as lignans of the 1-phenyltetralin variety. Although the chemistry, stereochemistry, syntheses, and diverse biological activities of these compounds have been extensively investigated,[1-3] an apparent discrepancy between the ^{1}H nuclear magnetic resonance (NMR) spectrum observed at room temperature and the expected spectrum has persisted. Specifically, an examination of models suggests convincingly that the 2′- and 6′-protons of the E ring should be fixed at diastereotopic locations. However, at room temperature, the ^{1}H NMR signal for these two hydrogens consists of *one* sharp two-proton singlet. This paper addresses the apparent discrepancy.



1

Podophyllotoxin

A scaled molecular model built with space-filling atoms (Courtauld) shows that fused rings A–B–C–D of podophyllotoxin (1) form a strained, rigid framework which, on the average, is coplanar with the B ring. The rigidity of the A–B–C–D fused rings system of 1 is also evident from an examination of Dreiding models. In constructing the Courtauld model, it is especially difficult to attach the E ring of 1 to the tetralin 1-position, and once attached, the E ring is forced into a conformation in which it is essentially perpendicular to the average plane of the fused rings A–B–C–D. Structure 2 is a perspective of this geometry of podophyllotoxin viewed with ring A closest and ring D farthest from the eye. According to the Courtauld model, the E ring has no torsional freedom; rotation about the 1–1′ bond appears to be severely restricted.



2

This preferred geometry (2) places the two aromatic protons of the E ring at different molecular and magnetic environments, i.e., the inner or endo position ($H_{6'}$ of 2) and

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[1] For example, two semisynthetic derivatives, prepared by Sandoz, Ltd. (Basel), and designated as VP-16-213 (4′-demethylepipodophyllotoxin ethylidene-β-D-glucoside) and VM-26 (4′-demethylepipodophyllotoxin thenylidene-β-D-glucoside), are currently in use as clinical anticancer agents.

[2] Gensler, W. J.; Gatsonis, C. D. *J. Org. Chem.* **1966**, *31*, 4004. Also cf.: Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 7082.

[3] See the reviews by: Jardine, I. In "Medicinal Chemistry Monographs", Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; Vol. 16, Chapter 9, p 319. Ayres, D. C. *Chem. Lignans* **1978**, 123; *Chem. Abstr.* **1980**, *93*, 220493. Hartwell, J. L.; Schrecker, A. W. *Fortschr. Chem. Org. Naturst.* **1958**, *15*, 83. We are indebted to Professor Ayres for providing a copy of his review.

