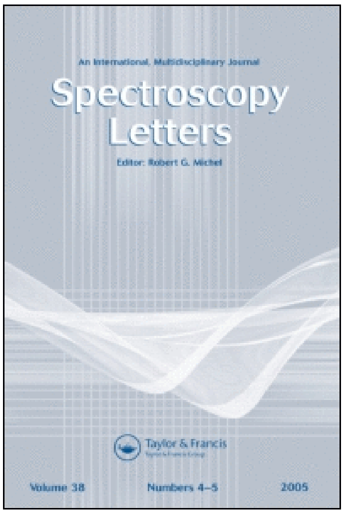

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Erol Azanli[a]; Robert Rothchild[ab]; Anne-Marie Sapse[abc]
[a] Science Department, John Jay College of Criminal Justice, City University of New York, New York, NY, U.S.A. [b] The Graduate Center, Doctoral Faculty, City University of New York, New York, NY, U.S.A. [c] Rockefeller University, New York, NY, U.S.A.

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AB INITIO STUDIES OF HINDERED ARYL ROTATIONS OF METHAQUALONE, MECLOQUALONE, AND 3-(2,6-DIFLUOROPHENYL)-2-METHYL-4(3H)-QUINAZOLINONE

**Erol Azanli,[1] Robert Rothchild,[1,2,*] and
Anne-Marie Sapse[1,2,3,*]**

[1]John Jay College of Criminal Justice,
Science Department, City University of New York
445 W. 59th Street, New York, NY 10019-1128, USA
[2]The Graduate Center, City University of New York,
Doctoral Faculty, New York, NY 10016
[3]Rockefeller University, 1230 York Avenue,
New York, NY 10021, USA

ABSTRACT

Rotational barriers for the rotation of an N-aryl group were investigated via ab initio (Hartree-Fock) calculations in methaqualone, mecloqualone and 3-(2,6-difluorophenyl)-2-methyl-4(3H)-quinazolinone. It was found that the N1 atom acquires an sp^3 character in conformations with high steric hindrance. The geometrical parameters of the molecules undergo small changes intended to alleviate the steric hindrance.

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*Corresponding authors. E-mail: rrothchild@jjay.cuny.edu

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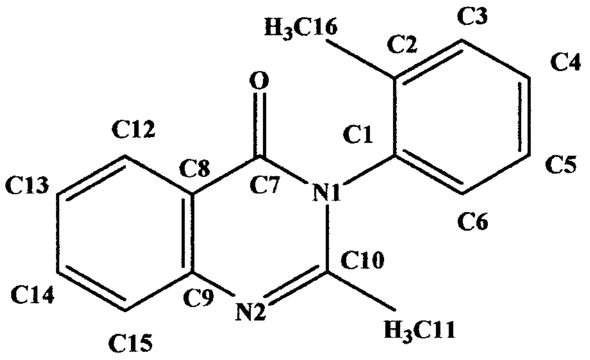
Key Words: Hindered rotation; 3-Aryl-2-methyl-4(3H)-quinazolinones; Methaqualone; Mecloqualone; Hartree-Fock 6-31G*; Axial chirality

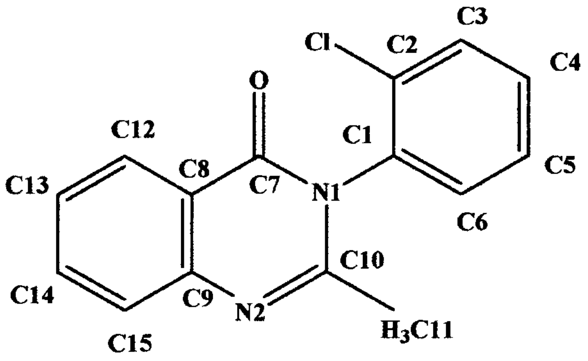
INTRODUCTION

The energy barrier for the rotation of an aromatic ring about a bond to an sp^2 or sp^3 hybridized atom has been the subject of many experimental and theoretical studies[1]. Previously, our group applied NMR methods to the study of crowded Diels-Alder adducts of phencyclone, and substantial evidence was found for hindered rotations of unsubstituted bridgehead phenyls and *N*-aryl imides in these systems[2]. These experimental NMR spectroscopy studies were recently complemented by ab initio calculations examining corresponding hindered motions in a simplified model of the phencyclone adducts. Detailed ab initio studies also focused on the hindered *N*-aryl rotation of N-2,6-difluorophenyl maleimide[3].

