of the nitroxide functionalities; the residual spectrum is shown in Figure 1E, and displays approximately the same line shape as Figure 1B at lower signal to noise. In this case the reaction took ~2 h to completion. When nickel ions in solution were added to this partially reduced material, the resultant EPR spectrum had a line shape similar to that of Figure 1D, again with reduced signal to noise ratio. Finally, addition of ferrous ions to **5** resulted in complete reduction of all spin labels.

The results of using divalent metal ions as both relaxing and reducing agents are consistent with the presence of the spin labels in **2** in more than one distinct site on the cellulose surface, as previously postulated. It would seem that, despite their similarity, ferrous and nickelous ions "select" nonequivalent populations of labels, the former a population of mobility similar to the average and the latter a population of mobility rather greater than average. The latter result, however, should be viewed with caution since the "residual" signal may still be partially broadened. Whether this difference simply reflects differences in the spatial and distance dependence of electron transfer (reduction) vs. electron exchange, or something about the cellulose surface, is not clear. The observation that a negligible proportion of the spins in **2** is accessible to ferricyanide ions suggests that most of the labels are present in pores that are small relative to the size of this ion. The fact that all nitroxides present in **5** are accessible to all of the reagents used in the study provides an additional pointer to the pore diameters involved, and further experiments will allow their quantitation.

The effective diameter of a pore may also be reduced by a surface layer of hydrogen-bonded water. It seems likely that participation of these cellulose surface water molecules in the first hydration sphere of $Ni(H_2O)_6^{2+}$ and $Fe(H_2O)_6^{2+}$, and even binding of these ions to cellulose hydroxyls or groups introduced during labeling, occurs during their penetration into the cellulose matrix. This cannot occur with the ferricyanide ion. A binding phenomenon of this kind may best explain the differences between the effects of metal ions and those of ascorbate and dithionite on **2**;[14] however, size, charge, hydrophilicity and even counterion variation are all important parameters which merit further investigation.

We are also investigating the application of these techniques to the study of soluble and insoluble cellulose derivatives, wood pulp, and native wood. The spectrum of the latter, provided in the form of a 50-μ vertical microtome section of an annual growth ring and labeled by the cyanogen bromide procedure (**6**), is shown in Figure 1F. It can be seen that the effect of lignin and other wood constituents has been to further immobilize the label compared with the purified cellulose shown in Figure 1B. Further decreases in mobility accompany drying of labeled samples and a detailed discussion of these systems will follow.

In conclusion, it is appropriate to remark upon the possible application of these methods to the study of other surfaces. In our hands, the combined use of variable-length "spacer arm" and chemical and physical manipulation of the labeled material has substantially facilitated the interpretation of EPR data, both in cellulose and in other systems.[3a] The enormous current interest in immobilized reagents both of a biological[15] and of a synthetic[16] nature fully justifies the development of techniques for the study of matrices, derivatized matrices, and their interaction in heterogeneous systems with species in solution.

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On the Role of Steric Effects in the Perturbational Molecular Orbital Method of Conformational Analysis[1]

Sir:

The perturbational molecular orbital (PMO) method of conformational analysis[2] proceeds in two stages. In the first stage, a polyatomic system A–B is disconnected conceptually into fragments, e.g., A and B. Then the nodal properties and relative energies of "important" orbitals of these fragments are somehow deduced, and two-orbital two-electron (stabilizing) and two-orbital four-electron (destabilizing) interactions between these "important" orbitals are estimated. When this process is performed for several relative orientations of the fragments (which correspond to different conformations of A–B), the eventual result is a prediction concerning the preferred conformation, and some insight concerning the factors responsible for this preference.

We have recently described[3] a quantitative procedure for the computation of orbital interaction energies, in which the required information concerning the fragment orbitals is generated from the ab initio wave function of the molecule A–B. The π-type orbital interaction energy differences calculated by this procedure parallel rather closely the calculated conformational energy differences. This has permitted a test of some of the usual assumptions of the PMO method. One of these is that the result of the analysis is independent of the fragmentation mode; i.e., in the case of a molecule A–B–C, the same result is expected for each of the choices A···B–C, A–B···C and A···B···C. A second assumption is that the PMO method should fail when "steric effects" become dominant.

