Free Rad. Res. Comms., Vol. 19 Supplement, pp. S17-S22
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FORCE FIELD CALCULATIONS ON FIVE MEMBERED RING AMINOXYL RADICALS

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Two force fields (MM2 and Genmol) have been applied to the modeling of five membered ring aminoxyl radicals. For the six molecules which were investigated the geometry of the conformation with the lowest strain energy was in very good agreement with the X-ray geometry. However owing to the high flexibility of five membered rings other conformations were shown to have a strain energy close to the energy minimum.

KEY WORDS: Force field calculations, aminoxyl radicals.

INTRODUCTION

Many five membered ring aminoxyl radicals are stable and find important applications as spin labels[1]. Different experiments are based on their relaxivity[2]. On the other hand a large number of persistent five membered ring aminoxyl radicals have been characterized in spin trapping experiments using 1-pyrroline-N-oxides as scavengers[3]. Most of the important features of these radicals as for example their EPR hyperfine coupling constants, depend on their conformation. In this communication we describe our preliminary results concerning the molecular mechanics modeling of five membered ring aminoxyl radicals using both the Genmol[4] and Allinger MM2[5] force fields. In the present study, the previously published X-ray data[6-11] for six five membered ring aminoxyl radicals (Scheme 1) have been used as a basis to extend the Genmol and MM2 force fields to include the nitroxyl moiety.

METHODS

The calculations were run on a VAX 6320 DEC computer or a personal Iris Silicon Graphics 4D/20. The MM2 force field was used unchanged and the parameters for the nitroxyl moiety (Table 1) were obtained using trial and error approach. For the N-O· bond, according to X-ray data, the equilibrium bond length r_0 was fixed at 1.27 Å, which should correspond to $k_s = 9.9$ mdyn Å^{-1} molecule^{-1}, using the general equation proposed by Hase[12], $(k_s(r_0 - 0.690)^3 = 1.94)$. For the bending

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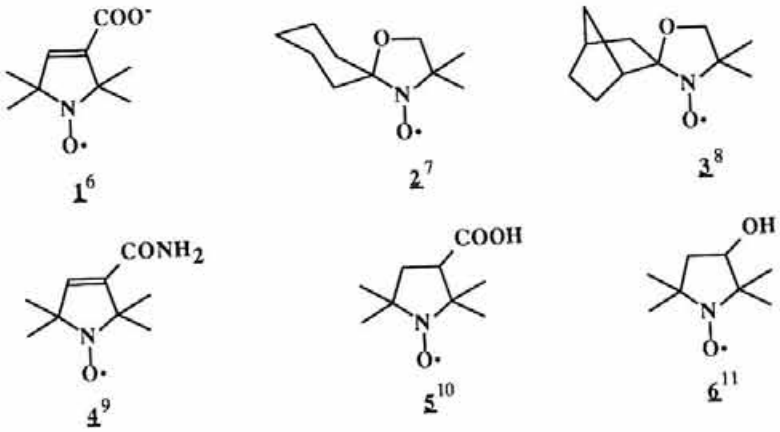


SCHEME I

TABLE I
MM2 Force Field Parameters [1] for Five Membered Ring Aminoxyl Radicals

Nonbonded Parameters

atom	r^*/Å	ϵ/kJ mol^{-1}
N(N-O·)	1.82	0.055
O(N-O·)	1.74	0.050

Bond-Stretching Parameters

bond type	r_0/Å	k_s/mdyn Å^{-1} molecule^{-1}
N-O·	1.27	9.0
N-C (sp^3)	1.47	3.52

Bond Bending Parameters

bond angle	θ_0/deg	k_θ/mdyn Å rad^{-2} molecule^{-1}
C (sp^3)-N(O·)-C (sp^3)	120	0.65
C (sp^3)-N-O·	120	0.56

Torsional Constants

torsion	V_1/kJ mol^{-1}	V_2/kJ mol^{-1}	V_3/kJ mol^{-1}
C (sp^3)-C (sp^3)-N-O·	0	0	0
O (sp^3)-C (sp^3)-N-O·	0	0	0

[1] all the other MM2 (1985) parameters were unchanged

constant, k_b, of the C(sp^3)-N(O·)-(C(sp^3) angle, a value of 0.65 mdyn Å rad^{-2} molecule^{-1} was obtained which is very close to the value (0.70 mdyn Å rad^{-2} molecule^{-1}) calculated from the equation ($k_b = -3.93\,10^{-2}\,k_s$ C-N(O·) + 0.844) proposed by Hase[12].

Genmol[4] is a fast program for molecular modeling which can perform a fast

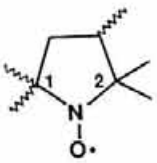
TABLE II

Comparison of the X-ray data and calculated geometries for the five membered ring aminoxyl radicals **1–6**.

