A Molecular Orbital Study of 3,3′,5-Trihalothyronine Analogs

Lemont B. Kier* and James R. Hoyland

Battelle Memorial Institute, Columbus Laboratories, Columbus, Ohio

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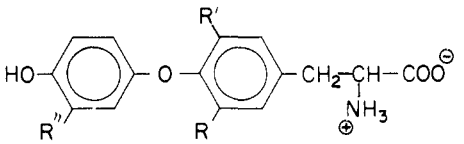
The conformational influence of halogen substituents upon the diphenyl ether moiety of 3,5,3′-trihalothyronine analogs has been calculated using molecular orbital theory. The thyromimetic bromo and iodo derivatives are found to prefer a conformation in which the plane of one ring bisects the second ring. The inactive chloro and unsubstituted analogs are found to prefer a conformation in which the planes of the two rings intersect at the O atom.

For some time the view has been held that the iodine atom was an essential feature of the thyroid-active thyronine hormones. Replacement of one or two I atoms with Br, Me, or *i*-Pr groups in the 3,3′,5,-triiodothyronine molecule (**1**) has resulted in some retention of activity, but no I-free analogs have been found active until recently. Jorgensen and Nulu have reported the synthesis of 3,5-dibromo-3′-isopropyl-L-thyronine (**2**) and have found that it is 1.7 to 7.3 times as potent as L-thyroxine in standard tests.[1] This finding negates the postulate of a unique role for I in these molecules.



(1) R=R′=R″=I
(2) R=R′=Br, R″=$(CH_3)_2CH$-

It has been proposed that the 3,5-iodo groups (or other substituents in these positions) serve to lock the phenolic ring into a bisecting conformation relative to the alanine ring (Figure 1).[2] The positions on the phenolic ring are now nonequivalent, that is, the 3′ position is not equivalent to the 5′ position unless the ring can freely rotate 180° (Figures 1a,b). The 3′ position has been shown to be of great importance for thyromimetic activity.

The influence of the 3,5 substituents in restricting rotation of the phenolic ring can be studied by the use of molecular orbital theory. In previous studies we have calculated the preferred conformations of numerous drug molecules in an effort to shed light on their structures relative to their biological activities.[3]

In the present study we sought to verify, by quantum chemical calculations, a prediction, based upon intuition, concerning the preferred conformations of several 3,5,3′-substituted thyronines. The model compounds chosen were the 3,5,3′-trichloro, 3,5,3′-tribromo, and the 3,5,3′-triiodo analgos, along with the unsubstituted molecule.

Methods.—The extended Hückel theory (EHT) was used in making the calculations, the parameters for which are listed in Table I. Bond lengths and angles were of standard dimensions.

Table I
EHT Parameters

Atom (X)	r(C–X), Å	μ	H_{ii} (2p), eV	H_{ii} (2s), eV
H		1.000		−13.60
C		1.625	−11.40	−21.40
N		1.950	−13.40	−26.00
O		2.275	−17.76	−35.30
Cl	1.69	2.033	−13.34	−25.23
Br[a]	1.88	1.710	−12.68	−23.97
I[a]	2.00	1.500	−12.01	−22.71

[a] Used Slater equation for 3s and 3p orbitals; see text.

The treatment of I and Br was somewhat troublesome, since the computer program available was not capable of calculating overlap integrals involving 4s, 4p, 5s, or 5p orbitals. Therefore, an alternative to a complete reprogramming was utilized which should produce realistic results, at least insofar as basic trends are concerned. This involved simulation of the Br and I orbitals with 3s and 3p orbitals. The orbital exponents were determined by maximizing the radial overlap integral between the simulating and actual orbitals. This led to the use of an orbital exponent of 1.50 for I and 1.71 for Br, the corresponding value for Cl being 2.033. The use of such a procedure can be justified in that the radial behavior of the simulating orbitals is not much different from that of the actual Slater orbitals. The approximate nature of extended Hückel theory does not justify concern about detailed behavior of the basis set, and the 4s, 4p, 5s, and 5p Slater orbitals are not very good approximations to the corresponding Hartree–Fock functions in any case. A similar approach has apparently been employed by Jordan in some EHT calculations on bromouracil.[4] Further remarks concerning these points are made in the Appendix.

In all calculations involving I and Br appropriate valence-state ionization potentials were chosen for the diagonal matrix elements. We feel strongly that the above procedure allows a simulation of Br and I that is completely sufficient for the conclusions drawn from the computations.

To simplify the calculations we have regarded the alanine moiety as being too remote from the ether O and the phenolic ring to influence the conformation of the latter moiety. We have previously justified this approach on theoretical grounds.[5] We have, ac-

* To whom correspondence should be addressed.

