Condensed phase conformational isomerisation of 5-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propoxy]-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid methyl ester

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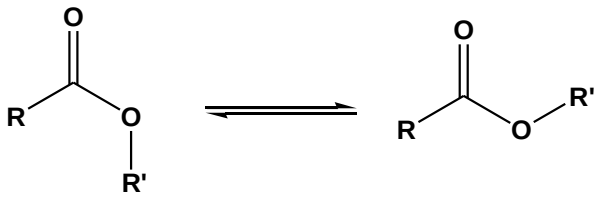
Abstract

Presence of ester group adjacent to methyl group in a pyrazole ring system results in a flexible hydrogen bond. This bond can be freely rotate to generate the conformational isomers. Conformational isomers can be separated if the barrier to rotation or the energy difference between the two configurations is large. In the present study, in solution state, this spinning is so fast that it was difficult to predict the conformational change whereas the condensation of molecules in solid state, existence of two conformations have been predicted.

Keywords: Conformation, isomers, interactions, equilibrium, NMR, X-ray crystallography

Introduction

The conformation of esters has been the subject of essential investigation from a very long back, revealing that the Z conformations of most esters are strongly favoured[1-3] by both steric interactions and dipole-dipole interactions over the E conformations (Figure 1). But it was also observed that in formate esters, the steric repulsion in E-conformer between the formyl hydrogen and R' will be smaller than the repulsion in the Z-conformations between the carbonyl oxygen and R', and the E-conformer will be favoured[3] by steric effects, although, such effects favour the E-conformers in these esters of formic acid, the Z-conformers have larger population due to other factors including more favourable dipole-dipole interactions.



E-conformer **Z**-conformer

Figure 1. Different conformations of ester.

It has been reported that compounds with Csp^2-Csp^2 bonds possess some double bond character[4] as they belong to conjugated systems. Such molecules have planar geometry and therefore, exist in two conformations, transoid (*s*-trans) and cisoid (*s*-cis). Examples with such systems are furfuraldehyde and 1,4-butadiene.[4] Since the energy required for interconversion is very small, conformers cannot be separated. The conformational preference of the acetyl group in 2-fluoroacetophenone has been discussed extensively.[5] The barrier to rotation about the Csp^2-Csp^2 exocyclic bond is estimated as 13 KJ/mol[6a] in vapour and 22.4 KJ/mol in solution.[6b] Molecular models for methyl-3-chlorobenzoate revealed that it exist in a conformational equilibrium of *s*-trans and *s*-cis form in a ratio of 70:30.[6c] On the basis of NMR data and INDO calculations, the *O*-trans conformer was found to be the most stable conformation for o- and m-fluorobenzaldehyde.[6d] Wasylishen and Schaefer suggested that electric moment measurements would provide conclusive evidence for the correct conformation of the fluorobenzaldehyde molecules. In case of *O*-trans conformation of o-fluoroacetophenone, the energy barrier to free rotation of the acetyl group is at least 5.643 KJ/mol and is high enough to prevent the free rotation of the acetyl group. O-Fluoroacetophenone exists in an equilibrium mixture of both conformers in ratio of 9/1 with the *O*-trans conformer predominating. For m-flouroacetophenone, the cis-trans energy barrier is at least 0.5434 KJ/mol and is evidently not high enough to prevent a free rotation of the acetyl group.[5a] VT (variable temperature) ^{1}H NMR spectroscopy[7] and X-ray single crystal studies[8] were extensively utilized for studying conformational behaviour of many compounds in solution state and in solid state, respectively. On lowering temperature, the molecule gets frozen and therefore rotation becomes restricted which is either reflected as splitting of related proton peak or shifting of peaks in proton NMR. X-ray crystallography provides clear view of different conformations in solid state. In view of these important properties, we attempted to extend our investigations as we prepared a number of pyrazole esters containing phenyl ring at N1-position and a trimethylene linker attached to oxygen at position 5 with different attachments. Only conformational isomers of compound **3** have been detected in condensed phase (Figure 2).

