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Molecular Orbital Studies of Antischistosomal Agents

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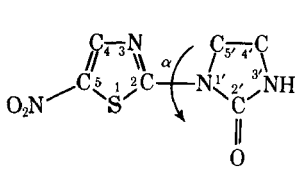
Abstract □ Molecular orbital calculations were used to investigate the antischistosomal agent, niridazole, and an inactive derivative, 1-(5-nitro-2-thiazolyl)-2-ethylurea. The CNDO/2 calculations revealed that the inactive derivative had a preferred conformation stabilized by an intramolecular hydrogen bond. The molecular profile, the relative three-dimensional arrangement of constituent atoms, of the inactive derivative was different than that of the niridazole compound. The likelihood of similar intramolecular interactions rendering niridazole derivatives inactive is discussed. The results of the calculations suggest select structural modifications that might increase the efficacy of niridazole derivatives.

Keyphrases □ Niridazole and derivative—preferred molecular conformations, effect on biological activity □ Molecular orbital calculations—preferred conformations of niridazole and derivative □ Structure–activity relationships—niridazole and derivative, preferred molecular conformations, effect on biological activity □ Antischistosomal agents—niridazole, preferred molecular conformation, effect on biological activity

Recent studies concerning the structure–activity relationships of antischistosomal agents revealed certain essential molecular features necessary for activity insofar as nitroheterocyclic compounds of the niridazole (I) type are concerned. One study (1) showed that the activity of niridazole was dependent upon the presence of the nitro and sulfuryl moieties and that the presence of a nonpolar side chain was necessary. This work was definitive and covered many structural variants.

However, one feature that remains unaccounted for is the inactivity of niridazole derivatives in which the imidazolidinone ring is ruptured at the N-1′–C-5′-position. Thus, 1-(5-nitro-2-thiazolyl)-2-ethylurea (II) possesses no antischistosomal activity. The potential importance of a biologically preferred conformation was noted previously (1) and, because of the increased lability of ureido side chain over the imidazolidinone ring, the conformational differences were studied using the molecular orbital approach.



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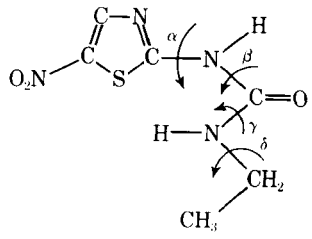
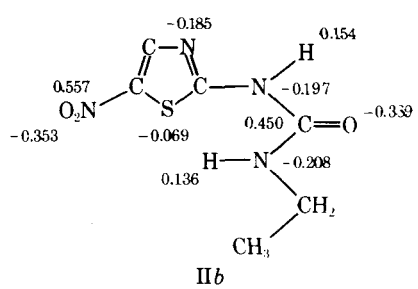


IIa



IIb

EXPERIMENTAL

A series of semiempirical molecular orbital calculations was performed to determine the preferred conformations of the active niridazole compound and its inactive derivative. The Complete Neglect of Differential Overlap (CNDO/2) molecular orbital technique was used for this purpose. The CNDO/2 method assumes that two center overlap integrals are zero, greatly simplifying the Hamiltonian matrix. The success of the method, providing that proper parameterization is used, has been well documented (2–4).

The CNDO/2 method has been used to compute stabilization energies for hydrogen-bonded systems as well as barriers to internal rotation (5, 6). Because of certain limitations concerning the CNDO/2 method, an *ab initio* approach may be preferable. Hydrogen bond energies are usually overestimated while internal barriers to rotation are underestimated. However, with a clear understanding of the method's limitations, one should, in principle, be able to compute potential surfaces in which intramolecular hydrogen bonding plays

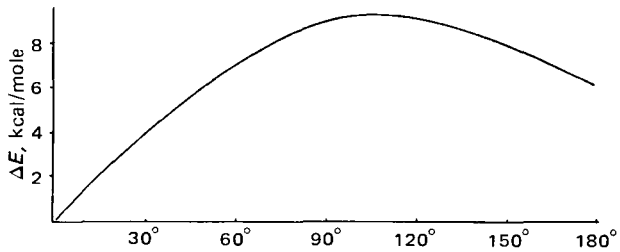


Figure 1—*Potential energy contour for the α-rotomer in niridazole. Energies are plotted relative to the lowest energy conformation, α = 0°.*