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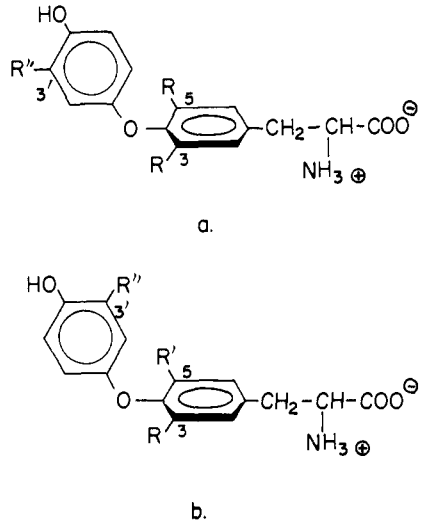

Figure 1.—Conformations of diphenyl ether moiety showing the plane of the phenolic ring bisecting the alanine ring.

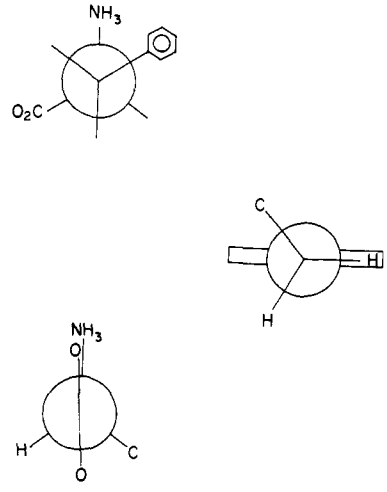

Figure 2.—Conformation of phenylalanine moiety from molecular orbital calculations.[6]

cordingly, adopted the conformation of phenylalanine, previously calculated, for the alanine side chain.[6] The calculation of the diphenyl ether conformation was accordingly calculated on the entire thyronine molecule, holding the alanine side chain in a conformation previously predicted for phenylalanine.

Results

The calculated conformation of the phenylalanine moiety is shown in Figure 2. If we reconstruct the triiodothyronine molecule with the amino acid moiety in its calculated conformation, we can see that no feature of the amino acid residue lies within 6 Å of a halogen atom or other feature of the phenolic ring. Thus, we would not expect any interaction from those parts of the triiodothyronine not included in the phenylalanine calculation, and we believe that our disection technique is justified.[5]

In Figure 3, the calculated relationship between the two rings for various 3,5,3'-substituents is shown.

The conformations at 180 and 0° are for the rings in a conformation shown in Figure 1. The potential

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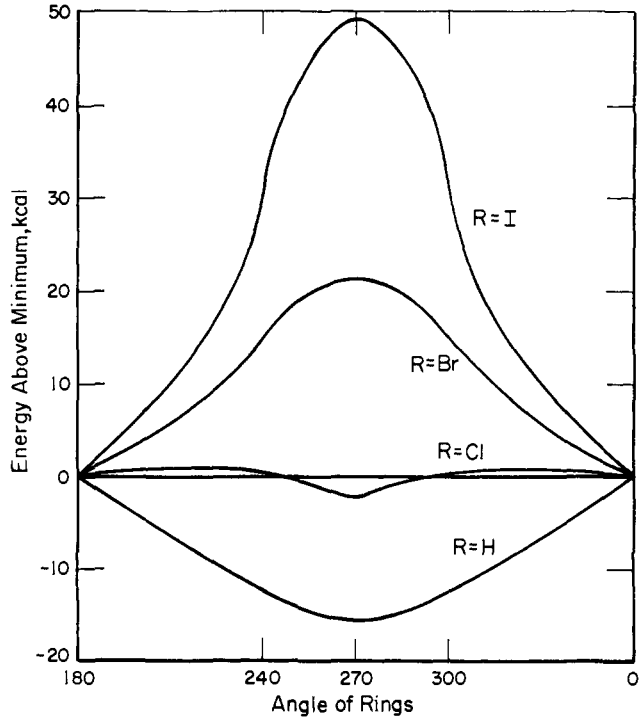

Figure 3.—Calculated relative energies for several analogues as a function of the rotation of the phenolic ring. At 180 and 0°, the conformations are as shown in Figure 1 a and b, respectively.

curve is symmetric about the arrangement at 270° except for minor differences which we feel are insignificant.

Discussion

The absolute value of the energy is not the important result here, since it is well known that barriers are sometimes considerably exaggerated in extended Hückel calculations. The trends, however, are extremely significant, in that the calculations clearly show that the tribromo and triiodo derivatives, which are biologically active, have a perpendicular arrangement of the rings that is "locked-in" by a considerable barrier to internal rotation. It is also apparent that the calculations do not discriminate energetically between the structures shown in Figure 1a,b, so that either structure may be invoked as the active form in the absence of substituents in the 2' and/or 6' positions.