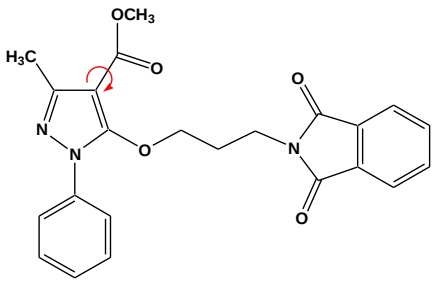
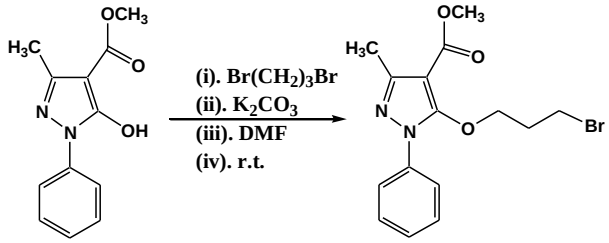


Figure 2. 5-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propoxy]-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid methyl ester **3**.

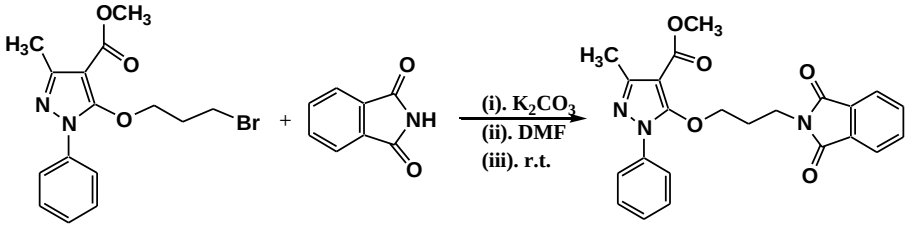
Results and Discussion

Compound **2** was synthesized by dissolving 5-Hydroxy-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid methyl ester **1**[9] in DMF along with 1, 3-dibromopropane and anhydrous K_2CO_3 for 18 hours at room temperature. Compound **3** was synthesized in a one pot synthesis by dissolving and stirring phthalimide, 5-(3-Bromo-propoxy)-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid methyl ester **2**, anhydrous K_2CO_3 in DMF for 24 hours at room temperature (Scheme 1 and 2). Crystals of **3** were obtained from 20% ethyl acetate in hexane solution at room temperature. The structure of **3** was well assigned and in accordance with ^{1}H NMR and ^{13}C NMR spectra.



1 **2**

Scheme 1



2 **3**

Scheme 2

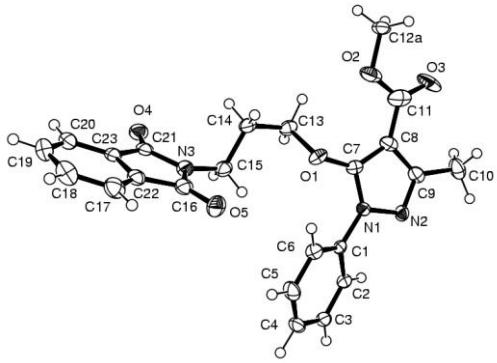
Unusual conformational properties of ester **3** were studied by performing VT ^{1}H NMR ($CDCl_3$; f.p. -64 ^oC). The spectra were recorded at different temperatures and the change was observed on cooling.

Table 1. Change in chemical shift of different proton signals in VT ^{1}H NMR spectra of **3**

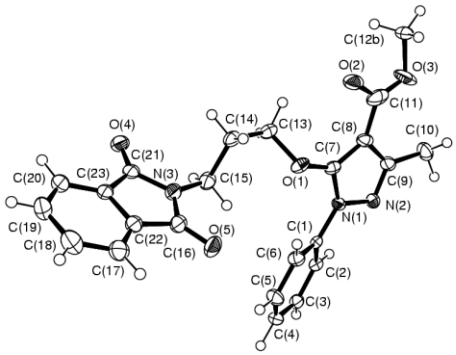
Temp.	Δ-value (ppm)				
(^oC)	-CH_3	-OCH_3	-CH_2-	-NCH_2	-OCH_2
25	2.456	3.821	2.066	3.730	4.255
5	2.466	3.831	2.063	3.734	4.253
-15	2.477	3.844	2.063	3.739	4.252
-35	2.488	3.858	2.059	3.746	4.249
-55	2.499	3.875	2.065	3.754	4.244