Table I—Interatomic Distances in Angstroms

	Niridazole	Niridazole Derivative
O_2N—O	7.27	5.82
O_2N—N	5.50	7.61
S—N	2.63	4.77
S—H	1.70	—

a dominant role. In this study, the pattern of net atom charges is considered concurrently with the preferred conformation because this approach is consistent with the remote recognition hypothesis postulated by Kier (7).

For the calculations, 30° increments were used for generating the potential surfaces for both niridazole and the inactive derivative. The niridazole compound has only one degree of freedom for internal rotation. The inactive derivative has been treated as a three-rotomer problem. The δ-rotomer has been held fixed at 180°. The terminal methyl group assumes a staggered conformation with respect to the C-4′-methylene hydrogens.

DISCUSSION

The potential surface for the niridazole compound is shown in Fig. 1. The preferred conformation of the imidazolidinone ring is *cis* (α = 0°). This conformation is somewhat unexpected but understandable. The dipole–dipole interaction of the carbonyl moiety with the sulfur of the thiazolyl ring is probably stabilizing or at least less destabilizing than the similar interaction with the N-3 atom of the thiazolyl ring.

Critical interatomic separations are shown in Table I for the preferred conformation. Figure 2 illustrates the potential surface for the inactive derivative. The preferred conformation (II*b*) must be stabilized by an intramolecular hydrogen bond between the amide proton and the sulfur. This conformation is, of course, impossible for most antischistosomal compounds of the niridazole family to assume.

The calculated barrier to rotation for niridazole is 8.90 kcal/mole. The barrier to rotation is substantial and implies that a large percentage of the compound should exist in the planar *cis*-conformation. The difference in energy between the preferred conformation of the inactive derivative and the closest secondary minima energetically is 12.6 kcal/mole. The corresponding conformation for the inactive derivative that is comparable to the preferred conformation of the niridazole compound is 7.00 kcal/mole higher in energy. There is a low probability that the open ring inactive derivative could assume the related conformation of the niridazole compound.

These results are consistent with previous findings for other open ring compounds. The calculations imply that the N-3′-methyl derivative should be more active than the derivative shown, since the favorable hydrogen bonding interaction with the thiazolyl ring would be replaced with a repulsive interaction. To date, activity for the N-3′-methyl derivative has not been reported.

SUMMARY

Semiempirical molecular orbital calculations have shown that there are significant conformational differences between the active antischistosomal agent niridazole and the inactive derivative, 1-(5-nitro-2-thiazolyl)-2-ethylurea. The derivative has a folded preferred conformation that causes the critical interatomic distances to differ greatly from those of niridazole. The preferred conformations of these two molecules have been obtained for vacuum free space; consequently, definitive correlations for the molecules in the biological milieu must be drawn carefully. However, the conformational differences are interesting and represent a possible basis for difference in efficacy.

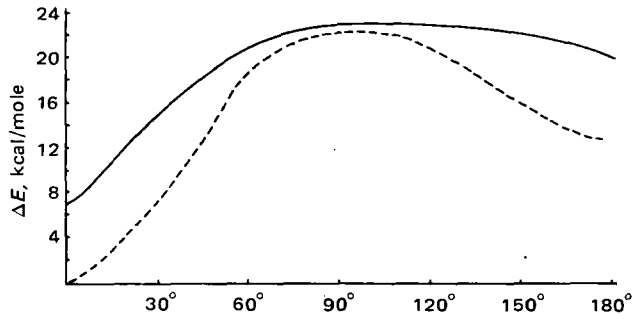


Figure 2—*Potential energy contour for the open ring derivative of niridazole. Dashed line corresponds to the α-rotomer with β = 0° and γ and δ = 180°.*

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