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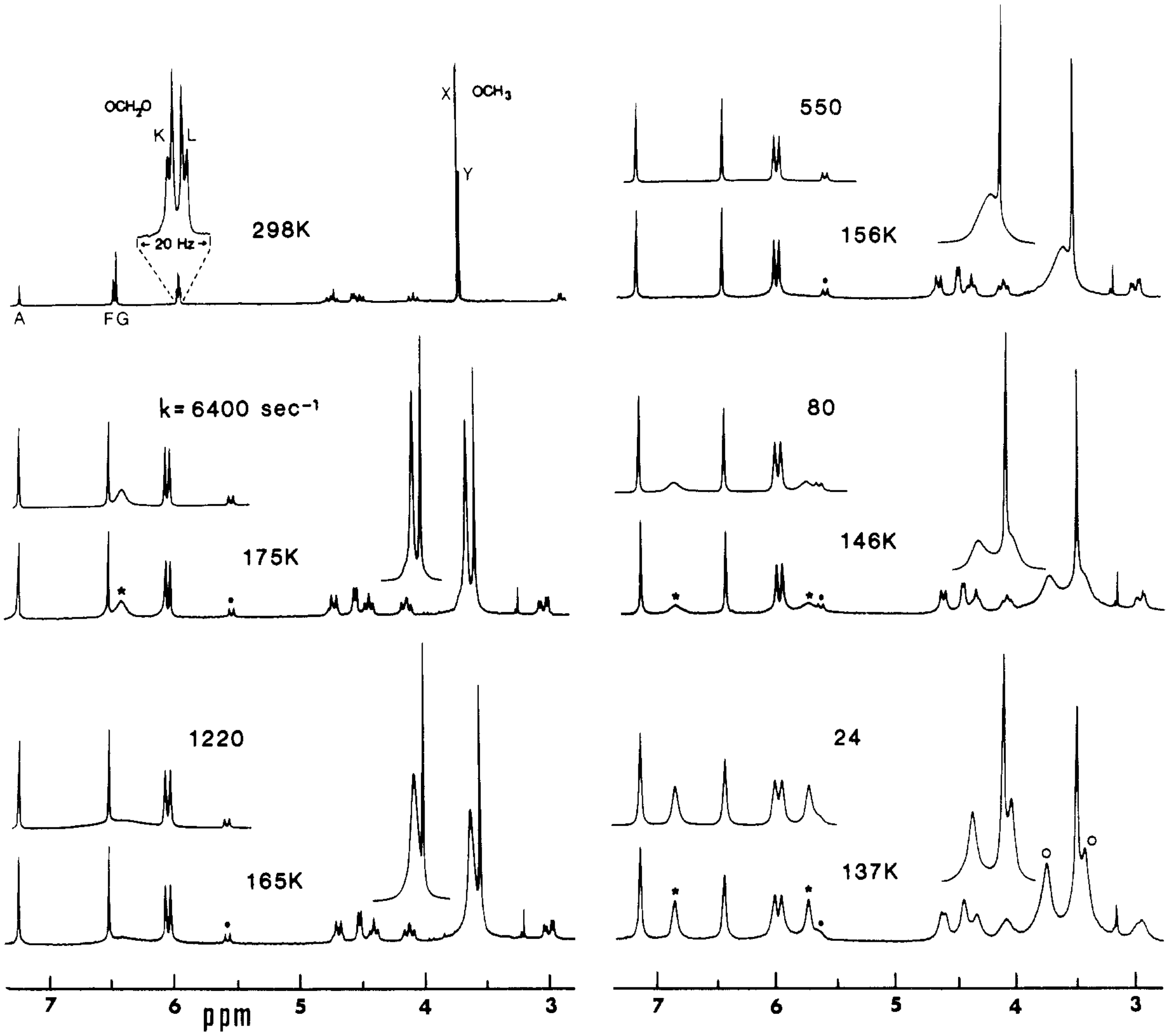

Figure 1. Experimental ^1H DNMR spectra (250 MHz) of podophyllotoxin (1; 0.008 M in 25% acetone-d_6/75% CF_2Cl_2, v/v). Theoretical DNMR simulations for the 2′ and 6′ aromatic protons are presented above each spectrum and for the 3′- and 5′-methoxyl protons above and to the left of each spectrum. *k* is the first-order rate constant for E-ring rotation about the 1–1′ bond. The solid black circle marks the position of the 4′-hydroxyl proton. The asterisks indicate the positions of the 2′ and 6′ aromatic protons. The positions of the decoalesced 3′- and 5′-methoxyl protons are marked with circles at 137 K.

the outer or exo position ($H_{2'}$ of 2). If rotation about the 1–1′ bond does not occur, it is reasonable to expect that $H_{6'}$ and $H_{2'}$ would give rise to *two signals* in the ^1H NMR spectrum at quite different chemical shifts (vide infra). ^1H NMR chemical shift assignments at room temperature have been made for 1 in chloroform previously, and it is apparent that $H_{6'}$ and $H_{2'}$ combine to give a *two-proton singlet* (δ 6.37) at room temperature.[4] This suggests that despite evidence to the contrary from a consideration of models (vide supra), the endo and exo aromatic protons of the E ring are interchanging positions via rotation about the 1–1′ bond at a rate which is fast on the ^1H NMR time scale at room temperature. A dynamic NMR (DNMR) study of 1 reported here corroborates this hypothesis of rapid E-ring rotation at room temperature.