The trichloro compound, on the other hand, shows very little conformational preference, and the most stable conformation is predicted to occur for the eclipsing arrangement of the rings. Finally, the unsubstituted molecule shows a clear conformational preference for the eclipsing arrangement. The intuitive predictions concerning the perpendicular ring arrangement in active species are therefore confirmed by these theoretical calculations. Furthermore, it would appear that the conformational details of the molecules studied here are governed by classical steric effects, since the preferred conformations and barriers to internal rotation seem to be functions of the "size" of the substituent rather than of hydrogen bonding, lone-pair repulsions, or other subtle influences.

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Appendix

The simulation of Br and I orbitals by 3s and 3p functions may at first appear somewhat controversial. Therefore, a detailed description is given here, along with additional data indicating that this procedure appears to be valid and should give reasonable predictions for the trends noted in this paper.

The orbitals to be fitted were chosen to be Slater functions with orbital exponents given by Slater's rules. The radial part of these orbitals is of the form

$$N_g r^{n_g-1} \exp(-\zeta_g r),$$

where $N_g = (2\zeta_g)^{n_g+1/2}/\Gamma(2n_g+1)^{1/2}$, $\Gamma(x)$ being the γ function. It is necessary to use this form since n_g for bromine is nonintegral. The radial part of the simulating orbital is

$$N_s r^{n_s} \exp(-\zeta_s r),$$

where $N_s = (2\zeta_s)^{n_s+1/2}/(720)^{1/2}$.

The overlap integral between the above two functions is

$$S = N_g N_s \Gamma(n_g + 4)/(\zeta_s + \zeta_g)^{\frac{n_g+4}{2}}$$

differentiating S with respect to ζ_s, and setting the result to zero leads to

$$\zeta_s = 7\zeta_g/(2n_g + 1).$$

The overlap integral between the actual Slater orbital and the simulating orbital is 0.998 for bromine and 0.996 for iodine, showing that there is a negligible difference between them.

Table II gives computed and experimental values for the barrier to internal rotation in C_2H_6, EtCl, EtBr, and EtI. The computed barriers are all exaggerated, which is not uncommon in EHT calculations. However, the use of simulated orbitals for bromine and iodine has led to an additional error of only about 1 kcal/mole. Therefore, even if the computed barriers in the thyronine derivatives are in error by a factor of 5, we feel the results for the trends predicted cannot be disputed.

TABLE II
COMPUTED AND EXPERIMENTAL BARRIERS TO INTERNAL ROTATION

Molecule	EHT barrier[a]	Experimental barrier[a,b]
C_2H_6	4.0	2.8
EtCl	5.7	3.7
EtBr	6.8	3.7
EtI	6.8	3.2 ± 0.5

[a] All values are in kcal/mole. [b] Experimental results taken from the tabulation given by J. P. Lowe, *Progr. Phys. Org. Chem.*, **6**, 1 (1968).

Quantitative Structure–Activity Models. Some Conditions for Application and Statistical Interpretation[1]

DONNA R. HUDSON, GEORGE E. BASS, AND WILLIAM P. PURCELL*

Department of Molecular and Quantum Biology, College of Pharmacy, University of Tennessee Medical Units, Memphis, Tennessee 38103

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The basis for a statistical analysis of the Free–Wilson structure–activity model is presented along with an explanation and interpretation of the multiple correlation coefficient, the F test of coefficient significance, and the explained variance. Ill conditioning is discussed as a problem of data suitability and a method for detecting this property is suggested. Two examples illustrate the methodology and interpretation.

With increasing emphasis on the application of mathematical and linear free energy related models to quantitative understanding of structure–activity relationships,[2,3] it becomes necessary to investigate the limitations and utilities of these methods. This work represents an attempt to establish criteria for the validity of the application of the Free–Wilson model.[4] The proposed model and the development of the basis for a statistical analysis of the data will be presented here. The problem of ill conditioning which sometimes occurs with this model will be presented along with two examples using the developed analysis.

The mathematical model developed by Free and Wilson to study structure activity relationships is applicable when dealing with an analogous series of compounds with corresponding biological activity data. A basic assumption of this model is that the activity of each compound can be resolved as the sum of contributions associated with the separate segments of the molecule. As a result, the activity of each compound in a series can be represented in the form of a linear equation as follows:

$$\text{biological activity} = \text{overall average} + \text{contribution of segment 1} + \ldots\ldots + \text{contribution of segment } n \quad (1)$$

* To whom correspondence should be addressed.

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