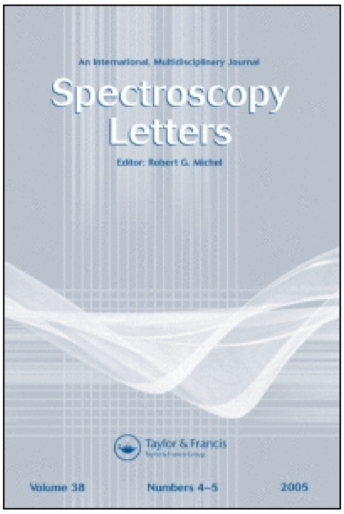

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Conformational and Structural Analysis of 6-(4-Methoxy-phenyl)-1,5,7a-triphenyl-tetrahydro-imidazo-[1,5-*b*][1,2,4]oxadiazol-2-one

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ABSTRACT

The cis stereochemistry of 6-(4-methoxy-phenyl)-1,5,7a-triphenyl-tetrahydro-imidazo[1,5-*b*][1,2,4]oxadiazol-2-one was studied by use of a PM3 semi-empirical quantum mechanical model, and x-ray crystallographic analysis. It crystallizes in the monoclinic space group $P2_1/n$ with $a = 10.812(1)$ Å, $b = 16.464(2)$ Å, $c = 13.379(1)$ Å, $\alpha = 90.00^\circ$, $\beta = 98.39(1)^\circ$, $\gamma = 90.00^\circ$, $V = 2356.07(4)$ Å^3, $Z = 4$, $D_{calc} = 1.3067$ g cm^{-3}, F(0 0 0) = 976.41, and $\mu = 0.086$ mm^{-1}. The structure was solved by direct methods and refined to $R = 0.066$ for 1257 independent reflections [$I > 4\sigma(I)$]. The results from x-ray diffraction were seen to

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be generally consistent with the results from previously reported spectroscopic investigations, beside theoretical calculations, except for conformations of five-membered fused heterocycles. Two inter- and intramolecular weak interactions in addition to carbon atoms (C1 and C3) with different chiralities were found in the structure. The conformational study was performed by randomly scanning the potential energy surface belonging to the title compound with respect to selected torsion angles.

Key Words: Crystal structure; PM3; *cis*-Imidazo[1,5-*b*][1,2,4]oxadiazol-2-one; 1,3-Dipolar cycloaddition.