Results and Discussion

The NMR chemical shifts of a number of protons in 1 which give signals in the chemical shift ranges relevant to our DNMR study have been assigned previously.[4] In the present work, examination of the ^1H NMR spectrum (250 MHz; Figure 1) of 1 (0.008 M in 25% acetone-d_6/75% difluorodichloromethane, v/v) at 298 K shows that the two protons on the B ring (H_5 and H_8) give two singlets at δ_A 7.18 and δ_F 6.45, $H_{2'}$ and $H_{6'}$ give a two-proton singlet at δ_G 6.42, and the methylene protons of the A ring give a closely spaced, coupled, two-spin system (δ_K 5.94, δ_L 5.93, $^2J_{KL}$ = 1.08 Hz). The methoxyl protons of the E ring give two singlets at δ_X 3.69 (6 H) and δ_Y 3.67 (3 H). These peaks are labeled with the appropriate letters on the 298 K spectrum of Figure 1. The doublet (δ 5.50, $^3J_{HH}$ = 9.0 Hz) marked with a solid black circle in the 175 K spectrum in Figure 1 is very likely the 4′-hydroxyl proton resonance which shifts to lower field as the temperature is lowered. Upon lowering the temperature, a DNMR decoalescence occurs for both the $H_{2'}$ and $H_{6'}$ aromatic protons and the 3′- and 5′-methoxyl protons resonances (Figure 1). The $H_{2',6'}$ singlet resonance observed at 298 K broadens at lower temperatures (e.g., see asterisked peak in 175 K spectrum), essentially disappears into the base line at 156 K, emerges as two peaks at 146 K (see asterisks), and is sharpened at 137 K into two broad singlets of equal area at δ 5.78 and 6.86. Below 137 K, both short T_2 values (i.e., very broad lines) and kinetic broadening from another rate process (vide infra) become pronounced, and no new meaningful information is obtained. This DNMR behavior is consistent with slowing rotation about the 1–1′ bond and the

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[4] We are using the values published by: Brewer, C. F.; Loike, J. D.; Horwitz, S. B.; Sternlicht, H.; Gensler, W. J. *J. Med. Chem.* **1979**, *22*, 215. These were obtained from an analysis of the ^1H NMR spectrum of 1 at 360 MHz.

direct observation at 137 K of signals for the diastereotopic exo and endo aromatic protons of the E ring (see 2). Splitting of these two broad singlets at δ 5.78 and 6.86 due to spin–spin coupling ($^4J_{HH}$) between $H_{2'}$ and $H_{6'}$ is not observed at 137 K. However, simulation of the DNMR behavior for the $H_{2'}$ and $H_{6'}$ resonances in the region of intermediate to severe exchange broadening was done by using an AX to XA exchange model with an assumed but typical $^4J_{AX}$ value of 1.5 Hz. All simulations were done with signals for the H_5, H_8, methylenedioxy, and hydroxyl protons superimposed.[5] Theoretical simulations are presented above each experimental spectrum in Figure 1. The rate constant *k* in Figure 1 is the first-order rate constant for interchange between the exo and endo protons of the E ring, i.e., the rate of E-ring rotation. From a DNMR line-shape simulation of the spectrum at 156 K, the free energy of activation ($\Delta G^{\ddagger}$) for E-ring rotation is 7.0 ± 0.2 kcal/mol. At room temperature (i.e., 298 K), the rate constant for E ring rotation is approximately 10^8 s^{-1}. Clearly, E-ring rotation about the 1–1′ bond is not nearly as restricted as might be concluded from an examination of the Courtauld model.

Inspection of structure 2 indicates that the 3′-methoxyl and 5′-methoxyl groups are also diastereotopic and under conditions of slow E-ring rotation about the 1–1′ bond should give rise to two different ^{1}H NMR signals. This is true even if rotation about the phenyl-oxygen bonds of the E ring is still very rapid. In addition, under conditions of rapid rotation about phenyl–oxygen bonds, symmetry considerations reveal that the 4′-methoxyl protons will not be subject to a DNMR effect due to slowing E-ring rotation. Indeed, the large six-proton methoxyl singlet observed at δ 3.69 at 298 K decoalesces at lower temperatures and is sharpened into two broad singlets (δ 3.83, 3.52) at 137 K consistent with slowing rotation about the 1–1′ bond (see circles on 137 K spectrum in Figure 1). The three-proton 4′-methoxyl singlet undergoes no DNMR effect (Figure 1).

Theoretical DNMR simulations are presented above and to the left of the methoxyl resonances in Figure 1, and the $\Delta G^{\ddagger}$ for rotation is 7.1 ± 0.4 kcal/mol at 156 K. This DNMR behavior is, of course, also consistent with slowing E-ring rotation and corroborates our interpretation of the DNMR spectra for the $H_{2'}$ and $H_{6'}$ signals.

