

**THEORETICAL STUDIES OF PSYCHOTROPIC DRUGS.
QUESTIONING THE IMPORTANCE OF FLEX-ANGLE IN DRUG EFFICACY**

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Abstract - MNDO calculations indicate that hetero-substituted 9,10-dihydroanthracenes are inherently planar molecules. Ring puckering is a very low energy process that can arise from intramolecular effects, e.g. peri-and/or transannular interactions as well as from intermolecular interactions like crystal packing forces. It is concluded that the angle of flexure, determined crystallographically and used as a descriptor of drug activity in several important CNS drugs, should be used with caution or not be used at all.

BACKGROUND

Drug molecules with the dibenotricyclic ring structure have been used for the treatment of depression and other central nervous system disorders.¹ More recently they are being used as diuretics.² Typical systems that display antipsychotic effects are represented in Figure 1.

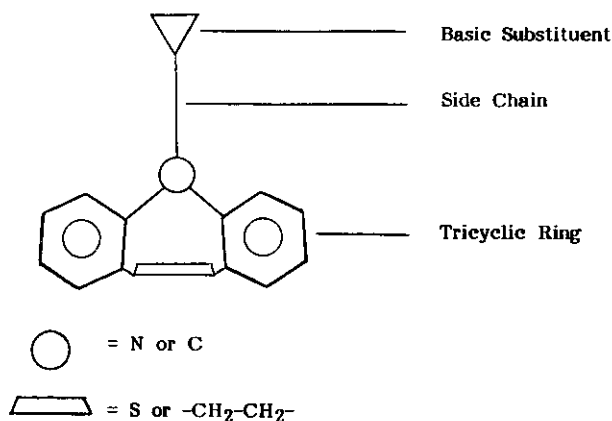


Figure 1: Schematic representation of the structure of tricyclic psycho-active drugs (taken from reference 3).

The rational design of these drugs has an interesting history. It has been suggested by Wilhelm that in the field of psycho-active drugs, drug design had more of a serendipitous progression than in any other branch of pharmaceutical research.³ Although it had been documented that tricyclic psycho-active drugs with a relatively flat topology served as neuroleptics, structurally similar tricyclic systems with an angled or bent topology displayed antidepressant properties.⁴ The rational design of dibenzotricyclic psycho-active drugs began with Wilhelm and Kuhn⁵ who developed structural parameters for the central ring which could be used as stereochemical descriptors for correlation with clinical activity. These so called "steric parameters" are depicted and defined in Figure 2.

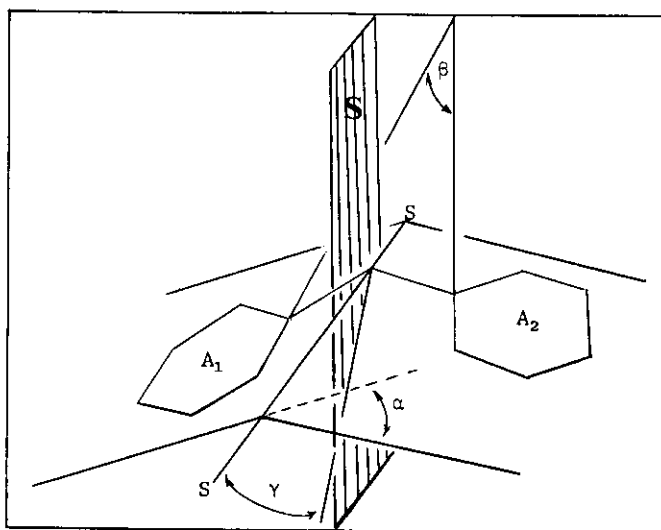


Figure 2: Definitions of Steric Parameters: α = angle of flexure; β = angle of annelation; γ = angle of torsion; A₁, A₂ = aromatics; s-s = axis of flexure; S = plane of symmetry (from ref. 3).