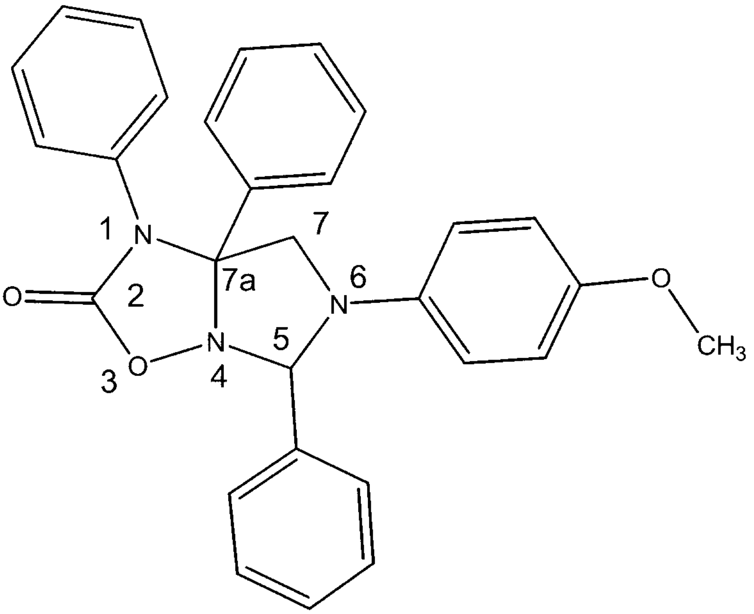
1. INTRODUCTION

1,3-dipolar cycloadditions of nitrones, with a variety of dipolarophiles occupy an important place among the methods for the synthesis of five-membered heterocyclic compounds.[1–4] In our recent work, we reported the regio- and diastereoselectivity of the 1,3-dipolar cycloadditions of imidazoline 3-oxides with dipolarophiles as isocyanates,[5,6] nitrile oxides,[7] DMAD,[8] and carbohydrate-derived nitrones[9–11] and oximes.[12] The steric hindrance of the aryl group at C-2 on the nitrone was assumed to be responsible for the approach of the 2π fragment from the opposite side thus leading to the formation of *cis*-imidazooxadiazolones. The cis structure of the tetrahydroimidazo adducts was tentatively assigned on the basis of nuclear Overhauser effect (NOE) experiments in the case of isocyanate adducts. These adducts were obtained from the imidazoline 3-oxides with DMAD, and isothiocyanates, and were shown to undergo concerted double cis elimination with secondary amines.[8] The DMAD adduct proved unequivocally to be the cis isomer by x-ray crystallographic analysis.

Herein, we report for the first time the stereoconfiguration and conformation of 6-(4-methoxy-phenyl)-1,5,7a-triphenyl-tetrahydro-imidazo[1,5-][1,2,4]oxadiazol-2-one, which is illustrated in Sch. 1, as an example of a 1,3-dipolar cycloaddition product of imidazoline 3-oxides with aryl isocyanates, by use of the x-ray diffraction method. The crystal structure and conformational aspects relating to the title molecule are also reported.

2. EXPERIMENTAL AND THEORETICAL SECTION

The racemate of 6-(4-methoxy-phenyl)-1,5,7a-triphenyl-tetrahydro-imidazo[1,5-*b*][1,2,4]oxadiazol-2-one was obtained in 90% yield according to the procedure previously described.[5,6] Suitable crystals were obtained as



Scheme 1. Chemical structure of the title molecule.

a white prism after recrystallization from acetonitrile. The measurements associated with single crystal x-ray diffraction were performed at room temperature on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromatic Mo K_α radiation of wavelength 0.71093 Å, and all intensities that belonged to the reflected x-ray beams were measured in $\omega/2\theta$ scanning mode. The cell constants and orientation matrix were determined by least-squares refinement of the diffractometer angles for 25 reflections collected in the range $2.58^\circ < \theta < 23.11^\circ$. Three standard reflections were selected and monitored every 120 min but no significant intensity decay was recorded (<1%). Also, using 25 centered reflections changing in the above range, unit cell parameters and some additional data were obtained as follows: $a = 10.812(1)$ Å, $b = 16.464(2)$ Å, $c = 13.379(1)$ Å, $\alpha = 90.00^\circ$, $\beta = 98.39(1)^\circ$, and $\gamma = 90.00^\circ$ in centric and monoclinic packing system and in $P2_1/n$ space group, $M = 463.52$ a.m.u., $V = 2356.07(4)$ Å^3, $Z = 4$, $D_{\text{calc}} = 1.3067\,\text{g cm}^{-3}$, $F(000) = 976.41$, and $\mu = 0.086\,\text{mm}^{-1}$. A total of 3285 reflections ranging through the Miller indices $0 < h < 11$, $0 < k < 18$, $-14 < l < 14$ were recorded. The intensities were corrected for Lorentz broadening and polarization, but not for absorption. The structure was solved by a direct method via the SHELXS-97 program.[13] The E-map was calculated from the phase set with the best Combined Figure of Merit (CFOM) which revealed the position of all non-hydrogen atoms. The structure was refined using full-matrix least-squares techniques with all non-hydrogen atoms being anisotropic. Since the difference synthesis did not clarify the position of the H atoms, they were placed in calculated positions at distances of 0.93, 0.98, 0.97, and 0.96 Å for aromatic C–H, methine C–H, methylene C–H, and methyl C–H, respectively, from the corresponding carbon atoms and a riding model was used during the refinement process by SHELXL-97.[13] Also, each hydrogen atoms was isotropically refined in traditional manner owing to the fact that its scattering factors and size are considerably less than the other atoms in the title molecule. The refinement converged to $R(\text{obs.}) = 0.066$ and Goof $S = 0.953$ by using the I (intensity) values of 1257 reflections satisfying the $I > 4\sigma(I)$ criterion of observability and 3067 reflections in refinement for 317 crystallographic parameters. In addition, an extinction coefficient correction was carried out in the refinement process by use of SHELXL-97. A weighting scheme was used during the refinement $w = 1/[\sigma^2(F_0^2) + (0.0579P)^2]$, where $P = (F_0^2 + 2F_c^2)/3$. The highest peak and the deepest hole in the final difference map were 0.22 and $-0.23\,\text{e}\,\text{Å}^{-3}$, respectively.