This present report now extends the earlier work by using ab initio quantum chemical methods (Hartree-Fock) to examine the rotational barriers of substituted phenyl groups in a set of closely related structures, including compounds of considerable pharmaceutical and forensic importance. The three compounds studied here are: methaqualone, *Compound 1*, (2-methyl-3-(2-methylphenyl)-4(3H)-quinazolinone); mecloqualone, *Compound 2*, (3-(2-chlorophenyl)-2-methyl-4(3H)-quinazolinone); and an analog of these quinazolinones, *Compound 3*, 3-(2,6-difluorophenyl)-2-methyl-4(3H)-quinazolinone. Structures are shown in Fig. 1. Methaqualone has sedative/hypnotic effects, and its use as a ‘‘recreational drug’’ resulted in its current classification as a Schedule I controlled substance. Side effects include poor judgment, decreased motor coordination, impulsive actions, and drowsiness. Hindered rotation of the 2-methylphenyl group results in axial chirality for methaqualone, with rotation of this moiety leading to enantiomerization. Mannschreck et al.[4] chromatographically resolved the enantiomers and demonstrated different potencies of the enantiomers with respect to hypnotic and anticonvulsant effects. Mecloqualone has similar sedative/hypnotic pharmacological properties as methaqualone, and is also controlled as a Schedule I substance; it also exhibits axial chirality. NMR studies with chiral lanthanide shift reagents have allowed observation of separate signals for the enantiomers of both methaqualone and mecloqualone[5]. Compound 3 cannot exhibit comparable axial chirality, but has been selected for study here as an analog of methaqualone and mecloqualone, to extend the earlier studies of Langowski, et al.[3], because of the potential importance of organofluorine compounds as medicinal agents.



Methaqualone (Compound 1)



Mecloqualone (Compound 2)

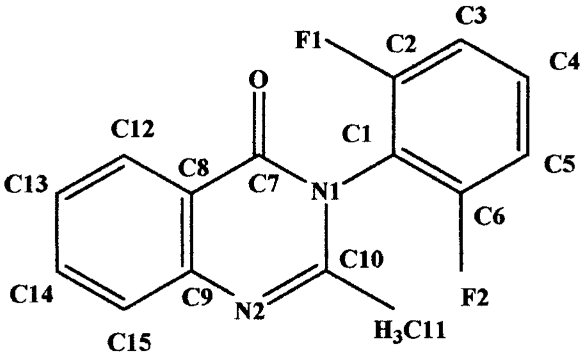


Figure 1.

METHODS AND RESULTS

The MacSpartan[6] and the Titan[7] programs were used to perform Hartree-Fock calculations on the systems. The basis set was the 6-31G* set which uses one Slater orbital for the core electrons, expanded in a series of six gaussian functions and two Slater orbitals for the description of the valence electrons, one expanded in a series of three gaussians and the other approximated by one gaussian. In addition, d orbitals are placed on the non-hydrogen atoms.

Figure 1 shows the numbering of the atoms for Compounds 1, 2 and 3. The molecules shown in Figs. 2a, 2b and 2c were first geometry-optimized by allowing all the parameters of the molecule to relax to their optimum values. The results of the optimizations are shown in Table 1. Subsequently, since the point of the calculations is to investigate the steric hindrance between the substituents on the phenyl and the oxygen or the methyl group on the quinazolinone moiety, the dihedral angle C1C2N1C7, called angle α, was frozen at different values, such as 0, -30, -60, -120, -150 and -180 degrees and the molecules were optimized by allowing all the parameters except the angle α to relax to their optimum values.

Table 2 shows the optimized values of the parameters belonging to the hindrance region for different values of α. Table 3 shows the energies of the three compounds at the stationary point as well as for the conformations corresponding to different α's.

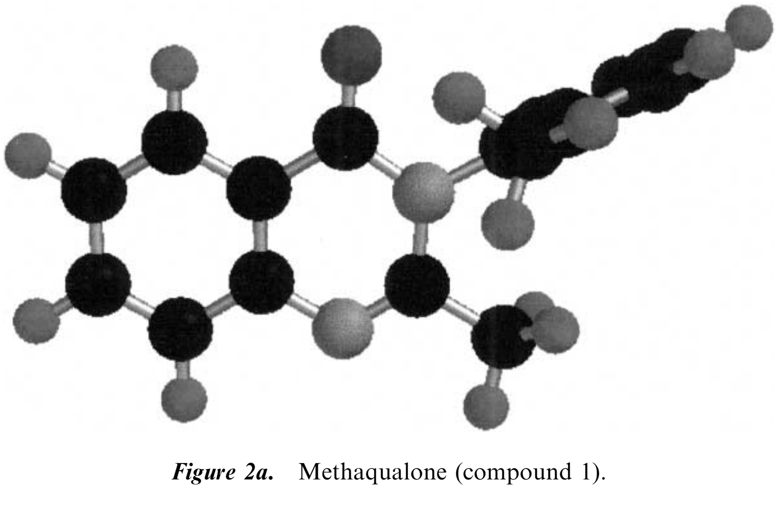


Figure 2a. Methaqualone (compound 1).

