

manner to the rearrangements of allylic diazenes described by Baldwin.¹⁰

The reaction is highly sensitive to the stereochemistry of the diene. Thus, *trans*-piperylene reacts exothermically with the *p*-nitrophenyldiazonium salt to give the corresponding 1,6-dihydropyridazine in 73% yield after 1 hr, whereas the *cis* isomer did not react even after 6 hr. This observation is difficult to rationalize on the basis of the aziridinium ion mechanism but is expected in a concerted 2 + 4 process.

The reactions of diazonium salts with dienes are conveniently carried out using the stable hexafluorophosphate salts of the diazonium ions in acetonitrile. Aqueous solutions of other diazonium salts, however, also appear to work well as evidenced by the reaction of *p*-nitrophenyldiazonium chloride with *trans*-piperylene above (Table I). A typical procedure is as follows.

p-Nitrophenyldiazonium hexafluorophosphate,¹¹ 4.42 g, was dissolved in 35 ml of acetonitrile. 2,3-Dimethyl-1,3-butadiene, 2.46 g, was added in 10 ml of acetonitrile at room temperature and a mildly exothermic reaction ensued. After 30 min the mixture was cooled to 0° and the product was collected on a filter. This gave 2.7 g of yellow needles (79%). The product was recrystallized from acetonitrile at -30°; mp 178-180° dec; NMR (CD₂Cl₂) δ 1.80 (s, 6 H), 4.18 (bs, 2 H), 6.79 (s, 1 H), ca. 7.60 (AB q, 4 H).

The reactions in which the pyridazinium salts were isolated required a modified procedure. *p*-Fluorophenyldiazonium hexafluorophosphate, 5.36 g, was dissolved in 50 ml of acetonitrile and 2,3-dimethyl-1,3-butadiene, 1.64 g, was added. After 90 min the reaction mixture was stirred with saturated sodium acetate solution and filtered and the acetonitrile layer separated and dried. Evaporation left 5.0 g of residue which was triturated with ether (chloroform works well in some cases) giving 4.3 g of crude product. The product was recrystallized from acetonitrile-ether, mp 221-223° dec. Anal. Calcd: C, 41.39; H, 3.47, N, 8.05. Found: C, 41.88; H, 3.63; N, 8.03.

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A Very Simple Quantum Mechanical Model of the Directed Covalent Bond

Sir:

Chemists use a variety of models¹⁻⁹ to predict bond angles and geometries in molecules. In attempting to correlate these models with one another and with quantum theory, it might be useful to search out the simplest quantum mechanical model which can predict a bond angle, given some specific number of valence electrons, bonding and nonbonding, about a central atom in a molecule. A very simple model is here presented, and the results are compared with established trends.

The wave function for *N* electron pair is a complicated function of 6*N* variables, three for each electron, plus spins. If, however, electron-electron repulsions are neglected, this problem is exactly separable into one three-coordinate problem per electron, and one need only find the orbitals in three-dimensional space, doubly occupy those of lowest energy, and sum the resulting electron energies to get a total energy for the system. If, in addition, we confine our attention to the plane in which the bond lies, and to one typical radius in that plane, we can hold two of the usual three spherical polar coordinates constant and study a function of only one angular variable per electron. If the potential energy is not dependent on ϕ , for this problem (an electron on a circle) the Schrodinger equation has the familiar solutions:¹⁰

$$\begin{aligned} \psi_0 &= 1/\sqrt{2\pi}; & u_0^0 &= 0 \\ \psi_{c,k}(\phi) &= \cos(k\phi)/\sqrt{\pi} & u_{c,k}^0 &= k^2 u_1^0; \quad k = 1, 2, 3, \dots \\ \psi_{s,k}(\phi) &= \sin(k\phi)/\sqrt{\pi} \end{aligned} \quad (1)$$