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Table I. Quantitative PMO Analysis of Isobutene, *cis*-2-Butene, and *trans*-2-Butene

Geometry	Molecule	Total energy[a] (rel)[b]	Fragmentation mode, $\Sigma\Delta e_{ij}$[c] (rel[b]) A	B
Idealized[d]	Iso	−154.24247 (0.0)	19.86 (0.97)	9.46 (0.0)
	Trans	−154.24164 (0.52)	19.03 (0.14)	10.17 (0.71)
	Cis	−154.22606 (10.30)	18.89 (0.0)	10.06 (0.60)
Exptl[e]	Iso	−154.24368 (0.0)	21.03 (0.83)	10.21 (0.0)
	Trans	−154.23519 (5.33)	20.20 (0.0)	10.97 (0.76)
	Cis	−154.22970 (8.78)	21.02 (0.82)	11.48 (1.27)
STO-4G[f]	Trans	−154.24498 (0.0)	18.65 (0.0)	10.03 (0.0)
	Cis	−154.24195 (1.90)	19.02 (0.37)	10.24 (0.21)

[a] In atomic units. [b] Relative energy with respect to the most stable calculated structure, in kilocalories/mole. [c] This is the sum of the π-type orbital interactions between the fragments, in kilocalories/mole. [d] The idealized geometry is r_{C-C} = 1.534 Å, $r_{C=C}$ = 1.337 Å, r_{C-H} = 1.09 Å; all valence angles associated with the C=C bond are 120°, and all other valence angles are tetrahedral. [e] Iso: L. H. Scharpen and V. W. Laurie, *J. Chem. Phys.*, **39**, 1732 (1963). Cis and trans: A. Almenninger, I. M. Anfinsen, and A. Haaland, *Acta Chem. Scand.*, **24**, 43 (1970). [f] See ref 4 for geometry optimization of the 2-butenes at the STO-4G level. The present data were obtained using these geometries and the STO-3G basis set.

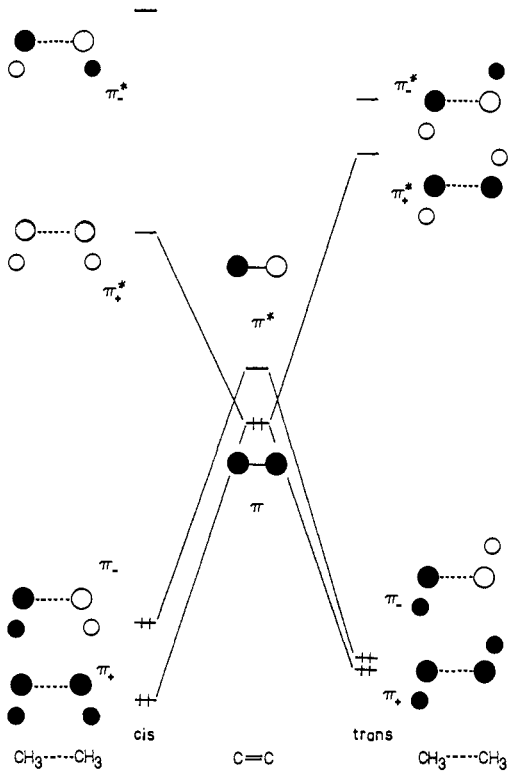

Figure 1. Interaction diagram for the PMO analysis of the 2-butenes by method A. The fragment orbitals and orbital energies have been obtained at the STO-3G level using idealized bond lengths and bond angles, and the ee conformation[4] (each methyl group has one hydrogen eclipsed with the C=C bond).