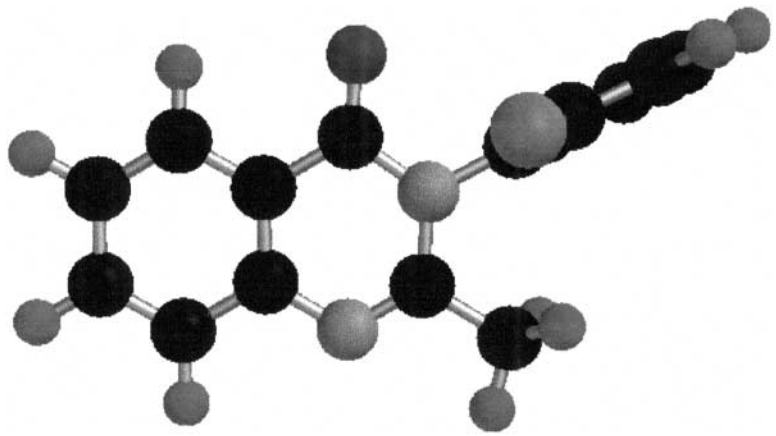


Figure 2b. Mecloqualone (compound 2).

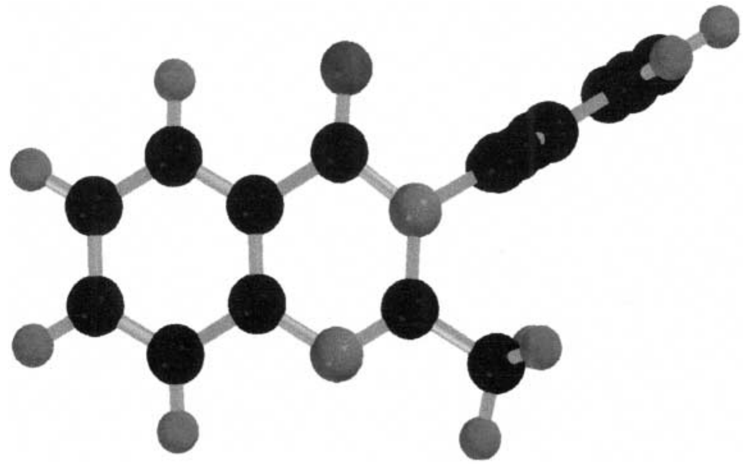


Figure 2c. 3-(2,6-difluorophenyl)-2-methyl-4(3H)-quinazolinone (compound 3).

Figures 3, 4 and 5 show the dependency of geometrical parameters of the molecules on α. Figures 6, 7 and 8 show the molecules in their state of highest hindrance.

The solvation energies of the three compounds in their different conformations are calculated using the SM5.4 method based on the model of Cramer and Truhlar[8]. The results are shown in Table 4.

Table 1. Optimized Geometric Parameters at 6-31G* Lengths in Angstroms, Angles in Degrees

Bond Angle	Compound 1 Optimized 85.04°	Compound 2 Optimized 90.86°	Compound 3 Optimized 90.61°
C1-C2	1.393	1.387	1.382
C2-C3	1.390	1.385	1.377
C3-C4	1.386	1.384	1.385
C4-C5	1.384	1.386	1.385
C5-C6	1.385	1.385	1.382
C6-C1	1.383	1.386	1.382
C1-N1	1.443	1.432	1.422
N1-C7	1.397	1.399	1.399
C7-O	1.198	1.196	1.196
C7-C8	1.466	1.465	1.463
C8-C9	1.389	1.389	1.389
C9-N2	1.384	1.386	1.386
N2-C10	1.269	1.267	1.266
C10-C11	1.505	1.504	1.503
C8-C12	1.399	1.398	1.398
C12-C13	1.373	1.373	1.372
C13-C14	1.401	1.401	1.399
C14-C15	1.374	1.374	1.373
C15-C9	1.400	1.399	1.399
C10-N1	1.387	1.389	1.388
C2-C16	1.510	–	–
C2-Cl	–	1.738	–
C6-F2	–	–	1.322
C2-F1	–	–	1.322
C1C2C3	117.62	120.52	122.47
C2C3C4	121.43	119.74	118.39
C3C4C5	120.08	120.20	121.05
C4C5C6	119.30	119.66	118.42
C5C6C1	120.22	120.70	122.43
C2C1N1	120.06	121.45	121.40
C1N1C7	117.22	116.68	116.23
N1C7C8	114.38	114.13	114.02
N1C70	121.06	120.88	120.81
C7C8C9	118.94	119.00	119.01
C8C9N2	121.99	122.07	122.14
C9N2C10	118.99	119.08	119.01
N2C10C11	118.16	118.55	118.84
C7C8C12	120.32	120.21	120.23
C8C12C13	119.72	119.70	119.75