In the course of simulating the DNMR spectra for the methoxyl protons at progressively lower temperatures, we observed that the effective rates derived from a two-site-exchange simulation of the methoxyl protons resonances begin to deviate (i.e., become faster) from the rates calculated from the $H_{2'}$ and $H_{6'}$ signals. In addition, at progressively lower temperatures, the Eyring plot of rates derived from the 3′- and 5′-methoxyl protons signals deviated more and more from linearity. This, of course, suggests that *another* rate process is contributing to a differential broadening of the methoxyl signals at very low temperatures, and it is apparent that this rate process has a less significant effect on the shape of the aromatic protons resonances. The only other dynamic process available to 1 which might contribute to a DNMR effect at these temperatures is rotation about the phenyl–oxygen bonds of the E-ring.

Indeed, examination of the ^{1}H DNMR spectra of 1,2,3-trimethoxybenzene at temperatures below 150 K reveals a significant differential broadening of the 1- and 3-methoxyl protons signal whereas the 2-methoxyl protons singlet remains as sharp as the tetramethylsilane reference singlet down to 95 K. This observation apparently contradicts earlier physical and theoretical evidence that 1,2,3-trimethoxybenzene prefers C_s symmetry.[6] Although we have not yet reached temperatures low enough to observe decoalescence, we are addressing this problem and will report the details of our findings later.

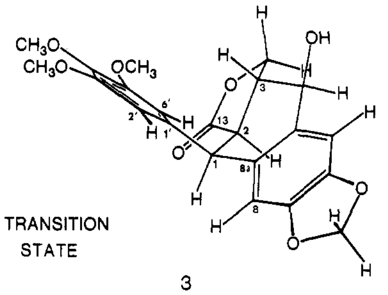
Table I. Calculations of the ^{1}H NMR Chemical Shift Difference between the 2′ and 6′ Protons for Five Conformations of the E Ring

dihedral angles, deg		approx conformational stability	^{1}H chemical shift difference,[a] $\Delta\delta_{2',6'}$, ppm
1-2-1′-2′	1-8a-1′-2′		
90 ($H_{2'}$exo)	150	stable	1.20[b]
90 ($H_{2'}$exo)	146	stable	0.95[c]
105 ($H_{2'}$exo)[d]	135	unstable	0.7[b]
120 ($H_{2'}$exo)[d]	125	unstable	0.35[b]
174[d]	60	transition state for E-ring rotation (see 3)	0.21[c]

[a] The experimental chemical shift difference from the ^{1}H NMR spectrum at 137 K is 1.08 ppm. [b] From coordinates measured from Dreiding models. [c] Calculated from coordinates for the MM2-optimized geometry (see Table II). [d] $H_{6'}$ tilted toward the lactone ring D.

Due to the apparent superposition of two rate processes on the DNMR spectra of 1 and the lack of a slow-exchange spectrum for methoxyl rotation, we hesitate to compute $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for E-ring rotation. However, the $\Delta G^{\ddagger}$ value calculated above should be reasonably accurate.

Early in this investigation, we were concerned with the possibility that, by coincidence, the magnetic environments at the exo and endo $H_{2'}$ and $H_{6'}$ locations in 2 might be the same, so that whether or not the E ring rotates, the signals for the two aromatic hydrogens would fortuitously appear as a two-proton singlet. Accordingly, estimates were made of the chemical shift difference between the $H_{2'}$ and $H_{6'}$ protons with the E ring in five conformations, four close to the preferred conformation (e.g., 2) and one in which the E ring is rotated approximately 90° about the 1–1′ bond, i.e., the presumed transition state for E-ring rotation (see 3). Table I gives pertinent dihedral angles for each geometry and the estimated chemical shift difference (Δδ) between $H_{2'}$ and $H_{6'}$ for the five trial geometries.



3

In calculating these chemical shift values, the contribution of the anisotropy of the lactone carbonyl group was dismissed as negligible. We reached this conclusion both because $H_{2'}$ and $H_{6'}$ were found in most cases to fall on, or close to, the nodal conical surface demarcating the carbonyl shielding and deshielding zones and also because

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(5) The DNMR line-shape simulation program used is a substantially revised version of DNMR3 written by: Kleier, D. A.; Binsch, G. "Quantum Chemistry Program Exchange"; Indiana University: Bloomington, IN; Program 165. Our local revisions are described in: Bushweller, C. H.; Bhat, G.; Letendre, L. J.; Brunelle, J. A.; Bilofsky, H. S.; Ruben, H.; Templeton, D. H.; Zalkin, A. *J. Am. Chem. Soc.* **1975**, *97*, 65.