If, however, the central atom is bonded to two or more neighbors, the bond directions correspond to regions of lowered potential energy, in which these oscillating functions will have enhanced second derivatives. A computationally tractable limit is that in which this sharp curvature is concentrated at the bond direction. This corresponds to a δ function in the potential energy, i.e., the limit of a very narrow potential well the product of whose depth and width is a constant λ . The resultant functions have a discontinuous first derivative at each bond, but elsewhere are made up of sinusoidal segments analogous to equations 1. For two bonds at angles $\phi = \alpha$ and $-\alpha$,

$$\begin{aligned} \psi_0(\phi) &= \begin{cases} N \cosh ak\phi & 0 < \phi < \alpha \\ N' \cosh ak(\pi-\phi) & \alpha < \phi < \pi \end{cases} \\ &= \psi_0(-\phi); & u_0 &= -a^2 u_1^0 \\ \psi_{s,k}(\phi) &= \begin{cases} N \sin ak\phi & 0 < \phi < \alpha \\ N' \sin ak(\pi-\phi) & \alpha < \phi < \pi \end{cases} \\ &= -\psi_{s,k}(-\phi); & u_{s,k} &= a^2 k^2 u_1^0 \\ \psi_{c,k}(\phi) &= \begin{cases} N \cos ak\phi & 0 < \phi < \alpha \\ N' \cos ak(\pi-\phi) & \alpha < \phi < \pi \end{cases} \\ &= \psi_{c,k}(-\phi); & u_{c,k} &= a^2 k^2 u_1^0 \end{aligned} \quad (2)$$

where *a* is in every case less than one. Two conditions at the bonds suffice to define *a* and *N*'/*N* in each case: the wave functions are continuous, and have cusps such that

$$[d\psi/d\phi]_+ - [d\psi/d\phi]_- = -\psi \cdot \lambda/u_1^0 \quad (3)$$

where the subscripts + and - denote derivatives approaching the bond angle from above and below, respectively.

Figure 1 shows the "molecular" energy obtained for $\lambda \cdot u_1^0 = 0.5$ for two-, three-, four-, and five-electron pair, by summing the orbital energies as a function of the bond

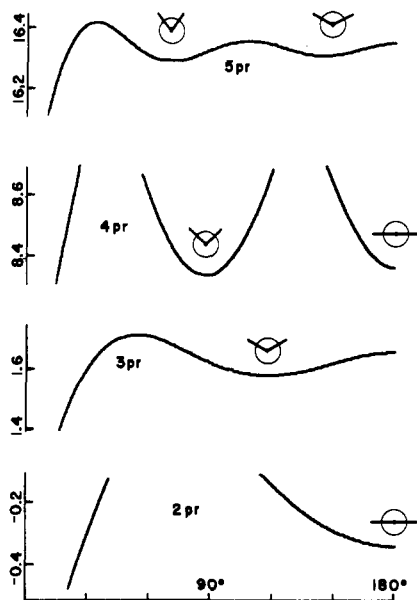


Figure 1. Energy vs. bond angle, for two-, three-, four-, and five-electron pair. The small figure above each minimum illustrates the corresponding predicted bond angle. The unit of energy is w_1^0 (see text).

angle 2α . In each case, minima appear at approximately $360^\circ/N$ and multiples thereof, as would be predicted by a valence-shell-electron-pair-repulsion (VSEPR)¹ model. A second VSEPR prediction, that angles between two bonding pair are smaller than angles involving lone pair, is also borne out. The three-pair bond angle energy minimum is actually at 118° , the smaller four-pair minimum at 88° , and the smaller five-pair minimum at 71° . Further, if the variable λ is taken to represent the electronegativity of the ligand terminating the bond, each of these bond angles becomes smaller as electronegativity is increased. Thus for λ values of 0.5, 1, and 2 respectively, the three-pair bond angle is 118° , 115° , and 109° ; the four-pair bond angle is 88° , 86° , and 82° ; and the five-pair bond angle is 71° , 69° , and 66° . Finally, where two minima are found, as for instance in the five-pair case, the deeper minimum is that in which the bonding pairs are adjacent, with the second occurring at the geometry corresponding to a lone pair between the bonding pair. The position of the latter minimum is, as expected, nearly independent of the value of λ .