Conformational searches were achieved by randomly scanning the potential energy surface computed by the PM3 semi-empirical method[14,15] using a spin-restricted Hartree–Fock (RHF)[16] level via application of the conjugate gradient method, called the Polak–Ribiere algorithm,[17] with RMS gradient 0.05 kcal Å^{-1} mol^{-1}. Throughout the conformational analysis, selected torsion angles [T1(C8–C9–N1–C2), T2(C13–C12–C1–N1), T3(C25–C24–N3–C3), and T4(C19–C18–C3–C2)] were randomly varied every 2° without changing the chiralities of the chiral centers, then the conformer was optimized on the potential energy surface. All of the calculations were performed by using the HyperChem 6.0 program.[18]

3. RESULTS AND DISCUSSION

Fractional atomic coordinates and equivalent isotropic displacement parameters for the non-hydrogen atoms are listed in Table 1. Selected bond distances and angles are listed in Table 2. The ORTEP[19] drawing shows the molecular structure of the title compound with thermal motions and in which is labeled its non-hydrogen atoms (Fig. 1). Unit cell packing diagram showing both inter- and intramolecular weak interactions is illustrated in Fig. 2. Details related to both inter- and intramolecular interactions, which can be regarded as extremely weak hydrogen bonding, are given in Table 3.

Table 1. Atomic coordinates and equivalent isotropic displacement parameters.

Atom	x (Å)	y (Å)	z (Å)	U_{eq} (Å)
O1	−0.1874(4)	0.2274(3)	−0.1730(3)	0.065(2)
O2	−0.0962(3)	0.2367(2)	−0.0105(3)	0.056(2)
O3	0.5531(4)	−0.0875(3)	0.1661(3)	0.067(2)
N1	0.2016(4)	0.1566(3)	0.0694(3)	0.040(2)
N2	0.0303(4)	0.2355(3)	0.0437(3)	0.045(2)
N3	0.0288(4)	0.2432(3)	−0.1287(3)	0.044(2)
C1	0.0672(5)	0.1471(3)	0.0599(4)	0.041(2)
C2	0.2265(5)	0.2121(3)	−0.0114(4)	0.052(2)
C3	0.1082(5)	0.2643(3)	−0.0337(4)	0.038(2)
C4	−0.0936(6)	0.2341(4)	−0.1122(5)	0.050(3)
C5	0.5149(6)	−0.1675(4)	0.1872(5)	0.083(3)
C6	0.4596(6)	−0.0328(4)	0.1418(4)	0.047(3)
C7	0.4973(5)	0.0445(4)	0.1232(5)	0.059(3)
C8	0.4125(6)	0.1068(4)	0.0986(4)	0.054(3)
C9	0.2849(5)	0.0915(3)	0.0917(4)	0.040(2)
C10	0.2483(5)	0.0142(4)	0.1108(4)	0.048(2)
C11	0.3344(5)	−0.0480(3)	0.1361(4)	0.049(3)
C12	0.0182(5)	0.1154(3)	0.1516(4)	0.037(2)
C13	0.0671(6)	0.1410(4)	0.2473(5)	0.057(3)
C14	0.0207(7)	0.1134(4)	0.3292(5)	0.069(3)
C15	−0.0771(7)	0.0615(4)	0.3188(5)	0.064(3)
C16	−0.1307(6)	0.0331(4)	0.2257(6)	0.063(3)
C17	−0.0816(5)	0.0613(3)	0.1412(5)	0.054(3)
C18	0.1293(5)	0.3556(3)	−0.0221(5)	0.043(2)
C19	0.1964(6)	0.3821(4)	0.0695(5)	0.058(3)
C20	0.2230(7)	0.4631(5)	0.0859(6)	0.073(3)
C21	0.1826(7)	0.5190(4)	0.0114(7)	0.070(3)
C22	0.1149(6)	0.4942(4)	−0.0777(6)	0.064(3)
C23	0.0885(5)	0.4121(4)	−0.0940(5)	0.053(3)
C24	0.0700(5)	0.2313(4)	−0.2235(4)	0.039(2)
C25	0.1704(5)	0.2733(4)	−0.2490(4)	0.050(2)
C26	0.2074(5)	0.2628(4)	−0.3411(4)	0.051(2)
C27	0.1473(6)	0.2092(4)	−0.4091(5)	0.059(3)
C28	0.0518(6)	0.1637(4)	−0.3828(5)	0.067(3)
C29	0.0099(6)	0.1749(4)	−0.2914(5)	0.058(3)