Nitroxide	$d_{N\text{-}O}$ (Å)	$d_{N\text{-}C_1}$	$d_{N\text{-}C_2}$	ONC_2 (deg)	ONC_1	C_1NC_2	RMS[i] ($\times 10^2$)
1 X-ray	1.276	1.490	1.497	121.6	123.6	114.8	
Genmol	1.278	1.475	1.478	122.9	122.0	115.2	0.3
2	1.260	1.476	1.469	123.3	123.8	112.9	
	1.275	1.459	1.460	122.8	125.1	112.1	0.2
MM2	1.270	1.473	1.474	123.3	123.3	113.5	3.0
3	1.260	1.487	1.470	123.6	123.2	112.6	
	1.275	1.462	1.463	124.1	124.0	110.1	1.0
	1.270	1.476	1.471	121.7	122.9	113.0	0.5
4	1.269	1.477	1.486	122.2	122.9	114.9	
	1.277	1.480	1.488	123.2	122.2	114.6	3.0
5	1.272	1.479	1.487	120.8	122.8	116.3	
	1.277	1.484	1.485	122.9	122.3	114.8	0.7
	1.270	1.484	1.487	121.9	122.0	116.1	3.3
6	1.264	1.489	1.478	122.1	122.7	115.3	
	1.277	1.490	1.486	122.4	122.6	115.0	0.3
	1.270	1.486	1.487	122.0	121.9	116.1	0.3

[i] When the best molecular fit has been performed the N distances d_i, between the corresponding atoms are calculated and the RMS is given by: $RMS = (\Sigma d_i^2)^{1/2}/N$.

[j] For the numbering see scheme 2.

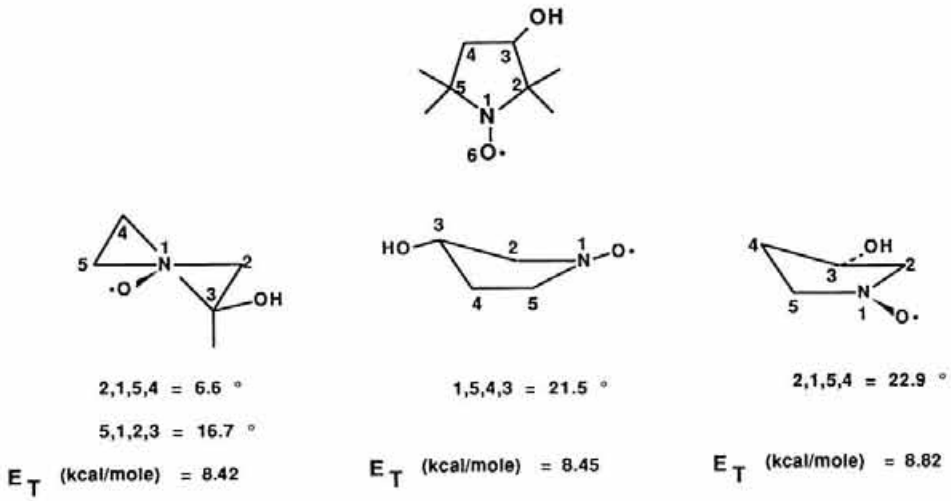


SCHEME 2

conformational analysis to determine the preferred molecular conformations. The program automatically recognizes the nature of each bond and takes into account the π systems. The conjugated gradient method is used to minimize the energy. Default values for stretching and bending parameters are those given in MMP2[5]. The chemical and stereochemical environments of each atom are automatically analyzed to define the most appropriate stretching and bending parameters. Coulombic interactions are computed in a monopole approximation. The net atomic charges for the σ framework are determined by the Del Ré's approach using a new set of atomic parameters[13], whereas the π charges are generated in an empirical way in order to reproduce the calculated Pariser and Parr values. Nonbonded, and hydrogen-bond parameters are derived from ECEPP[14]. The torsional potential function and the corresponding parameters are specific to Genmol.

RESULTS AND DISCUSSION

Characteristic features of the calculated geometries for the six aminoxyl radicals (Scheme 1) studied in the present work are shown below (Scheme 2 and Table II) and



SCHEME 3

compared with the X-ray geometries. The overall success of the new Genmol and MM2 force fields in modeling five-membered ring aminoxyl radicals is illustrated by the comparison given in Table II. A detailed comparison of the calculated and experimental structures showed that all the important structural elements were adequately modeled (the mean RMS value is 0.01 with the Genmol force field).

In liquid solution generally, five-membered rings do not possess well-defined conformational preferences therefore calculation of molecular properties must be averaged over all the contributing individual conformations[15]. Using the Genmol force field we found that at least three individual conformations must be considered in the case of the 2,2,5,5-tetramethyl-3-hydroxypyrrolidinyl-1-oxy **6**. These conformations and their total energy E_T (kcal/mole) are shown on scheme 3.

The unsymmetrical half-chair conformation **A** is very close to the X-ray geometry (RMS = 0.003 Å) but its calculated total energy is almost identical to that of conformer **B** exhibiting an envelope form with the tip of the envelope at the carbon C3. In the same way the energy of the other envelope conformation **C**, with the tip of the envelope at the carbon C4, is close to that of **A** and **B**. It is worth to mention that in all three conformers the oxygen of the nitroxide lies approximately in the C2N1C5 plane, and it is obvious that all these conformations would have to be considered to correlate the EPR hyperfine coupling constants of **6** with its geometrical characteristics.

CONCLUSION

Our preliminary results show that five membered ring aminoxyl radicals, one of the most important class of aminoxyl radicals, can be adequately modeled by molecular mechanic calculations using force field like. MM2, and the parameters given in Table I. On the other hand Genmol a new powerful force field is very appropriate to give calculated geometries in good agreement with the X-ray geometries.

For all the calculated molecules the conformation which has the best fit with the X-ray geometry was shown to correspond to the lowest total strain energy. However other contributing conformations were found by including geometrical constraints in the calculations. Force field modeling should be easily extended to other types of aminoxyl radicals and should become soon a very powerful tool to analyze their molecular properties and to design new nitroxides exhibiting specific properties.

Acknowledgements

We gratefully acknowledge the ATOCHEM company for a travel grant to present this work at the 3rd International Symposium on Spin Trapping and Aminoxyl Radical Chemistry (Kyoto, Japan, November 22–24, 1991).

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