The maximum change in chemical shift of methyl protons indicated a downfield shift of 0.043 ppm only, the methoxy protons and NCH_2 linker protons indicated a downfield shift of 0.054 ppm and 0.024 ppm, respectively. Thus it can be explained as, the rotation around Csp^2-Csp^2 carbon-carbon single bond is very rapid and flipping so fast which maintains equilibrium between the two conformers in solution state and the spectra recorded indicates the most stable conformer only, but upon cooling, the molecule condensed which creates hindrance and restricts rotation around Csp^2-Csp^2 bond, but not much reasonable to predict the conformational change in solution state.

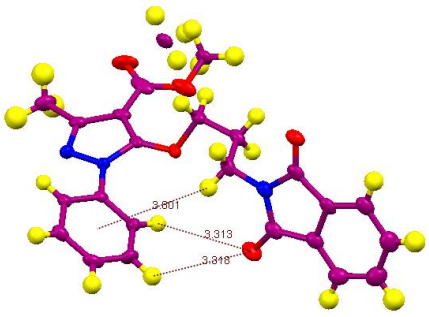
Probable conformations of ester **3** have been predicted in close packed solid state. The solid state single crystal X-ray analysis of **3** revealed the presence of two conformational isomers out of which one conformer predominates (75%) and other is minor conformer (25%). The major conformer was found to be the E-conformer in which the sp^2-sp^2 C (8)-C (11) bond system represents sterically more stable trans geometry (CH_3 and OCH_3 groups are present in slightly different planes with an angle of 7.67^o) whereas in case of minor less stable Z-conformer, the sp^2-sp^2 C(8)-C(11) bond system represents steric hindrance created due to the presence of bulky CH_3 and OCH_3 groups on same side. Even though, the Z-conformer is less stable but its existence was revealed in X-ray single crystal analysis. The DFT energy calculation also supported the fact that the E-conformer is more stable due to less energy and the energy difference among the two conformers was found to be 4.927 KJ/mole.



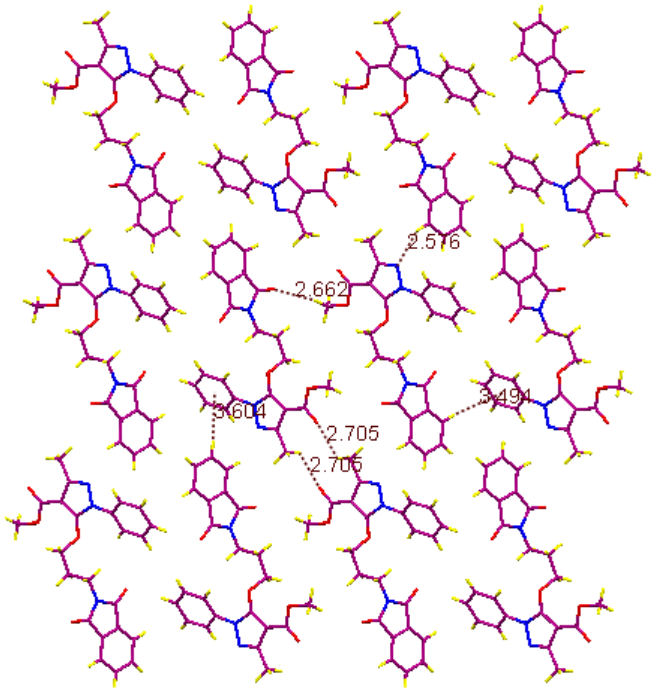
a. Major Orientation (75%)



b. Minor Orientation (25%)



c. Single molecule



d. Packing diagram

Figure 3. a and **b** represents ORTEP view of **3** in major and minor conformations; **c** is normal view of single molecule and **d** represents packing of **3**.

The calculations were performed using the Gaussian 03 package [10] and the B3LYP [11, 12] methods with the basis set of double-zeta quality, Pople's[13] 6-31G (d, p). The assignment of the calculated structure was aided by the animation option of Gauss View3.0 graphical interface for Gaussian programs, which give a visual presentation of the shape of the molecule.

