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# QUANTUM-CHEMICAL ANALYSIS OF THE CONFORMATIONAL AND DIASTEREOMERIC COMPOSITION OF 1,3-DIMETHYL-4-(S-PHENYLETHYLIMINO)PIPERIDINE

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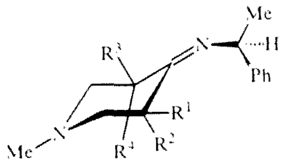
*The semiempirical quantum-chemical methods MNDO, AM1, and PM3 are used in a complete conformational analysis of 1,3-dimethyl-4-(S-phenylethylimino)piperidine.*

In a conformational sense, 1,3-dimethyl-4-(S-phenylethylimino)piperidine I is a complex stereochemical model. Data of $^1$H NMR spectroscopy show that the imine I consists of a pair of (3S, 4'S) and (3R, 4'S) diastereoisomers in a ratio of 1:1, which subsequently react as individual compounds. For each of the diastereoisomers of imine I, one then observes the simultaneous processes of imine-enamine tautomerism, E-Z isomerism, and inversion of the piperidine ring and nitrogen. Such a complex conformational pattern for the molecule of imine I undoubtedly greatly complicates the possibility of predicting the stereochemical direction of the reactions of imine I. It is important, therefore, to study by theoretical methods the conformational and diastereomeric composition of imine I as well as its reactivity in reactions with various reactants.

In this paper, the quantum-chemical semiempirical methods MNDO [1], AM1 [2], and PM3 [3] are used to calculate the geometry and energy of all possible spatial, configurational and conformational isomers and N-rotation isomers of 1,3-dimethyl-4-(S-phenylethylimino)piperidine. The calculation involved total optimization of the geometry by means of the PRECISE keyword for the purpose of improving the precision of the calculation. We calculated the surfaces of the potential energy of rotation of the N-phenylethyl 1,3-dimethyl-4-(S-phenylethylimino)piperidine. The calculation involved total optimization of the geometry by means of the PRECISE keyword for the purpose of improving the precision of the calculation. We calculated the surfaces of the potential energy of rotation of the N-phenylethyl group about the N−C bond for four 3-S (Ia-Id) and four 3-R (Ie-Ih) isomers of I.



I a-h

I a,e $R^1 = Me, R^2 = R^3 = R^4 = H$; b, f $R^2 = Me, R^1 = R^3 = R^4 = H$; c, g $R^3 = Me, R^1 = R^2 = R^4 = H$;
d,h $R^4 = Me^1, R = R^2 = R^3 = H$

Table 1 lists the relative energies of the most stable rotational isomers of each of the isomers Ia-Ih, together with experimental data, obtained by $^1$H NMR spectroscopy [4, 5], on the percent content, in the equilibrium mixture, of the E and Z isomers as well as the equatorial and axial 3-methyl conformation isomers.

A comparison of the data listed in Table 1 shows that the best agreement with experiment is obtained when the calculations are carried out by means of the AM1 method. The most stable isomer is the E isomer of 1,3-dimethyl-4-(S-phenylethylimino)piperidine, with an equatorial orientation of both methyl groups. The energies of the two diastereoisomers are practically equal. The (1f, 3a) isomer is less stable, by 0.4-0.5 kcal/mole. At the same time, the diastereoisomer with a 3-S orientation of the methyl group is somewhat more stable than the 3-R analog. In contrast to the E isomer, the Z isomer

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TABLE 1. Energies of Formation (kcal/mole) of Isomers Ia-Ih, Calculated by the Semiempirical Quantum-Chemical Methods MNDO, AM1, PM3, and Experimental Data on their Percent Content in the Equilibrium Mixture

| Isomer of I | a | e | b | f | c | g | d | h |
|---|---|---|---|---|---|---|---|---|
| MNDO | 40.5 | 40.6 | 34.5 | 34.3 | 35.3 | 35.3 | 34.2 | 34.2 |
| AM1 | 36.4 | 36.9 | 34.2 | 33.3 | 33.1 | 33.1 | 33.5 | 33.6 |
| PM3 | 21.6 | 21.6 | 19.1 | 18.4 | 19.9 | 19.9 | 19.4 | 19.3 |
| $^1$H NMR | 0 |  | 23% |  | 61% |  | 16% |  |

is conformationally uniform: The conformational isomer with equatorial orientation of the methyl group in the 3 position is appreciably less stable than the (1f, 3a) conformational isomer. The stability of the latter is intermediate between that of the (1f, 3f) and (1f, 3f) conformational isomers of the E isomer. The ratio, calculated from these data, of the E and Z isomers in the equilibrium mixture at 298 K, (3:1), is consistent with the experimental data. The calculated ratio (1f, 3f): (1f,3a) for the E isomer, however, is slightly lower (2:1) than the experimental ratio.

Calculations using the MNDO and PM3 methods yield similar results in terms of the relative energies of the E and Z isomers, but exaggerate the stability of the (1f, 3a) conformational isomer of the E isomer in comparison with the (1f, 3f) conformational isomer. One can thus conclude that the semiempirical methods satisfactorily reproduce the experimental data on the relative stability of different isomers of 1,3-dimethyl-4-(S-phenylethylimino)piperidine. The best agreement with experiment is obtained when the AM1 calculation scheme is used, which can therefore be recommended for theoretical studies of the reactivity and regio- and stereoselectivity of reactions of imines of substituted piperidines.

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