For molecules with similar side chains, base groupings and substituents, it was suggested that flat tricyclic systems ($\alpha = 35^\circ \pm 10^\circ$) exhibit neuroleptic behavior while more puckered systems ($\alpha = 55^\circ$) are more representative of thymoleptic reagents. Indeed, the basic psychotropic behavior of dibenzotricyclic compounds has for many years been assumed to rely predominantly on the pucker of the central ring, and, a large number of crystal structures have been determined with the intent of studying the flex angle, α , as a function of atom type, atom hybridization and substitution on or near the central, benzannelated ring.⁶

The steric parameters α , β and γ , if not available from crystallographic analyses, are traditionally measured with the aid of Dreiding stereo models (see e.g. Figure 4, reference 3). In earlier papers

concerning the conformational analysis of 1,4-dihydrobenzenes, 1,4-dihydronaphthalenes and 9,10-dihydroanthracenes we pointed out that the tendency of these rings to adapt boat forms is grossly overestimated by mechanical models.⁷ Based on mechanical models it had been assumed for many years that the boat-to-boat interconversion of dihydroanthracene and dihydrobenzenes went through a planar, high energy transition state (see Figure 3). Careful spectroscopic and theoretical analysis of dihydrobenzenes, naphthalenes and anthracenes demonstrated that these tricyclic systems do not have double well potentials but rather have flat potential surfaces that allow for low energy, wide-amplitude fluctuations of the central ring.⁷

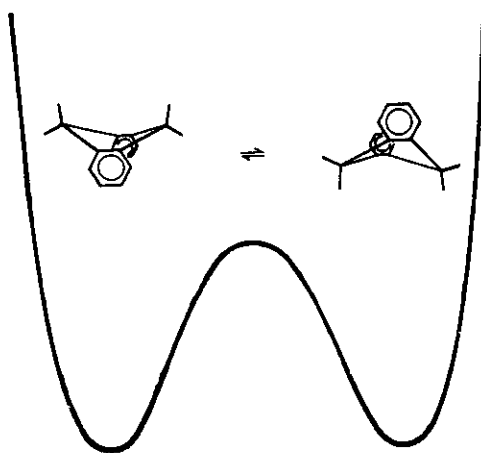
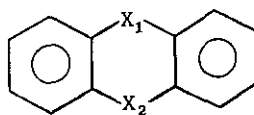
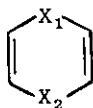


Figure 3: Presumed boat-to-boat interconversion of dihydroanthracene.

Extending this idea from the all carbon tricyclic systems to the 9,10-heterosubstituted dihydroanthracenes suggested to us that the angle of flexure, α , in these drugs is not a determining factor in drug efficacy and that the observed crystallographic flex angles are more a consequence of crystal packing forces than an inherent conformational preference of the drug. To lend credence to this we point out that conformational polymorphism, where two different structures in a unit cell differing only in their flex angle, exist for 12 of the tricyclic ring systems listed in reference 6.

To further explore the topological properties of these important molecules we present here a self-consistent-field molecular orbital conformational analysis of the hetero-substituted dihydrobenzenes and dihydroanthracenes listed below. We omit from these studies the nitrogen containing heterocycles because two molecular orbital analyses of the molecular conformations of 1,4-dihydropyrazines have already appeared.⁸ By choosing the ring puckering mode as a reaction coordinate we can evaluate how torsionally rigid these systems really are and then be able to address how perturbations like intramolecular peri-interactions and intermolecular packing forces may affect the flex angle.



- | | |
|--------------------------|---------------------------|
| 1. $X_1=X_2=CH_2$ | 7. $X_1=X_2=CH_2$ |
| 2. $X_1=X_2=O$ | 8. $X_1=X_2=O$ |
| 3. $X_1=X_2=S$ | 9. $X_1=X_2=S$ |
| 4. $X_1=X_2=SiH_2$ | 10. $X_1=X_2=SiH_2$ |
| 5. $X_1=SiH_2$; $X_2=O$ | 11. $X_1=SiH_2$; $X_2=O$ |
| 6. $X_1=SiH_2$; $X_2=S$ | 12. $X_1=SiH_2$; $X_2=S$ |

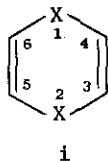
COMPUTATIONAL METHODS

There are two principal approaches to calculating three dimensional structure and other physicochemical properties of molecules; through a self-consistent-field molecular orbital (SCF-MO) analysis or by the use of an empirical force field as employed in molecular mechanics.⁹ During our studies of dihydrobenzenes, dihydronaphthalenes and dihydroanthracenes we used both SCF-MO and molecular mechanics to study ring puckering. Unfortunately molecular mechanics parameters for aryl-conjugated heteroatoms are not yet available so we employ here only the molecular orbital method (molecular mechanics and molecular orbital methods give similar results in the all-carbon rings). Furthermore, because of the size of the systems being studied we restrict ourselves to the semiempirical methods rather than the computationally intense ab initio techniques. More specifically we employ Stewart's MOPAC¹⁰ that has been modified to run on an IBM computer with a CMS operating system. All calculations were done with the MNDO hamiltonian unless specified and C_2 symmetry was maintained throughout the reaction path calculations. All minimum energy structures were computed without symmetry constraints and, unless specified, all internal degrees of freedom were relaxed. Furthermore, all molecules were assumed to be ground-state singlets.