The abandonment of electrostatic valence-electron repulsions, and of two of the three spatial coordinates describing each electron, is, of course, the grossest of approximations, and can only be justified by success in mimicking nature as summarized by the VSEPR and similar models. A point worth noting is that the stereoactivity of the lone pair as here reflected arises from the Pauli exclusion principle alone.

The extension of this model to two angular coordinates, and to systems with three or more bonds, should be straightforward in principle.

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Novel Maytansinoids. Naturally Occurring and Synthetic Antileukemic Esters of Maytansinol¹⁻³

Sir:

Maytansine (**1**),⁴ a novel ansa macrolide isolated from several *Maytenus* species,⁴⁻⁶ is an exceptionally interesting antitumor agent. It shows high inhibitory activity against several murine tumors, at the level of micrograms per kilogram body weight and over a wide dosage range.⁷ The compound has undergone extensive preclinical toxicological studies and has recently been selected for clinical trial by the National Cancer Institute. Furthermore, recent biological studies have shown that maytansine is a highly active inhibitor of cell division^{2,8} and of transformation of mouse cell cultures infected with murine sarcoma virus.⁹

We report herein the isolation, structural elucidation, and chemical interrelation of two new maytansinoids, maytanacine (**2**) and maytansinol (**3**), from *Putterlickia verrucosa* Szyszyl. (Celastraceae),¹⁰ the richest reported source of maytansine (**1**) and related antileukemic esters. Maytanacine (**2**), which exhibits potent antileukemic activity,^{11,12} is the first reported maytanside ester which does not bear an amino acid residue at C-3. Maytansinol (**3**), the parent alcohol of the potent maytanside esters, lacks antileukemic activity and shows ca. 1/100,000 the cytotoxicity of maytanacine (**2**).

The alcoholic extract of *P. verrucosa* stems was fractionated by the general procedure outlined earlier,⁴ to yield maytansine (**1**, 12 mg/kg), maytanprine⁵ (**4**, 8.5 mg/kg), and maytanbutine⁵ (**5**, 4.5 mg/kg). Further separations by column and preparative layer chromatography gave maytanacine (**2**, 0.36 mg/kg) $C_{30}H_{39}ClN_2O_9$, mp 234–237°; $[\alpha]^{23}_D -119^\circ$ (c 0.100, $CHCl_3$); uv (EtOH) 233 (ϵ 3.03×10^4), 242 (sh, ϵ 2.8×10^4), 252 (ϵ 2.79×10^4), 281 (ϵ 5.36×10^3), 289 nm (ϵ 5.36×10^3); ir (KBr) 5.70, 5.80, 6.00, 6.34 μ ; and maytansinol¹³ (**3**, 0.025 mg/kg) $C_{28}H_{37}ClN_2O_8$, mp 173–174.5°, $[\alpha]^{23}_D -309^\circ$ (c 0.110, $CHCl_3$); uv (EtOH) 232 (ϵ 3.27×10^4), 244 (sh, ϵ 3.08×10^4), 252 (ϵ 3.16×10^4), 281 (ϵ 5.81×10^3), 288 nm (ϵ 5.70×10^3); ir (KBr) 5.85, 6.06, 6.35 μ .

The mass spectral characteristics of **2** (m/e 545.2180 ($M^+ - H_2O - HNCO$); m/e 485.1969) indicated that it was a maytanside ester similar to **1** except for differences in the R group of the ester side chain. The NMR spectrum of **2** contained an acetate methyl signal at τ 7.82 (3 H, s) and lacked the C(2')H-CH₃ and N-CH₃ signals of the maytansine amino ester side chain.

Maytansinol (**3**) was prepared by $LiAlH_4$ treatment¹⁴ of maytanbutine (**5**) in dry THF at -23° for 3 hr (40% yield). The NMR spectrum ($CDCl_3$) of **3** was identical with that of **1** or **2** except for the lack of the signals due to the ester moiety at C-3. The C-3 proton signal was shifted upfield and obscured by other peaks, and the C-3-OH proton signal appeared as a singlet at τ 6.56. Similar reductive cleavage of maytanacine (**2**) also gave maytansinol (**3**) and treat-