Conformational Behaviour of Non-Fused Biheterocycles. Part XV. Isomeric Phenylisoxazoles

Nino Russo* and Marirosa Toscano

Dipartimento di Chimica, Università della Calabria,
87030 Arcavacata di Rende (CS), Italy

Vincenzo Barone

Dipartimento di Chimica, Università di Napoli, Via Mezzocannone 4,
80134 Napoli, Italy

Received March 18, 1988

The conformational behaviour of isomeric phenylisoxazoles has been investigated at the STO-3G level optimizing the most significant geometrical parameters. The energy minima of the two isomers having an heteroatom in an *ortho* position correspond to planar structures, whereas the 4-isomer has a twisted equilibrium conformation. This confirms that H-H non-bonded repulsions are stronger than (lone-pair)-H ones. The similar conformational behaviour of corresponding phenylfurans and phenylisoxazoles shows that the second heteroatom has a negligible effect and that the conformational behaviour of non-fused biheterocycles is dictated by the nature of the *ortho* substituents.

J. Heterocyclic Chem., **25**, 1709 (1988).

Introduction.

In a series of papers [1-14] we have investigated the modification induced by the presence of heteroatoms on the conformational behaviour of heteroaromatic systems consisting of two rings linked together by essentially single bonds. We have considered until now both five- and six-membered rings, but only equivalent substituents (N, O or S). In order to better ascertain the interplay of electron redistribution and steric effects, we considered it interesting to investigate the contemporary presence of two electronegative atoms on the same ring. Phenylisoxazoles provide a particularly adequate class for this purpose since they are experimentally well characterized [15-18] and the three different isomers cover a wide range of topological situations. In view of previous experience [9-14, 19,20] the full rotational potentials of isomeric phenylisoxazoles have been computed at the STO-3G *ab-initio* level.

Computational Procedure.

As a first step the torsional potentials of isomeric phenylisoxazoles were computed by the GAUSSIAN/82 package [21], using the STO-3G basis set [22], the microwave structure of the isoxazole ring [23], the STO-3G optimized geometry of benzene [7,9], and an inter-ring C-C distance of 1.45 Å [17]. The torsional angle θ between the planes of the two rings was spanned in steps of 15°. The benzene-isoxazole bond distance R, its vicinal angles, and the valence angles of the *ortho* hydrogens (see Figure 1) were then optimizing at values of θ spaced by 30° using the analytical gradient procedure [24] implemented in the GAUSSIAN/82 package. This partial optimization should be sufficient since significant (conformation dependent) geometry modifications usually occur only in the environment of the twisting bond [20,25,26]. For purposes of comparison the same points were computed also maintaining the above geometrical parameters at the values optimized for the planar conformation.

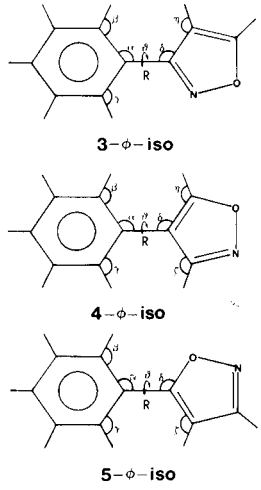

Figure 1. Schematic drawing of isomeric phenylisoxazoles. The labelling of the variable geometrical parameters is also reported.

Results and Discussion.

The structures, variable geometrical parameters, and labelling of isomeric phenylisoxazoles are shown in Figure 1.

The optimized values of the variable geometrical parameters for the different conformations are collected in Table I.

It is quite apparent that both bond length and bond angle variations are generally negligible. In agreement with experimental data (18) the angle δ (see figure) is very similar for the 3- and 4-isomers and significantly larger for the 5-isomer.