(6) Anderson, G. M.; Killman, P. A.; Domelsmith, L. N.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 2344 and references within.

Table II. Molecular Mechanics (MM2) Results

geometry of E ring	dihedral angles, deg		internuclear distances,[a] Å		rel energy kcal/mol
	1-8a-1′-2′	1-2-1′-2′	nuclei	distance	
perpendicular (see 2)	146	90	$H_{2'},O_{13}$	2.65	0.0
			$H_{2'},H_1$	2.37	
			$H_{6'},O_{13}$	4.97	
			$H_{6'},H_8$	3.98	
			$H_{6'},H_3$	2.33	
			$H_{6'},C_{13}$	4.34	
transition state for E-ring rotation (see 3)	60	174	$H_{2'},O_{13}$	5.06	5.7
			$H_{2'},H_1$	2.67	
			$H_{6'},O_{13}$	2.82	
			$H_{6'},H_8$	2.06	
			$H_{6'},H_3$	4.83	
			$H_{6'},C_{13}$	2.42	

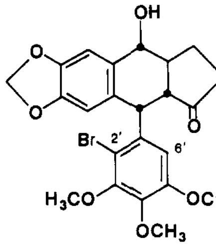
[a] See 2 for position numbering.

both protons are removed by two to three bond lengths from the carbonyl group.[7] We further assumed that significant differences in chemical shifts at the two positions would originate predominantly from the anisotropic ring current effects of the B ring. To find the differences in chemical shift between $H_{2'}$ and $H_{6'}$ for these various conformations, we relied on tabulations which give values for shielding (or deshielding) of protons as a function of location in space in the neighborhood of the benzene ring.[8]

Using these three-dimensional shielding curves in conjunction with distance and angle measurements from molecular mechanics calculations (vide infra) and from measurements made from Dreiding models, we found good agreement with the observed chemical shift difference ($\Delta\delta$) of 1.08 ppm between $H_{2'}$ and $H_{6'}$ (vide supra) and $\Delta\delta$ values calculated for those conformations having geometries close to 2 (Table I). $H_{2'}$ of 2 is in a region where the anisotropy of ring B is deshielding; however, $H_{6'}$ of 2 is in a shielding region of ring B. Thus, in the spectrum of 1 at 137 K, the resonance at δ 6.86 may be assigned to $H_{2'}$, and the resonance at δ 5.78 may be assigned to $H_{6'}$. Clearly, the chemical shift values for these protons are a sensitive and presumably accurate probe of the local molecular topology.

In order to corroborate predictions of preferred geometry in podophyllotoxin derived from a consideration of molecular models and from the NMR data, we also performed empirical force field calculations using Allinger's MM2 force field.[9] The optimized MM2 geometry found to be most stable is indeed the one in which the plane of the E ring lies nearly perpendicular to the rest of the molecule (i.e., as in 2). Table II presents salient structural parameters derived from the MM2 calculations for this geometry.[10] In this geometry, strain energy is at a minimum. An MM2 computation of the barrier to E-ring rotation using the dihedral angle driver method[9] also revealed conformation 3 to be the transition state for rotation, and 3 is computed to be 5.7 kcal/mol higher in energy than 2. This MM2 barrier is in reasonable agreement with the DNMR-deduced barrier of 7.0 ± 0.2 kcal/mol. It is interesting to note that the $\Delta\delta_{2',6'}$ value computed from the MM2 optimized geometry (0.95 ppm; Table I) is in good agreement with the experimental value (1.08 ppm).