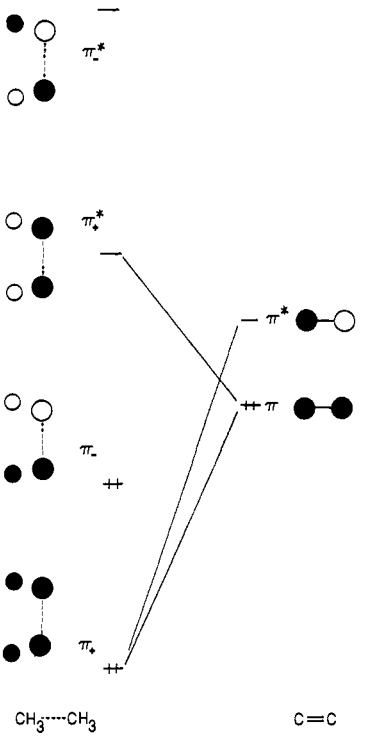

Figure 2. Interaction diagram for the PMO analysis of the ee conformation of isobutene by method A.

For example, a failure of the PMO method to predict that *trans*-2-butene is more stable than *cis*-2-butene has been attributed[4] to "steric effects".

However, since the concept of steric effects is not defined rigorously in molecular orbital calculations, one could, in principle, bring every PMO analysis into perfect agreement with experiment by the simple expedient of invoking the appropriate contribution of such effects. Obviously, this kind of argument weakens the credibility of the method.[5]

The principal objective of this communication is to suggest that "steric effects" may enter naturally into a PMO analysis when the different geometries of the molecules concerned are taken into account. The reason for this is that the different steric effects in isomers such as *cis*- and *trans*-2-butene are already manifested to some extent in the different bond lengths, bond angles, and, especially, the different methyl tilt in the two compounds.

A second objective of this communication is to point out that a particular fragmentation mode can be said to be "acceptable" only if it accounts for the relative stabilities of *all* isomers of a system. In the case of the dimethylethylenes, this requires a consideration of isobutene in addition to the 2-butenes.

Figure 1 is the interaction diagram appropriate to the analysis of the 2-butenes by the fragmentation $CH_3\cdots CH{=}CH\cdots CH_3$ (method A). Figure 2 is the corresponding diagram for isobutene by method A. Figure 3 is the interaction diagram for all three molecules based on the fragmentation $CH_3\cdots CH{=}CH{-}CH_3$ (method B). The fragment orbitals and orbital energy levels shown as solid lines in Figures 1–3 have been obtained by STO-3G computations at *idealized geometries* (C—C = 1.534 Å; C=C = 1.337 Å; ∠CCC = 120°; tetrahedral angles at the methyl groups; methyl groups eclipsed with the carbon–carbon double bond[4]). Figure 1 has precisely the appearance predicted for it by a qualitative analysis of the problem,[4] and, as expected, the calculated π-type orbital interaction energies predict (incorrectly) that the cis isomer is more stable.

Table I summarizes the results of the quantitative PMO

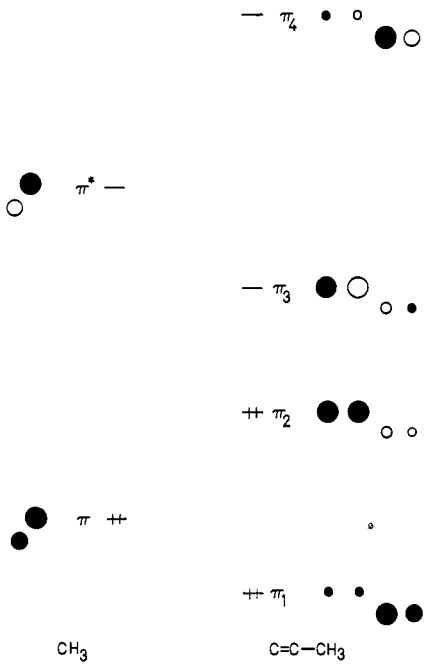

Figure 3. Interaction diagram for the PMO analysis of the ee conformations of the butenes by method B.

analyses. As seen in this table, both method A and method B predict *trans*-2-butene to be less stable than *cis*-2-butene when idealized geometries are employed. However, when the analyses are based upon *optimized* or *experimental* geometries, both fragmentation modes lead to the correct result. In the case of method A, this is found to be due mainly to a difference in the π levels of the two isomers, leading to a larger $\pi_+ - \pi$ destabilizing interaction in the cis isomer; such a result could not have been anticipated by qualitative arguments.