Although greater than the X-ray value adopted in RR computations (1.45 Å ref [17]), the optimized value of the

Table I

Isomer	Parameter	θ = 0°	θ = 30°	θ = 60°	θ = 90°	θmin = 2.7°
3-ϕ-iso	R	1.500	1.500	1.506	1.510	1.499
"	α	120.5	120.3	120.1	120.0	120.5
"	β	120.3	120.3	120.3	120.3	120.2
"	γ	120.1	120.0	120.0	119.9	120.1
"	δ	127.7	127.4	127.0	126.9	127.9
"	η	128.5	128.5	128.5	128.5	128.4
"	μ	2.46	2.52	2.61	2.65	2.46
"	$2P_\pi$	0.232	/	/	/	/
"	ΔE	-468.24517	1.86	10.47	15.99	-1.21
Isomer						
4-ϕ-iso	Parameter	θ = 0°	θ = 30°	θ = 60°	θ = 90°	θmin = 15.2°
"	R	1.493	1.492	1.498	1.503	1.492
"	α	120.0	119.9	119.9	120.0	120.0
"	β	120.3	120.0	119.8	119.8	120.2
"	γ	120.3	120.0	120.2	120.2	120.2
"	δ	128.0	127.9	127.8	127.8	128.0
"	ζ	127.9	127.6	127.4	127.4	127.8
"	η	132.5	132.5	132.1	132.1	132.4
"	μ	2.81	2.84	2.90	2.92	2.81
"	$2P_\pi$	0.242	/	/	/	/
"	ΔE	-468.24370	0.47	7.67	12.77	-0.16
Isomer						
5-ϕ-iso	Parameter	θ = 0°	θ = 30°	θ = 60°	θ = 90°	θmin = 0°
"	R	1.492	1.493	1.500	1.506	/
"	α	120.4	120.1	119.8	120.0	/
"	β	120.1	120.1	120.0	120.0	/
"	γ	119.5	119.6	119.6	119.6	/
"	δ	132.3	132.0	131.9	131.9	/
"	ζ	129.1	128.6	128.5	128.5	/
"	μ	2.89	2.93	2.97	2.98	/
"	$2P_\pi$	0.265	/	/	/	/
"	ΔE	-468.24895	3.52	13.73	19.60	0.0

Geometric (see text and figure 1 for the definition and units) and electronic (dipole moments μ/D and total energies in a. u.) parameters for isomeric phenylisoxazoles.

Table II

Parameter	Molecule								
	3-ϕ-iso			4-ϕ-iso			5-ϕ-iso		
	RR	RR'	PFR	RR	RR'	PFR	RR	RR'	PFR
V (30°)	1.79	1.89	1.86	0.56	0.61	0.47	3.75	4.02	3.52
V (60°)	11.70	10.61	10.47	8.92	8.13	7.67	15.49	14.18	13.73
V (90°)	18.40	16.28	15.99	14.72	13.27	12.77	22.52	20.08	19.61
V_2	18.91	16.67	16.40	15.71	13.60	13.30	22.84	20.16	19.88
V_4	-3.19	-2.45	-2.49	-3.47	-2.95	-3.12	-2.15	-1.25	-1.57
V_6	-0.47	-0.39	-0.41	-0.56	-0.49	-0.54	-0.32	-0.08	-0.27
V_8	-0.09	-0.07	/	-0.07	-0.05	/	-0.04	-0.02	/
θ_{min}	0°	0°	0°	16.30°	16.20°	16.50°	0°	0°	0°
V_{min}	0.00	0.00	0.00	-0.13	-0.15	-0.16	0.00	0.00	0.00
E (0°)	-468.24325	-468.24517	-468.24517	-468.24282	-468.24370	-468.24370	-468.24744	-468.24895	-468.24895

Conformational characteristics of isomeric phenylisoxazoles in the rigid (RR and RR') and partially flexible (PFR) rotor approximations from STO-3G computations. Total energies are in a. u., energy differences with respect to planar conformations (V (θ)) and potential constants (V_i) are in KJ/mol and angles are in degrees.

inter-ring C-C distance (1.49-1.50 Å) is typical for this class of molecules [10,13] and shows the well known lengthening going from planar to perpendicular conformation [20,27,28]. The computed dipole moments are in reasonable agreement with experimental data [15] for the 4-isomer and underestimated by about 0.3 Debye for the other two isomers.