Note: ESDs are given in parentheses. U_{eq} is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

Table 2. Selected bond distances (Å), bond angles, and torsion angle (deg.).

Bond distances	X-ray	PM3	Bond angles	X-ray	PM3
O1–C4	1.209(8)	1.212	C5–O3–C6	115.8(5)	117.39
O2–N2	1.452(6)	1.509	C1–N1–C2	107.0(4)	108.93
O2–C4	1.366(8)	1.361	O2–N2–C1	107.1(4)	110.14
O3–C5	1.421(8)	1.406	O1–C4–O2	122.4(6)	116.92
O3–C6	1.357(8)	1.381	O2–N2–C3	103.5(4)	107.92
N1–C1	1.449(7)	1.505	N2–C3–N3	101.9(4)	103.28
N1–C2	1.470(7)	1.494	C3–N3–C4	109.9(4)	109.41
N1–C9	1.404(7)	1.447	N2–O2–C4	110.0(4)	107.94
N2–C1	1.516(7)	1.502	C1–N2–C3	103.8(4)	110.14
N2–C3	1.504(7)	1.511	N1–C1–N2	98.5(4)	106.69
N3–C3	1.468(7)	1.512	N2–C3–C2	103.0(4)	105.31
N3–C24	1.418(7)	1.443	O2–C4–N3	108.4(5)	111.71
C2–C3	1.534(7)	1.547	N3–C3–C18	112.4(4)	113.48
N3–C4	1.381(8)	1.430	N1–C2–C3	104.7(4)	107.68

Note: ESDs are given in parentheses and their values calculated by PM3 semi-empirical method.

Values of selected T1, T2, T3, and T4 torsion angles from the x-ray investigations are 44.2(7)°, 40.4(7)°, −31.5(9)°, and −52.2(7)°, respectively. When the experimental data (Table 2) are contrasted with results from theoretical calculations related to the optimized geometry of the title molecule, both of them are seen to be generally consistent. All the phenyl and substituted phenyl rings in the molecule, as expected, are nearly planar. The oxygen atom of the methoxy group lies in the same plane as the 4-methoxyphenyl.

The angle between planes that are, respectively, defined by the C18–C23 and C24–C29 atoms is 62.6(3)°. The fact that these phenyl rings have a different orientations relative to other phenyl rings can be explained by their dominating both weak interactions. Five-membered rings through O2, N2, C3, N3, and C4 atoms adopt a twisted conformation and the other through N1, C1, N2, C3, and C2 atoms adopts an envelope conformation. The C1 atom has a maximum deviation [−0.291(5) Å] from the average ring plane of five-membered rings, which consist of the N1, C1, N2, C3, and C2 atoms adopting an envelope conformation. C18⋯C23 and C12⋯C17 phenyl rings are attached to the five-membered ring under discussion as bisectional (neither pseudo-equatorial nor pseudo-axial) and pseudo-equatorial orientation to minimize steric interactions respectively. Additionally, the 4-methoxyphenyl ring is pseudo-equatorially linked to this ring, and finally, the