RESULTS AND DISCUSSION

1. Hetero-1,4-dihydrobenzenes

The numbering system of these heterocycles is shown in i below. We define the puckering of the ring by the "improper torsion angle"¹¹ ω_{4125} (This corresponds to the flex angle α). Using this as a reaction coordinate, the ring was distorted in 10° increments from a planar form to a 50° bent form while maintaining two-fold symmetry. The results are shown in Figure 4.



The point to be made is that all these rings, like the parent hydrocarbon, are planar molecules. Furthermore, the shapes of these curves reveal the relative conformational flexibilities of these six membered rings. 1,4-Cyclohexadiene, 1, is the least flexible of the group. The 1,4-disilacyclohexadiene, like its parent hydrocarbon, is also relatively inflexible but is capable of wider amplitude fluctuations than 1.

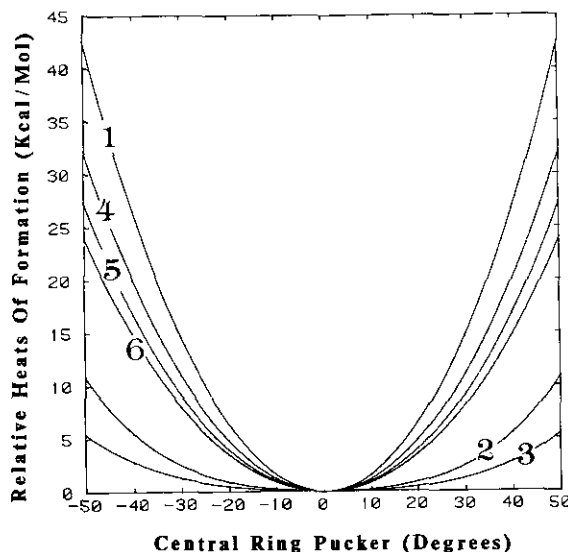


Figure 4. MNDO heats of formation as a function of central ring pucker.

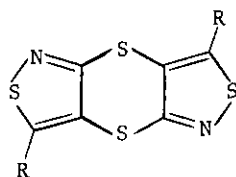
In contrast, the most flexible system is the 1,4-dithiin, 3. Like 3, the *p*-dioxin, 2, is also very flexible and is capable of wide amplitude fluctuations. Consequently even though all molecules are predicted by MNDO to be planar, we can divide these heterocycles into two groups; ones like cyclohexadiene and its disila derivative which are relatively inflexible, and, another group like the dithia and dioxo analogs that are very flexible. Mixing the oxa and thia groups with the more rigid sila group (empds 5 & 6) results in a conformationally stiff system.

Dioxin, 2, and dithiin, 3, are especially interesting molecules because they contain heteroatoms with lone pair electrons that can effectively interact with the alkene π electrons to create an 8π -electron, antiaromatic system. For this reason 3 and 4 have been studied with a variety of molecular orbital techniques. All computational methods predict planar structures for dioxin;^{12,13,14,15} in agreement with our work.

Studies on dithiin, in contrast, are conflicting. HMO,¹⁶ EHT¹⁵ and ab initio STO-3G basis set calculations with partial geometry optimization¹⁷ all predict boat forms with boat-to-boat interconversion barriers of 6.4, 2.2 and 14.6 kcal mol⁻¹ respectively. Ab initio STO-3G gradient optimization¹⁸ and MNDO calculations¹⁸ predict planar structures. However, more detailed ab initio studies have been performed. Calculations using the split-valence, 3-21G basis set make the boat form 3.0 kcal mol⁻¹ more stable than the planar form while the 6-31G basis set reduces this energy difference to 2.6 kcal mol⁻¹.¹⁹ Using a 3-21 G* basis set further reduces the energy difference to 2.3 kcal mol⁻¹ while the 6-31G* single point calculation reduces the energy difference to 1.8 kcal mol⁻¹.²⁰ Full geometry optimization with the latter basis set would further lower the energy difference and here we point out a trend; as the flexibility of the basis set increases the energy difference between boat and planar forms decreases. An even more complete basis set would be expected to further reduce the energy difference between puckered and planar forms. In any event, one may conclude that high quality basis set, single determinant, Hartree Fock theory predicts a boat-to-boat interconversion with a barrier no greater than 1.8 kcal mol⁻¹.