The relative stability of the different isomers, $5>3>4$, points out the destabilizing role of the inter-ring H-H interactions since the order provided by inter-ring conjugation alone (as revealed by the pertinent π bond orders) would be $5>4>3$.

Nine potential energy curves for internal rotations around the central C-C bond were generated, corresponding to two rigid rotor models (experimental structure denoted as RR and STO-3G partially optimized structure of the planar conformation denoted as RR') and one partially flexible rotor model (denoted as PFR), for each isomer.

As in analogous systems [20,29,30] the results obtained by RR and PFR approximations are very similar, although the partially short inter-ring distance adopted in the RR model leads to some discrepancy.

In particular energy maxima always correspond to perpendicular conformation ($\theta = 90°$) and minima are located in a very flat energy region corresponding to $0° < \theta < 30°$.

The structures of isomeric phenylisoxazoles are thus quite flexible, with the two rings freely oscillating in a significant angle interval around ther equilibrium structure. Only the 4-isomer has a shallow minimum at a twist angle of about 15° whereas the other two isomers prefer planar conformations. Furthermore the barrier heights at 90° increase in the order $4<3<5$. This shows once again that H-H repulsive interactions are larger than lone-pair-H ones and that in the presence of similar steric hindrances ($3 \cong 5$) the conformational behaviour is determined by inter-ring conjugation. In fact the barrier height at 90° is larger for the isomer with the larger inter-ring π bond order. A comparison of 4 and 5 phenylisoxazoles with the corresponding phenylfurans (respectively 3 and 2) shows quite similar conformational characteristics as would be predicted on the ground of the identical nature of *ortho* substituents. The minor role of the second heteroatom is revealed by slight differences in the potential constants. In particular the values of θ_{min} and of the barrier height at 90° suggest a greater inter-ring conjugation for phenylisoxazoles than for corresponding phenylfurans [10] although the pertinent π bond orders are very similar. The different sets of conformational energies $V(\theta)$ (expressed as the total energies $E(\theta)$ minus the energy $E(0°)$ of the planar conformation) have been fitted by a truncated Fourier expansion

$$V(\theta) = \Sigma \tfrac{1}{2} V_j [1-\cos(j\theta)] \quad (1)$$

in which the physical origin of the low-order potential constants is well recognized [9]. The fitting allows a quantitative comparison of different molecules and/or methods and the analytical location of energy minima and maxima on the potential curve [3,9,29,30].

In the case considered here the potential is symmetric about $\theta = 90°$ so that only even values of j are allowed. The spacing of 15° adopted in the RR computations allow the determination of up to six terms and confirms that the first three potential constants are sufficient to give a good fitting of the torsional potential. This is just the number of terms which can be determined with the spacing of 30° adopted in the PFR computations. The reliability of the fitting at this level receives further support by the comparison between the values of θ_{min} and V_{min} computed *via* direct energy minimization (15.2° and -0.16 Kjoule/mole) or *via* the Fourier expansion of the potential (16.5° and -0.16 Kjoule/mole).

The torsional potential is determined by the combined effects of inter-ring conjugation (which only contributes to the V_2 potential constant) and of interactions between *ortho* substituents (which contribute to all potential constants). On these grounds comparison of V_4 terms allows to discard the conjugative interactions. The trend of these potential constants (which is confirmed by the trend of V_6 terms) for the different isomers indicates that C-H...C-H interactions are more repulsive than C-H...N ones, which, in turn, are larger than C-H....O interactions.

Concluding Remarks.

Ab-initio computations were used to build up a comprehensive picture of the conformational behaviour of isomeric phenylisoxazoles. Together with the particular results described above, some general features deserve further mention. In particular it has been shown that: 1) The rigid rotor approximation is usually sufficient to obtain reliable torsional potentials of non-fused biheterocycles. 2) The torsional potential is always well represented by three term Fourier expansions. 3) Molecules with the same *ortho* substituents show very similar torsional curves also in the presence of further heteroatoms in *meta* and/or *para* position.

REFERENCES AND NOTES

[1] V. Barone, P. L. Cristinziano, F. Lelj, A. Pastore, and N. Russo, *Gazz. Chim. Ital.*, **112**, 195 (1982).