(*Continued)*

Table 1. Continued

Bond Angle	Compound 1 Optimized 85.04°	Compound 2 Optimized 90.86°	Compound 3 Optimized 90.61°
C12C13C14	119.63	119.62	119.61
C13C14C15	120.97	120.98	120.97
C15C9N2	118.81	118.74	118.76
C14C15C9	119.74	119.73	119.81
C10N1C1	121.00	121.21	121.53
C16C2C1	121.52	–	–
C16C2C3	120.85	–	–
ClC2C1	–	120.63	–
ClC2C3	–	118.86	–
F1C2C1	–	–	118.15
F2C6C1	–	–	118.17
Dihedral angle			
C1C2C3C4	0.52	0.42	0.73
C2C3C4C5	0.34	0.21	−0.25
C3C4C5C6	−0.40	−0.24	0.20
C4C5C6C1	−0.40	−0.35	−0.61
C5C6C1N1	−178.96	−179.68	−178.21
C6C1N1C7	−94.71	−88.47	−86.39
N1C1C2C3	178.92	179.67	178.16
C2C1N1C7	85.04	90.86	90.61
OC7N1C1	−1.80	0.46	0.01
OC7C8C9	−178.83	179.42	−179.97
C7C8C9N2	0.05	0.11	−0.03
C8C9N2C10	−0.61	0.10	0.03
C9N2C10C11	179.93	179.90	179.93
C8C12C13C14	0.07	0.00	0.01
C12C13C14C15	−0.02	0.02	−0.01
C14C15C9N2	179.84	−179.92	−179.99
C10N1C1C6	85.14	91.97	93.62

DISCUSSION

NMR studies in related compounds indicated the change in hybridization of a nitrogen atom (from sp^2 to sp^3), in order to alleviate the steric hindrance produced by the co-planarity of a phenyl ring with the moiety which contains the nitrogen (1a).

Other theoretical calculations[3] also examined in detail the deformations associated with hindered rotations of a bridgehead phenyl about a C(sp^2)-C(sp^3) bond. In addition, the phenyl carbon bound to that nitrogen

Table 2. Parameters for the Hindered Region

	$\alpha = -0°$			$\alpha = -30°$			$\alpha = -60°$		
Parameter	Compound 1	Compound 2	Compound 3	Compound 1	Compound 2	Compound 3	Compound 1	Compound 2	Compound 3
N1C1	1.466	1.464	1.447	1.454	1.445	1.443	1.444	1.429	1.423
N1C7	1.406	1.428	1.416	1.406	1.414	1.411	1.399	1.400	1.402
N1C10	1.429	1.432	1.435	1.406	1.409	1.408	1.392	1.393	1.392
C10C11	1.518	1.517	1.513	1.510	1.510	1.507	1.506	1.514	1.504
C1C2	1.406	1.402	1.398	1.396	1.394	1.390	1.393	1.407	1.385
C1C6	1.411	1.408	1.411	1.398	1.397	1.393	1.388	1.405	1.382
C7O	1.192	1.192	1.190	1.196	1.193	1.194	1.197	1.231	1.195
C1N1C7	124.22	118.58	121.36	119.66	118.68	117.79	118.00	117.05	116.46
C10N1C1	115.63	116.12	114.52	118.15	117.94	118.47	120.43	120.50	121.33
N1C1C6	109.41	112.48	112.10	114.31	115.70	117.90	117.34	118.45	121.30
C2C1N1	129.33	127.57	129.20	124.51	124.99	124.09	121.60	122.18	121.45
OC7N1	123.42	119.51	122.44	121.67	120.91	121.22	121.40	125.26	120.96
C11C10N1	121.23	122.28	120.36	119.71	119.64	119.05	118.38	118.19	117.98
C6C1N1-C10	−56.50	−66.16	−69.46	−69.48	−73.10	−76.09	−75.11	−79.25	−76.16
C2C16	1.523	–	–	1.514	–	–	1.510	–	–
C2Cl	–	1.751	–	–	1.741	–	–	1.731	–
ClC2C1	–	122.91	–	–	122.20	–	–	122.20	–
C2F1	–	–	1.318	–	–	1.319	–	–	1.319
C6F2	–	–	1.329	–	–	1.326	–	–	1.325
F1C2C1	–	–	121.27	–	–	119.36	–	–	119.40
F2C6C1	–	–	117.80	–	–	118.15	–	–	118.27

Lengths (angstroms), Angles x(degrees)