The calculations from references¹²⁻¹⁴ are, by today's standards, inadequate and should not be further considered. Minimum basis set ab initio calculations and MNDO results are thus in conflict with high quality ab initio results. The effect of polarization functions (d orbitals) on rotation and inversion barriers is profound.²¹ Our calculations include only S and P functions on sulfur as does Hayakawa in his ab initio study. Kao et al.¹⁹ and Saebo²⁰ both include polarization functions and, in this regard, may better reflect the shape of the dithiin potential energy surface.

Experimentally too there are ambiguities concerning the conformation of dithiins. Nematic phase NMR studies²³ and photoelectron spectral studies²³ do not discriminate between planar and boat forms. The dithiin derivative 13a is planar²⁴ but 13b is puckered.²⁵ Most important, though, is that dithiin itself has a permanent dipole moment.²⁶



a R = CO₂H

b R = CN

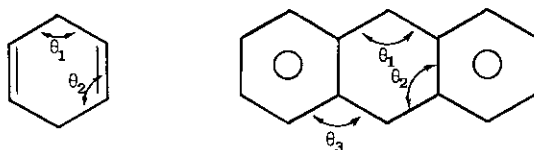
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The 1,4-dithiadiene ring, once interpreted as an antiaromatic 8 π -e⁻ system with negative resonance energy²⁷ has been reassessed¹⁸ with the third order perturbation treatment for cyclic conjugation

developed by Inagaki.²⁸ Here the extent of delocalization depends on donor/acceptor units with the proper orbital phase relationships. The cyclic conjugation in 3 is in Inagaki's parlance, discontinuous, and so antiaromatic destabilization is not an important factor that would make these rings deviate from planarity. In any event, whether the dithiin is planar or puckered with a boat-to-boat inversion barrier under $1.8 \text{ kcal mol}^{-1}$ is not important; the system, for all intents and purposes, is effectively planar and capable of wide amplitude flexing.

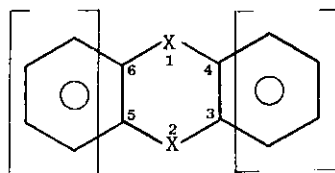
II. Hetero-9,10-dihydroanthracenes

In its planar form, dihydrobenzene has the methylene angle, θ_1 , bent above its standard tetrahedral value while the internal olefin angle, θ_2 , is compressed below its digonal value. Such angle strain could be relieved by ring puckering. However, the torsional potentials are strong enough to keep the cyclic diene planar. Dihydroanthracene, having similar torsional and angular forces as dihydrobenzene, has an addi-



tional olefinic carbon angle, θ_3 , not found in dihydrobenzene. The inflexibility of this angle, as argued by Allinger,²⁹ counter balances the torsional potentials that keep the ring planar and so, the 9,10-dihydroanthracene is expected to pucker more than the 1,4-dihydrobenzene. This has been found computationally with quantum mechanics and molecular mechanics.⁷ Hence, the curves for heterosubstituted rings are expected to look like their cyclohexadiene analogs but with flatter surfaces around the minimum.

The numbering system of the dihydroanthracenes is presented in ii below. Again the angle of flexure, α , is defined as the improper torsion angle ω_{4125} which also served as the reaction coordinate. In these



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systems two-fold symmetry was again maintained and, rather than relax all internal degrees of freedom, the aromatic rings were held fixed at the geometry corresponding to the minimum energy structure.

These fixed parameters involve the bracketed portions of the molecule in ii above. The difference between full optimization and partial optimization was tested and found to be negligible in the reaction coordinate calculations. The results are shown in Figure 5.