Two compounds structurally related to podophyllotoxin, 2′-bromopodophyllotoxin (4)[11] and 5′-demethoxy-4-deoxy-5-methoxypodophyllotoxin (5),[12] have been examined crystallographically. In the bromo derivative 4, two conformations are found in the unit cell, both with the bromine in exo positions (e.g., see $H_{2'}$ of 2). The respective 1–8a–1′–2′ dihedral angles for the two conformations are 129° and 138°; i.e., the E ring is almost perpendicular to the fused A–B–C–D rings in both conformations. In 5, the E ring is also essentially at a right angle to the C ring (88.8°), and $H_{2'}$ is in an exo position (e.g., see 2). These observations are consistent with the preferred conformation of podophyllotoxin derived from NMR chemical shift differences and MM2 calculations (vide supra). The consistently stable geometry in these systems is the one in which the E ring is essentially perpendicular to the mean plane of the other rings.



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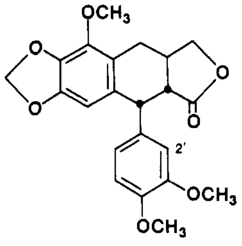

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Thus, this work settles the apparent discrepancy between the room-temperature ^1H NMR spectrum and the obvious preferred geometry of podophyllotoxin by revealing restricted, albeit rapid, E-ring rotation. It is apparent that even carefully constructed space-filling molecular models can lead to erroneous conclusions about the degree of steric crowding and inhibition of internal molecular motion. It is also now apparent that structural data for podophyllotoxin and its analogues obtained from NMR spectroscopy, X-ray crystallography, empirical force field calculations, and a consideration of models are all in substantial agreement.

Experimental Section

The 250-MHz ^1H DNMR spectra were recorded on a Bruker WM250 pulsed Fourier transform NMR spectrometer by using

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(7) See the discussion in: Jackman, L. M. "Applications of Nuclear Magnetic Resonance in Organic Chemistry"; Macmillan: New York, 1959; pp 122–125.

(8) Johnson, C. E.; Bovey, F. A. *J. Chem. Phys.* **1958**, *29*, 1012. Bovey, F. A. "Nuclear Magnetic Resonance Spectroscopy"; Academic Press: New York, 1969; p 264. We are indebted to Dr. Bovey for his kindness in supplying a supplementary table.

(9) Allinger, N. L.; Yuh, Y. J. "Quantum Chemistry Program Exchange"; Indiana University: Bloomington, IN, 1980; Program No. 395. The stretching parameters for the phenyl carbon atoms were added at run time in the manner described in the MM1 documentation (QCPE Program No. 318). For a recent review of empirical force field calculations, see: Osawa, E.; Musso, H. *Top. Stereochem.* **1982**, *13*, 117.

(10) Several topologies were tried for the 3′-, 4′-, and 5′-methyl groups in these calculations. In general, the energy differences calculated between the ground-state (2) and transition-state geometry (3) of 1 were not sensitive to the conformation of the methoxyl groups.

(11) Petcher, T. J.; Weber, H. B.; Kuhn, M.; von Wartburg, A. J. *J. Chem. Soc., Perkin Trans. 2* **1973**, 288.

(12) Bates, R. B.; Wood, J. B., III. *J. Org. Chem.* **1972**, *37*, 562.

the Bruker BVT-1000 variable-temperature control unit. Temperature measurements are accurate to ±2 K. All NMR samples were prepared in precision NMR tubes on a vacuum line and degassed three times, and the NMR tubes were sealed.

Acknowledgment. C.H.B. is grateful to the National Science Foundation for support (Grants No. CHE78-21161, CHE79-26243, and CHE80-24931). We also acknowledge National Science Foundation Grant No. CHE79-16210 from the Chemistry Division in support of the Northeast Regional NSF-NMR Facility at Yale University. We appreciate the assistance of the University of Vermont Academic Computing Center staff in providing outstanding computational support. We are indebted to A. von Wartburg of Sandoz, Ltd., for a generous gift of podophyllotoxin and to Mervyn V. Leeding, ICIANZ, Victoria, Australia, for some preliminary estimates of ring current effects on chemical shift.

Registry No. 1, 518-28-5; 4, 40456-15-3; 5, 32970-80-2.