α = −90°			α = −120°			α = −150°			α = −180°		
Compound 1	Compound 2	Compound 3	Compound 1	Compound 2	Compound 3	Compound 1	Compound 2	Compound 3	Compound 1	Compound 2	Compound 3
1.442	1.432	1.422	1.444	1.433	1.424	1.451	1.438	1.434	1.449	1.436	1.421
1.397	1.399	1.399	1.400	1.401	1.402	1.407	1.408	1.412	1.418	1.420	1.432
1.387	1.389	1.388	1.392	1.395	1.393	1.411	1.416	1.412	1.429	1.438	1.427
1.505	1.504	1.503	1.506	1.506	1.505	1.510	1.510	1.508	1.516	1.515	1.513
1.393	1.387	1.382	1.389	1.387	1.381	1.394	1.393	1.386	1.406	1.403	1.399
1.383	1.386	1.382	1.392	1.389	1.386	1.396	1.395	1.395	1.398	1.397	1.399
1.198	1.196	1.196	1.197	1.196	1.195	1.196	1.196	1.194	1.191	1.191	1.182
117.24	116.72	116.24	117.20	116.95	116.06	118.46	118.32	115.43	123.28	122.82	124.42
120.98	121.20	121.52	120.79	121.32	121.46	118.97	119.13	119.93	120.01	120.13	123.19
118.61	119.40	121.31	118.32	119.70	121.17	119.62	120.96	121.40	121.18	122.39	125.95
120.05	121.41	121.39	120.70	121.32	121.92	119.52	120.23	121.30	120.13	121.00	120.83
121.07	120.87	120.81	121.26	121.08	120.78	122.11	122.02	120.59	125.21	125.05	124.31
117.93	117.84	117.57	118.65	118.65	118.41	120.33	120.23	120.49	121.53	121.29	120.64
−85.60	−91.97	−92.92	−102.56	−103.26	−105.18	−109.86	−109.54	−102.85	−141.30	−139.58	−164.85
1.510	–	–	1.513	–	–	1.518	–	–	1.523	–	–
–	1.738	–	–	1.741	–	–	1.748	–	–	1.754	–
–	120.62	–	–	121.00	–	–	120.92	–	–	121.64	–
–	–	1.322	–	–	1.325	–	–	1.329	–	–	1.332
–	–	1.322	–	–	1.319	–	–	1.318	–	–	1.319
–	–	118.16	–	–	118.41	–	–	118.19	–	–	118.78
–	–	118.16	–	–	118.40	–	–	119.66	–	–	121.57

Table 3. Energies (au) at 6-31G* vs. α

α	Compound 1	Compound 2	Compound 3
Optimized	−797.85433	−1217.71325	−956.51459
−0°	−797.79894	−1217.65245	−956.46429
−30°	−797.83195	−1217.68797	−956.49655
−60°	−797.85049	−1217.70803	−956.51251
−90°	−797.85434	−1217.71326	−956.51459
−120°	−797.84840	−1217.70907	−956.51186
−150°	−797.83176	−1217.69280	−956.49386
−180°	−797.80215	−1217.66304	−956.45506

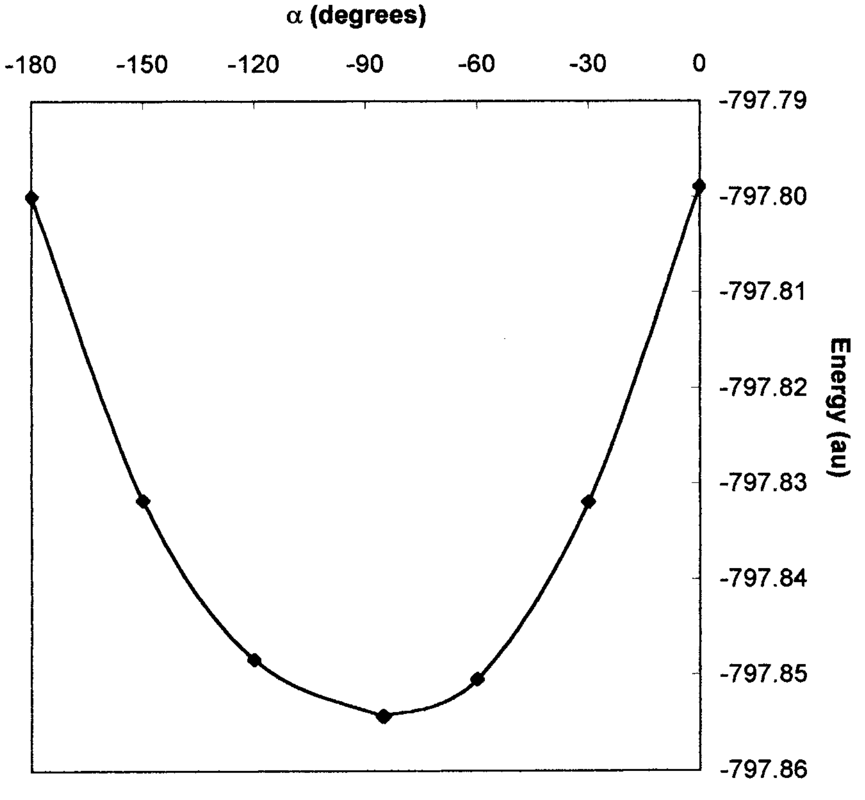


Figure 3. Graph of methaqualone energy vs. α@6-31G*.