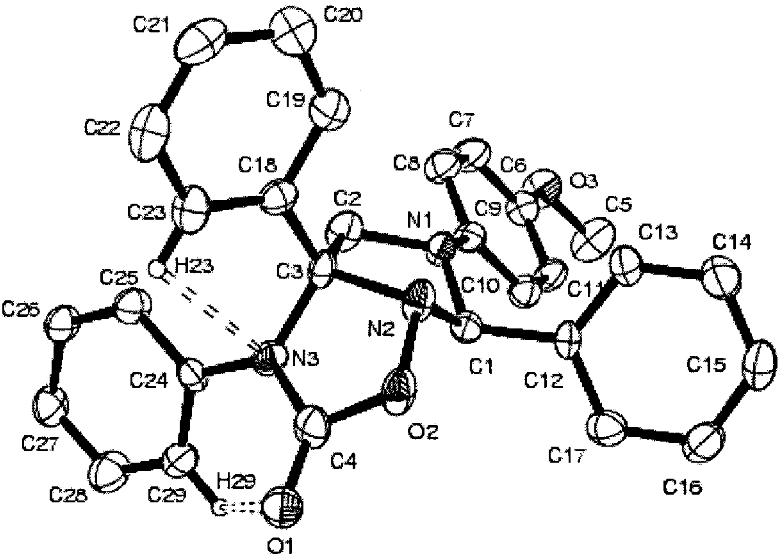


Figure 1. ORTEP drawing of the title molecule showing intramolecular weak interactions with the non-hydrogen atoms and their displacement ellipsoids at the 30% probability level.

phenyl ring C24 ··· C29 is also pseudo-equatorially attached to the twisted five-membered ring. The five-membered ring adopts a twisted conformation, and is fused with a ring having an envelope conformation by bonding (N2-pseudo-axial orientation, C3-bisectional). There are two asymmetric carbon atoms (C1 and C3) in the molecule. The C1 and C3 carbon atoms have *R* and *S* chiral configurations, respectively. In all reasoning related to clarify molecular and crystal structure, it can be stated that the structure is stabilized by both inter- and intramolecular weak interactions.

In order to define the conformational flexibility of the title molecule, semi-empirical calculations using the PM3 self-consistent field molecular orbital method was performed. The molecular energy can be thought as being separated into two parts. One is a bonded energy term, which is independent of changes in torsion angles, and the other is non-bonded, which depends on changes in torsion angles such as torsion, steric, and electrostatic contributions. Steric effects have been of great significance in the determination of conformational flexibility of a molecular system. In a conformational search, approximately 10^3 conformers were revealed that satisfied RMS gradient criteria. Some considerable conformers are listed in Table 4 with total energy and gradient values. One agreement with crystallographic results is

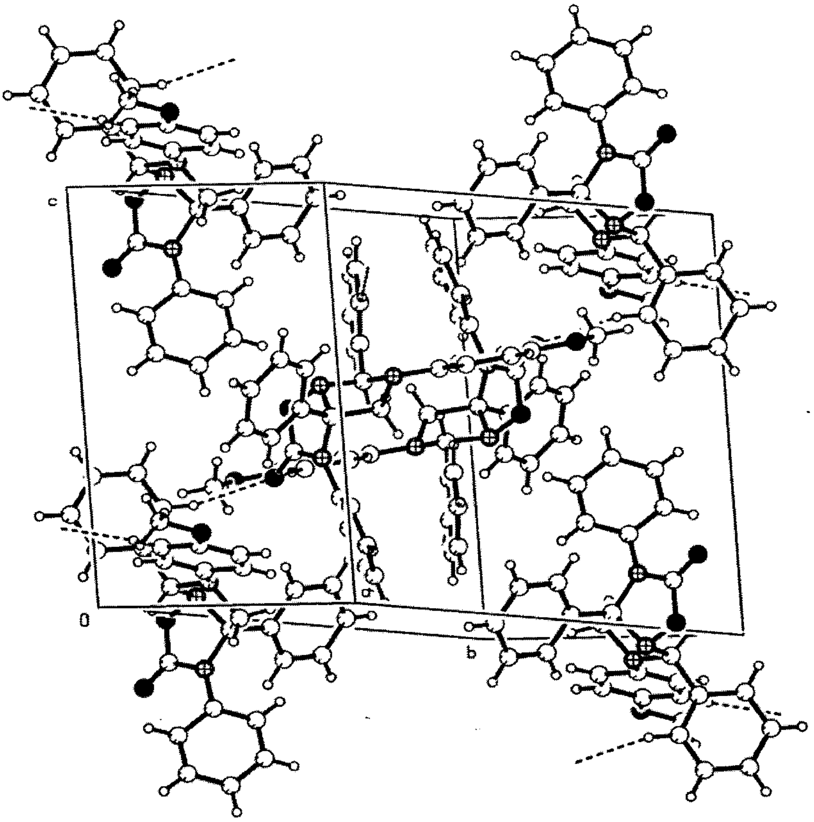


Figure 2. Molecular packing diagram in unit cell.