Some Aspects of Nitration of Aromatics by Lower Oxidation States of Nitrogen

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Nitration of benzene and toluene in trifluoroacetic acid (TFA) solution with sodium nitrite (N(III)) and nitrogen dioxide (N(IV)) occurs relatively slowly to produce mononitroarenes and oxidized byproducts. The yield of nitroarene improves as the ratio of nitrogen reagent to substrate increases over the stoichiometric requirement and can be good (greater than 90%) if the ratio is sufficiently high. Nitric oxide is the principal reduction product accompanying the conversion of N(III) or N(IV) to the N(V) state found in the nitroarene product. Evidence is presented against the intermediacy of nitrosoarenes, and the oxidation of nitrosobenzene with nitrogen dioxide in methylene chloride solution is found to produce a mixture of benzenediazonium nitrate and nitrobenzene. Palladium acetate and thallium trioxide have no detectable beneficial effect upon the rate of nitration or the yield of nitration by nitrogen dioxide in TFA. Wilkinson's catalyst does not effect reaction of nitrogen dioxide with benzene or toluene without solvent as reported.

Aromatic nitration is usually accomplished with nitric acid or some other form of nitrogen in oxidation state (V), and no redox change accompanies the formation of the resulting nitroaromatic product. However, the chemical literature is replete with fragmentary reports of the use of reagents containing nitrogen in lower oxidation state to form nitroaromatics. Although redox processes must accompany such reactions, little attention has been focused on the reduction products and the mechanisms by which they and the nitroarenes are formed. The efficiency of any procedure using lower oxidation states is directly related to the possibility of recycling the reduction product(s). When reduction products are nitrogen in oxidation states II or III, oxidation with air or oxygen is a feasible means of recycle. On the other hand, formation of still lower states of nitrogen, such as nitrous oxide or nitrogen, or substrate reduction products would make a process inefficient and unattractive unless other features were sufficiently attractive to offset the penalty of lost materials. Attention here is primarily upon the reactions of N(III) and N(IV) in acidic media.

Early reports of nitration with nitrogen dioxide have been summarized.[1] Coombes has reported that low concentrations of nitrogen dioxide in carbontetrachloride convert toluene slowly to nitrotoluenes with a high (44%) proportion of meta isomer while at higher concentrations a more normal isomer mix is obtained.[2] Diphenyl ether in 10.4 M perchloric acid was converted by a 100-fold excess of nitrous acid to 2,4-dinitrophenol, and *p*-nitrosophenol was converted to the same product under comparable conditions in the hands of of Challis, Higgins, and Lawson.[3] Spitzer and Stewart[4] found that benzene and toluene were converted in low yields (3% and 2%, respectively) to mononitro compounds by sodium nitrite in trifluoroacetic acid (TFA) in 4 h. Uemura, Toshimitsu, and Okano obtained considerably better results in the same system.[5] Norman, Parr and Thomas[8] also observed benzene nitration in TFA by sodium nitrite but found that passing nitrogen dioxide through the solution was more efficient. Moore and Lapp nitrated the methanesulfonamide of *o*-phenoxyaniline in 60% yield with sodium nitrite in TFA,[6] and Crivello observed in a related process that trifluoroacetic anhydride in chloroform caused the formation of nitrobenzene from benzene and sodium nitrite.[7]

Nitration by way of nitroso intermediates is a commonly accepted mechanism for highly activated aromatics, but nitrosation of unactivated aromatics such as benzene and toluene has received relatively little attention. Challis, Higgins, and Lawson[3] and Challis and Higgins[9] have measured the rates of nitrosation of benzene, toluene,

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[1] Conner, A. Z.; DeVry, F. E.; Plunguian, M.; Spurlin, H. M.; Wagner, R. B.; Wright, C. M. "Nitrogen Textroxide"; Hercules Incorporated, 1968; pp 28–31.

[2] Coombes, R. G. "Industrial and Laboratory Nitrations"; Albright, L. F., Hanson, C., Eds.; American Chemical Society: Washington, DC, 1976; p 81.

[3] Challis, B. C.; Higgins, R. J.; Lawson, A. J. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1831.

[4] Spitzer, U. A.; Stewart, R. *J. Org. Chem.* **1974**, *39*, 3936.

[5] Uemura, S.; Toshimitsu, A.; Okano, M. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1076.

[6] Moore, G. G. I.; Lapp, L. R. U.S. Patent 3 856 859, 1974; *Chem. Abstr.* **1975**, *82*, 170368m.

[7] Crivello, J. *J. Org. Chem.* **1981**, *46*, 3056.

[8] Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1974**, 369.

[9] Challis, B. C.; Higgins, R. J. *J. Chem. Soc. Perkin Trans. 2* **1975**, 1498.

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