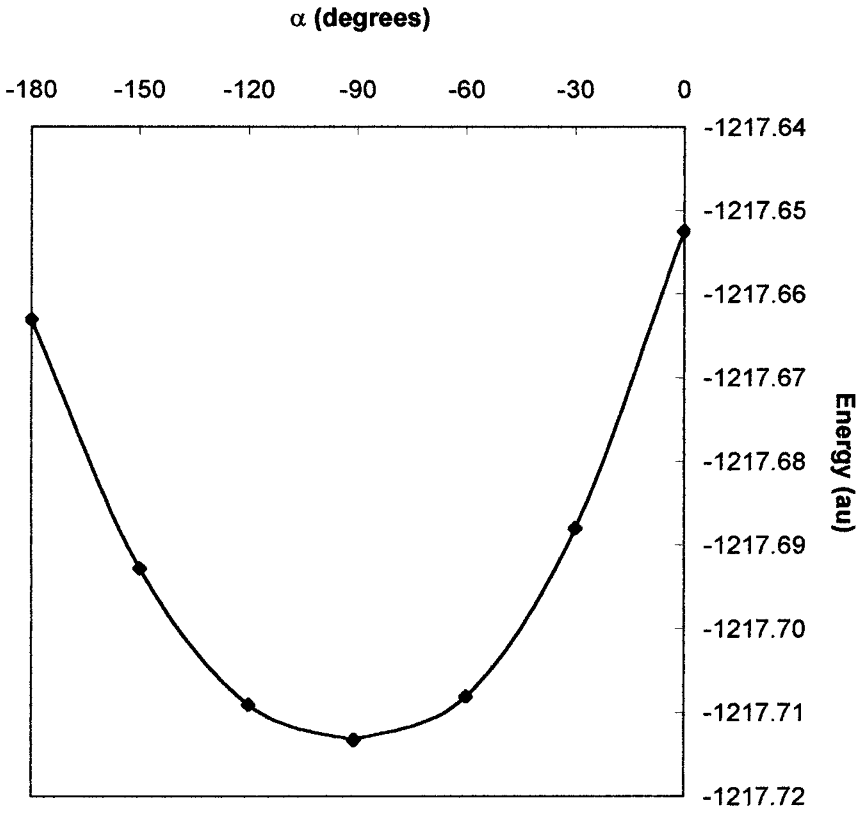


Figure 4. Graph of mecloqualone energy vs. α@6-31G*.

also changes hybridization, acquiring sp^3 character, leading to the nonplanarity of the phenyl ring.

The same process is observed for the N1 and C1 atoms in the three compounds investigated in this work.

Examining Table 3, one sees that for mecloqualone and methaqualone, the highest energies are obtained for α = 0°, while for Compound 3, the highest energy is obtained for α = 180°. These conformations, shown in Figs. 6, 7 and 8, indicate the significant distortions present in the phenyl ring, as well as the distortion from planarity of the N1 region, corresponding to the change in hybridization of N1. The changes, due to the attempt of the molecule to alleviate the steric hindrance, are observed by examining Table 2 and Figs. 3, 4 and 5. For example, the C1C2 and the C1C6 bonds are elongated in the high steric hindrance conformations, as opposed to the