Table 3. Details related to both inter- and intramolecular weak interactions (Å, deg.).

D–H···A	D–H	H···A	D···A	D–H···A
C(11)–H(11)···O(1)[a]	0.930	2.509	3.424	168.09
C(29)–H(29)···O(1)	0.930	2.498	2.965	111.54
C(23)–H(23)···N(3)	0.930	2.539	2.877	101.70
C(13)–H(13)···O(1)[b]	0.930	2.565	3.471	164.73

[a] Symmetry code: −x, −y, −z.

[b] Symmetry code: (1/2) + x, (1/2) − y, (1/2) + z.

Table 4. Some conformers satisfying convergence criteria obtained by randomly scanning on potential energy surface via PM3 method.

Conformer	Energy	Gradient	T1	T2	T3	T4
1	−119574.8	0.001	35.66	31.31	−22.34	−58.68
2	−119580.3	0.051	−2.16	−71.48	72.51	57.07
3	−119580.2	0.050	173.53	116.48	−110.37	57.21
4	−119580.2	0.052	173.34	−66.61	−109.61	−121.99
5	−119579.4	0.048	170.35	−65.39	68.89	50.54
6	−119579.4	0.045	174.83	97.77	−115.65	−139.21
7	−119579.3	0.041	175.62	−85.00	−115.64	13.71
8	−119579.3	0.047	−0.02	103.16	−115.26	40.69
9	−119578.6	0.050	−159.13	−105.63	−113.77	−172.73
10	−119577.6	0.049	−46.91	45.59	−88.86	−158.75

Note: Torsion angles in (deg.), and energy and gradient values in kcal mol^{-1} and kcal $\mathrm{Å}^{-1}$ mol^{-1}, respectively.

conformer 1. The most evident difference between results from the x-ray investigation and the theoretical study is the conformation of the fused heterocycles at the core of the molecule (Table 5). According to the computational results, both the five-membered rings approximately adopt a nearly planar conformation, whereas according to results from the x-ray study, five-membered rings through C1–N1–C2–C3–N2 and N2–C3–N3–C4–O2 atoms adopt an envelope and twisted conformation, respectively. A reason for this situation is that the molecule is regarded as an isolated (or free) molecule without periodic boundary conditions.

4. CONCLUSIONS

In summary, the PM3 optimized geometry of the molecule is generally consistent with one crystallographically observed, except for the five-membered fused heterocyclic rings at core of the molecule. Any semi-empirical method, as well the PM3 method cannot take into account intra- and intermolecular interactions. For that reason, it is not astonishing that five-membered fused rings of the molecule prefer to be in nearly planar conformation as evidenced by different results obtained by x-ray crystallographic study. According to crystallographic and previously reported spectroscopic studies, molecular and crystal structures and conformational flexibility of the title molecule were elucidated, and it was shown that results obtained from each of these studies agree generally. During continuous

Table 5. Comparison of results between PM3 semi-empirical method and x-ray study for selected torsion angles (deg.).

Torsion	X-ray	PM3	Torsion	X-ray	PM3
C8–C9–N1–C2	44.1(7)	35.66	C8–C9–N1–C1	179.6(5)	166.6
C13–C12–C1–N2	−69.9(7)	−86.8	C13–C12–C1–N1	40.4(7)	31.31
C25–C24–N3–C4	150.4(6)	173.32	C25–C24–N3–C3	−31.5(9)	−22.33
C19–C18–C3–C2	−52.4(7)	−58.7	C19–C18–C3–N3	175.5(5)	172.1
C18–C3–N2–C1	−153.5(4)	−124.6	C12–C1–N2–O2	−83.3(5)	−122.3

Note: ESDs are given in parenthesis.

rotation, steric hindrances arising between ortho-hydrogens, to be regarded as non-bonded energy term, play an important role in determination of the conformational flexibility of the molecule. When contributions arising from both intra- and intermolecular contacts are contrasted with steric contributions, steric hindrances between ortho hydrogen atoms dominate the other interaction terms and make a leading contribution to the total energy for the molecule.

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