[2] V. Barone, C. Cauletti, F. Lelj, M. N. Piancastelli, and N. Russo, *J. Am. Chem. Soc.*, **104**, 4571 (1982).

[3] V. Barone, F. Lelj, C. Cauletti, and M. N. Piancastelli, *Mol. Phys.*, **49**, 599 (1983).

[4] V. Barone, N. Bianchi, F. Lelj, N. Russo, and G. Abbate, *Theochem.*, **108**, 35 (1984).

[5] V. Barone, C. Cauletti, L. Commisso, F. Lelj, M. N. Piancastelli, and N. Russo, *J. Chem. Res. S*, 338 (1984).

[6] V. Barone, L. Commisso, F. Lelj, and N. Russo, *Tetrahedron*, **41**, 1915 (1985).

[7] V. Barone, F. Lelj, L. Commisso, N. Russo, C. Cauletti, and M. N. Piancastelli, *Chem. Phys.*, **96**, 435 (1985).

[8] V. Barone, F. Lelj, N. Russo, and M. Toscano, *J. Chem. Soc., Perkin Trans. II*, 907 (1986).

[9] V. Barone, F. Lelj, and N. Russo, *Int. J. Quantum Chem.*, **29**, 541 (1986).

[10] N. Russo, M. Toscano, V. Barone, and C. Minichino, *J. Chim. Phys.*, **84**, 735 (1987).

[11] V. Barone, C. Minichino, S. Fliszar, and N. Russo, *Can. J. Chem.*, in press.

[12] V. Barone, F. Lelj, C. Minichino, N. Russo, and M. Toscano, *J. Chem. Soc., Perkin Trans. II*, in press.

[13] V. Barone, C. Minichino, N. Russo, and M. Toscano, *Gazz. Chim. Ital.*, in press.

[14] V. Barone, F. Fraternali, P. L. Cristinziano, F. Lelj, and N. Russo, *Theochem.*, submitted.

[15] G. Del Re, *J. Chem. Soc.*, 3324 (1962).

[16a] S. Biagini, M. Cannas, and G. Marongiu, *J. Heterocyclic Chem.*, **6**, 901 (1969); [b] S. Biagini, M. Cannas, and G. Marongiu, *Acta Cryst.*, **B25**, 2108 (1969); [c] *ibid.*, **B25**, 1050 (1969).

[17] M. Cannas, A. Cristini, and G. Marongiu, *J. Chem. Soc., Perkin Trans. II*, 237 (1979).

[18] C. A. Veracini, A. De Munno, G. Chidichimo, M. Longeri, and V. Bertini, *J. Chem. Soc., Perkin Trans. II*, 572 (1979).

[19] S. Marriot and R. D. Topsom, *Aust. J. Chem.*, **39**, 1157 (1986).

[20] G. Hafelinger and C. Regehnann, *J. Comput. Chem.*, **8**, 1057 (1987).

[21] J. S. Binkley, M. J. Frisch, D. J. De Frees, K. Raghavachari, R. A. Whiteside, H. B. Schlegel, E. M. Fluder, and J. A. Pople, GAUSSIAN 82, Carnegie-Mellon University, 1982.

[22] W. J. Hehre, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.*, **51**, 2657 (1969).

[23] O. L. Stiefvater, *J. Chem. Phys.*, **63**, 2560 (1975).

[24] H. B. Schlegel, *J. Comp. Chem.*, **3**, 214 (1982).

[25] G. R. De Mare' and D. Neisius, *Theochem.*, **109**, 103 (1984).

[26] C. W. Bock, P. George, and M. Trachtman, *Theor. Chim. Acta*, **64**, 293 (1984).

[27] J. Almlöf, *Chem. Phys.*, **6**, 135 (1974).

[28] G. H. Penner, *Theochem.*, **137**, 191 (1986).

[29] E. Von Nagy-Felsobuki, *Chem. Phys. Letters*, **127**, 245 (1986).

[30] E. Ortì, J. Sanchez-Marìn, M. Merchan, and F. Tomás, *J. Phys. Chem.*, **91**, 545 (1987).