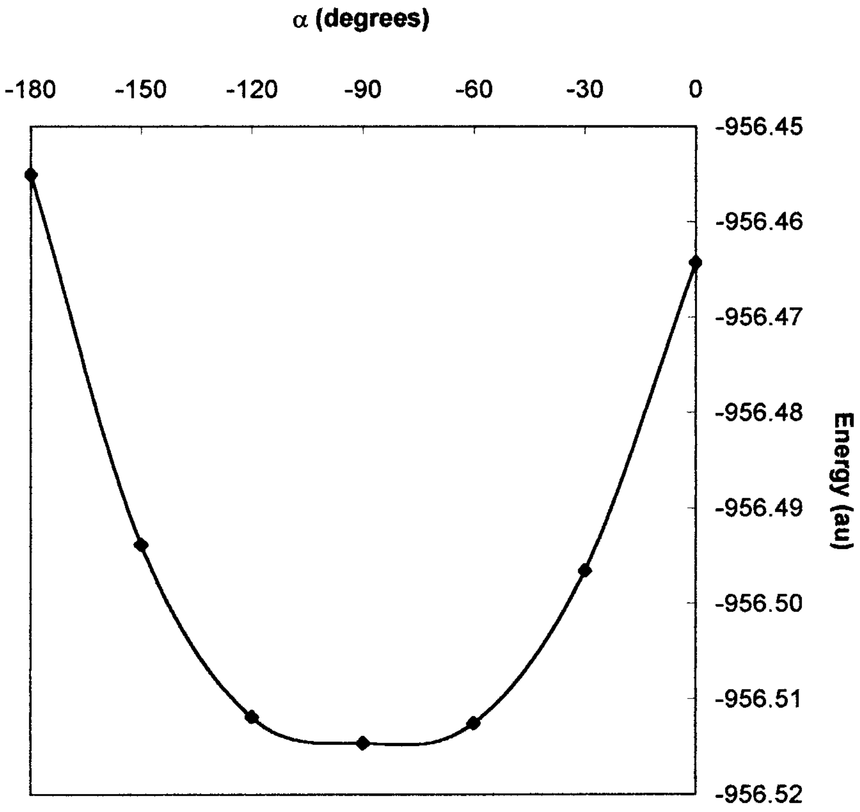


Figure 5. Graph of 3-(2,6-difluorophenyl)-2-methyl-4(3H)-quinazolinone energy vs. α@6-31G*.

optimized ones, in all three compounds. C1C6 increases by as much as 0.028 angstroms in methaqualone. The C1N1 bond length also increases significantly for the conformations with α = 0° and 180°. For Compound 3, one observes the maximum length of C1N1 for α = 150°. This effect might be due to the steric hindrance present on both sides and not compensated enough by the angular and dihedral angular deformations, so lengthening of the C1N1 bond becomes necessary.

The same effect is observed with the angles that, by increasing, relieve the hindrance. For instance, in methaqualone, the C1N1C7 angle increases by 7 degrees from the optimized conformation to the one with α = 0°. The angle C2C1N1 increases by 9.2, 6.1 and 7.8 degrees for Compounds 1, 2 and 3 respectively from the optimized state to the α = 0° conformation.

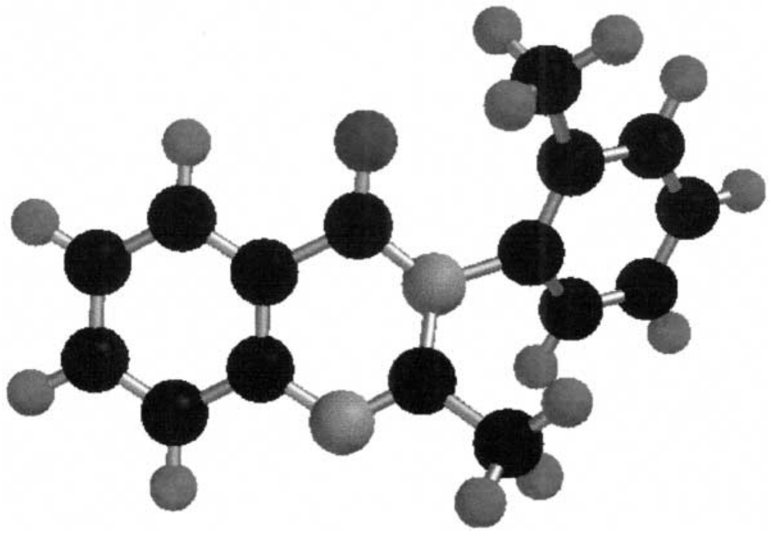


Figure 6. Methaqualone $\alpha = 0°$.

The variation of the dihedral angles is even more spectacular. For all three compounds, at their optimized conformations, the angle α and the angle C10N1C1C6 are almost equal. However, in highly hindered conformations ($\alpha = 180°$), there is a 56 degrees difference between α and C10N1C1C6 for methaqualone, 48 degrees for mecloqualone and 71 degrees for Compound 3.

Several indicators can be used to illustrate and characterize the striking array of deformations in the three compounds for the severely hindered conformations with $\alpha = 0$ or 180 degrees. Pyramidalization at N1 can be indicated by measuring its distance from the plane defined by the three attached atoms, C1C7C10. For $\alpha = 0°$, the distances were 0.214, 0.264 and 0.264 angstroms for Compounds 1, 2 and 3, respectively, and for $\alpha = 180°$, the corresponding distances were 0.215, 0.224 and 0.125 angstroms. Substantial pyramidalization is also observed at C1 in the substituted phenyl ring. Here, the three directly bonded atoms of C2C6N1 define the relevant reference plane, and distances from C1 to this plane (at $\alpha = 0°$) were 0.184, 0.209 and 0.219 angstroms for Compounds 1, 2 and 3, respectively. At $\alpha = 180°$, the corresponding distances were 0.050, 0.053 and 0.026 angstroms. Rather surprisingly, larger distances from C1 to the plane were seen when $\alpha = 150°$ than when $\alpha = 180°$, with values of 0.094, 0.091 and 0.132 angstroms respectively.