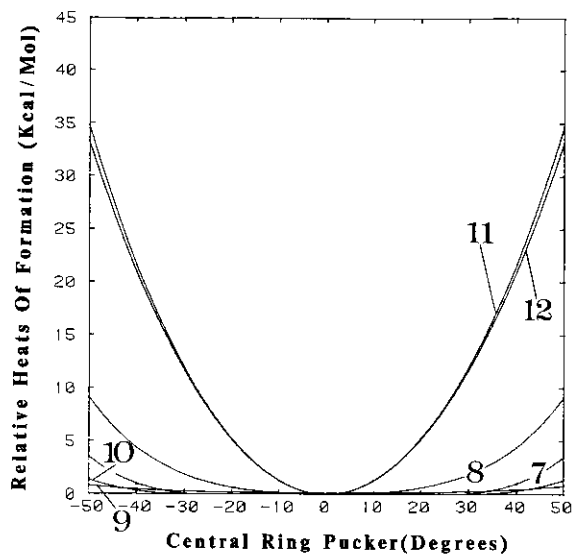


Figure 5. MNDO heats of formation as a function of central ring pucker.

Several important structural features of these dibenzotricyclic rings must be pointed out. First, completely geometry optimized structures are flat. Second, with the exception of 11 and 12 the potential surfaces are more shallow than their dihydrobenzene analogs. This is in accord with Allinger's rational outlined above. Third, for symmetrically substituted rings i.e. $x_1 = x_2$ the ease of cyclohexadienyl deformation follows the order $S > O > SiH_2 > CH_2$, but, for the anthracene the order is $S > SiH_2 > CH_2 > O$. Finally, the curvature of lines 11 and 12 appear to be completely out of character with the other dihydroanthracenes. The steepness of these curves is even larger than for curves 4 and 5 in figure 4. This implies 11 and 12 are conformationally less flexible than 4 and 5.

The origin of this is found in Table 1 where the relative electronic energies and core-core repulsion energies are presented. By relative we mean compared to the most stable conformation. Interestingly the stabilizing electronic interactions are only modestly offset by the destabilizing core repulsions in all but 11 and 12. In these instances there is proportionately a much larger increase in core repulsions. Precisely which core repulsions are giving rise to these anomalous curves is not clear; perhaps the inherent dissymmetry of 11 and 12 compared to the other anthracenes may be important.

A referee has questioned how these results would compare with Dewar's AM1 program.³⁰ Without having this program all we can do is speculate. It appears that in the reparameterization used to create AM1, an NDDO approximation, several deficiencies of MNDO have been corrected. In particular, the core repulsion function, which overestimated repulsions between atoms in MNDO has been modified in AM1. With less repulsive interactions we expect flatter potential surfaces and that compounds 11 and 12 will be more in line with 1-10.

Table I - Electronic and Core Energies (eV)

ring pucker	180°	170°	160°	150°	140°	130°
7 electronic	0.000	3.941	16.062	37.276	69.130	113.707
7 core	0.000	3.941	16.059	37.280	69.171	113.861
8 electronic	0.000	4.056	16.443	37.886	69.426	113.077
8 core	0.000	4.062	16.442	37.968	69.617	113.475
9 electronic	0.000	3.679	14.989	34.646	63.756	104.106
9 core	0.000	3.675	14.976	34.627	63.745	104.144
10 electronic	0.000	3.207	13.353	31.171	58.983	99.318
10 core	0.000	3.207	13.350	31.167	58.992	99.378
11 electronic	0.000	4.057	16.422	37.565	67.610	108.466
11 core	0.000	4.114	16.650	38.084	68.552	109.974
12 electronic	0.000	4.218	16.498	37.346	67.158	107.195
12 core	0.000	4.274	16.721	37.853	68.069	108.636

CONCLUSIONS

The intention of this study was to explore the wide amplitude flexing of hetero substituted dihydro-benzenes and anthracenes because the latter serve as the structural basis of psychotropic drugs. It has been postulated that the angle of flexure is a key factor in describing the clinical outcome of these drugs. The results of our theoretical studies on the unsubstituted parent ring structures consistently demonstrate that the shape of these molecules, like the all carbon systems, are inherently flat, and, if puckered, require little energy for the deformation.

We conclude that the inherent flexure angles in these dibenzotricyclic rings are very sensitive to intramolecular perturbations like peri- and transannular interactions; furthermore, they are expected to be very sensitive to intermolecular effects like hydrogen bonding and crystal packing forces. In summary, the steric parameter, α , used as a descriptor in psychotropic drug design should be used with caution or, better yet, discarded.

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