Regardless of the geometry employed, the analysis based on method A predicts isobutene to be less stable than either 2-butene. This is the wrong result.

The three isomers are ordered correctly by method B. This finding demonstrates that the PMO analysis is not independent of the fragmentation mode, and it appears to be general for 1,1- and 1,2-disubstituted alkenes.[6] The reason for the failure in the case of method A can be seen upon inspection of Figures 1 and 2. In isobutene, the appropriate $CH_3 \cdots CH_3$ orbital for interaction with π^* is π_+ but, in the 2-butenes, the orbital which interacts with π^* is π_-. For the PMO analysis to be applicable to a series of compounds, e.g., positional isomers, the fragmentation method employed should lead not only to the same set of fragment orbitals, but also to the same *interactions* in every case. Both method A and method B are appropriate for the examination of *cis*- and *trans*-2-butene since these criteria are met, but only method B is suitable when isobutene is included.

We conclude that the PMO method is applicable to isomeric olefins, without the necessity of introducing steric effects in an ad hoc manner, provided that (1) the different geometries of the different molecules are taken into account and (2) the analysis is based upon a one-bond fragmentation.[7]

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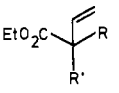
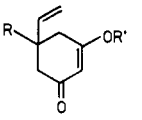
Total Synthesis of (±)-Vernolepin

Sir:

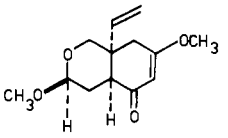
Vernolepin (**29**) and vernomenin (**30**)[1] have been the subject of intense synthetic investigation,[2] recently culminating in the description of two total syntheses leading to the attendant formation of both naturally occurring products.[3] Herein, we describe our own work in this area which results in the exclusive formulation of vernolepin. Our synthesis begins with the preparation of compound **5**, a harbinger of the vernolepin B ring and conjoiner of rings A and C. Elaboration of **5** into the *cis*-2-oxydecalin **10** constitutes the next phase of the synthesis.



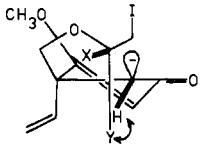
1 R = I; R' = H
2 R = $CH_2C{\equiv}CH$; R' = H
3 R = $CH_2C{\equiv}CH$; R' = CH_2CO_2Et
4 R = CH_2COCH_3; R' = CH_2CO_2Et



5 R = CO_2Et; R' = H
6 R = CO_2Et; R' = CH_3
7 R = CH_2OH; R' = CH_3
8 R = $CH_2OCH(OCH_3)CH_2Br$; R' = CH_3
9 R = $CH_2OCH(OCH_3)CH_2I$; R' = CH_3



10



11 X = H; Y = OCH_3
12 X = OCH_3; Y = H

The presence of a remote chiral center, not present in the natural product, imparts sufficient conformational rigidity to **10** to permit its stereospecific conversion into the expoxide **20.** Regiospecific ring opening of the aforementioned epoxide followed by successive establishment of the C and A lactone rings yields the molecule prevernolepin, **25.**[4]

Preparation of **5** was initiated by kinetic deprotonation of ethyl crotonate, using a mixture of lithium diisopropylamide and hexamethylphosphoramide (LDA/HMPA), to generate the anion **1** which was caused to react with propargyl bromide affording the acetylene **2** (bp 78 °C at 10 mm).[5] Further alkylation of **2,** adjacent to the ester residue, was realized via kinetic deprotonation (LDA/HMPA) followed by treatment with ethyl bromoacetate. The resulting acetylene diester **3** (bp 84–85 °C at 0.29 mm),[6] by mercuric sulfate mediated hydration, gave rise to the methyl ketone **4** (bp 94 °C at 1×10^{-3} mm) which, on reaction with potassium *tert*-butoxide in *tert*-butyl alcohol, was converted into the dione ester **5**[6] (waxy solid, 75% yield from **1**).

Having now established the elements of ring B of vernolepin, we then turned our attention to the manipulation of this material into a suitable precursor of the *cis*-2-oxydecalin **10.**

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