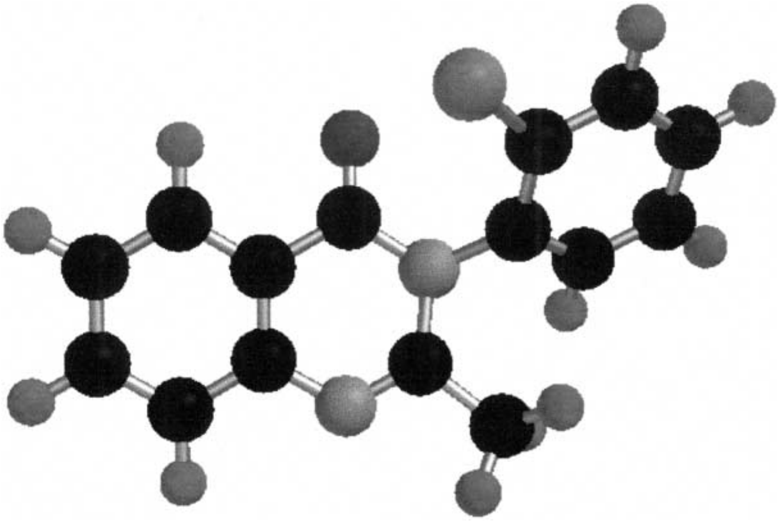


Figure 7. Mecloqualone $\alpha = 0°$.

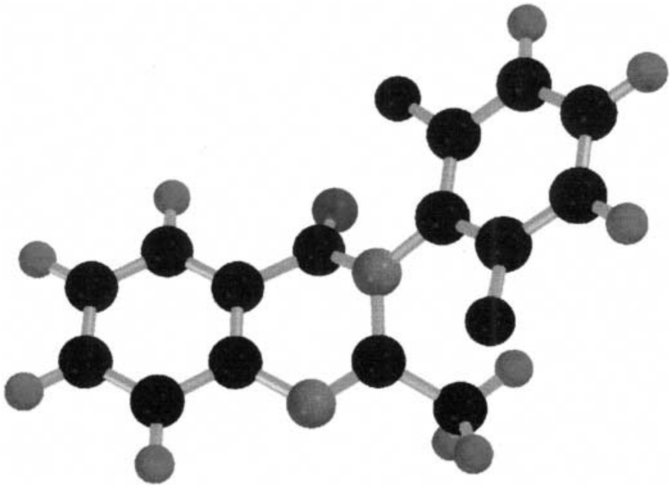


Figure 8. 3-(2,6-difluorophenyl)-2-methyl-4H(3H)-quinazolinone $\alpha = 180°$.

Table 4. Solvation Energies (au) at 6-31G* vs. α

α	Compound 1	Compound 2
Optimized	−6.224	−7.48
−0°	−5.771	−8.03
−30°	−6.072	−7.68
−60°	−6.043	−7.56
−90°	−6.228	−7.48
−120°	−6.302	−7.02
−150°	−5.841	−6.49
−180°	−5.558	−6.00

Finally, we defined a reference plane of C13, C14 and C15 to characterize distortions involving the "amide" moiety of the carbonyl and N1. The atoms comprising this reference plane were selected because of their remote location relative to the region of greatest hindrance. With respect to this plane, the carbonyl oxygen was displaced by 0.056, 0.086 and 0.061 angstroms (for α = 0°, 30° and 180°) in Compound 1. In Compound 2, the oxygen displacements were 0.298 and 0.035 angstroms (for α = 0° and 180°, respectively) and in Compound 3 the distances were 0.092 and 0.299 angstroms (for α = 0° and 180°). At C7, displacements were 0.146, 0.090 and 0.138 angstroms for Compounds 1, 2 and 3 (at α = 0°), and 0.183, 0.205 and 0.137 angstroms (at α = 180°). The most dramatic displacements from the plane of C13C14C15 were found for N1. Distances of 0.586, 0.095 and 0.542 angstroms (at α = 0°) increased to 0.783, 0.826 and 0.829 angstroms (at α = 180°) for the three compounds. This suggests the profound distortions in the heterocyclic ring in response to highly hindered conformations.

The rotational barriers correspond to the differences in energy from the optimized conformations to the highest energy and second highest energy conformations. In the case of methaqualone and mecloqualone, the highest conformations are those with α = 0° and for Compound 3 the highest conformation features α = 180°. The values of the higher rotational barriers are: 34.77, 38.15 and 37.36 Kcals/mol for the three compounds respectively. The values of the lower rotational barriers are: 32.75, 31.51, and 31.56 Kcals/mol for the three compounds respectively. The lower rotational barriers correspond to rotating α to 180° for methaqualone and mecloqualone, and to 0° for Compound 3.

The solvation energies do not show any correlation with the gas-phase energies of the conformations. For instance, for mecloqualone, the highest energy conformation also features the highest solvation energy, while in the case of methaqualone the highest solvation energy is found for $\alpha = 120°$. This may be explained if the accumulation of the negative charge on the chlorine and oxygen in the same region leads to an increased solvation energy.

Such theoretical results should stimulate experiments and calculations relating to the activity of the molecules in terms of binding to receptors located in the central nervous system.

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