The energy of E-conformer was found as -1429.5826 a.u. (-3754268.898 KJ/mole) and energy of Z-conformer was found to be -1429.5808 a.u. (-3754263.971 KJ/mole). This also supported that E-conformer is more stable because of less energy (energy difference being 4.927 KJ/mole). The energy difference between the two conformers is very small which causes rapid interconversion and restricts isolation. The cell parameters, space group and crystal structure were determined from single crystal X ray diffraction data collected at ambient temperatures. Compound **3** possesses monoclinic crystal system with $P2_1/c$ space group. Table 2 indicates the geometry of non-covalent interactions in **3**.

Compound **3** possess intramolecular as well as intermolecular network of various non-covalent interactions (like C-H···π, C-H···O, C-H···N, π···O-C, π···N-C, C-N···O, C-C···O, O···O) out of which C-H···π[8a-e] and C-H···O[14b-g] interactions seems to play major role in stabilizing assembly of molecules of **3**. These were indicated in ORTEP and packing diagrams through different axes (Figure 3). Compound **3** is an asymmetrical molecule in which the pyrazole moiety and phthalimide moiety are attached through propylene (Leonard)[15] linker. The molecule is non-planar in which the pyrazole ring lies in one plane and the N-phenyl ring lies in another plane (or it is slightly twisted out of the plane of pyrazole ring). The pyrazole and N-phenyl rings make an angle of 72.69° to each other.

Table 2. Geometry of non-covalent interactions in **3**

a. Intramolecular interactions

S.No.	Interaction	C-H/ O···O (A°)	C-H···O (°)
1.	C-H-(15B)···O(5)	2.500	104.74
2.	C-H(14A)···O(4)	2.930	112.08
3.	C-H(15B)···O(1)	2.604	99.94
4.	C-H(13B)···O(2)	2.286	132.17
5.	C-H(10C)···O(3)	2.807	89.62
6.	O(1)···O(2)	3.037	-

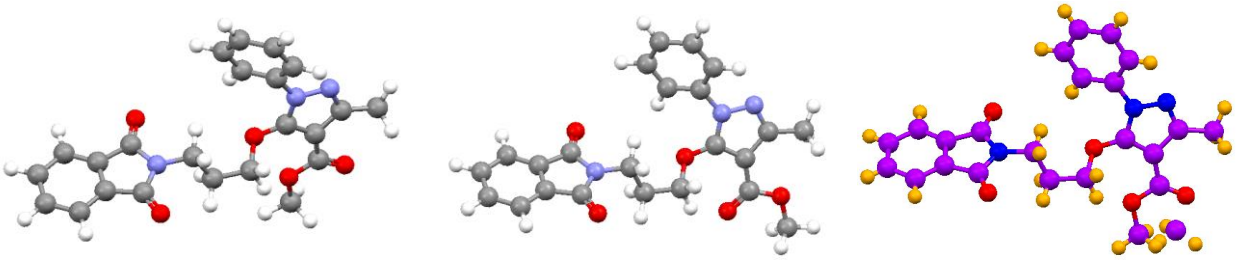
b. Intermolecular interactions

S.No.	Interaction	C-H···π/ O/ N distance in A°(angastron) (angle in degree)
1.	C-H(17)···π (pyrazole)	3.550 A° (85.44°)
2.	C-H(2)···π (phthalimide-6-membered ring)	3.360 A° (139.24°)
3.	C-H(2)···π (phthalimide-5-membered ring)	3.203 A° (104.36°)
4.	C-H(12A)···π (phthalimide-5-membered ring)	3.633 A° (104.50°)
5.	C-H(10B)···π (phthalimide-6-membered ring)	3.644 A° (141.97°)
7.	C-H(14A)···π (phenyl)	3.202 A° (103.67°)
8.	C-H(14B)···π (phenyl)	2.924 A° (122.77°)

Table 2. Continued
b. Intermolecular interactions

S.No.	Interaction	C-H···π/ O/ N distance in A^o(angastron) (angle in degree)
9.	O(3)···π (phthalimide-6-membered ring)	3.677 A^o
10.	O(2)···π (phthalimide-5-membered ring)	3.295 A^o
11.	N(2)···π (phthalimide-6-membered ring)	3.680 A^o
12.	C-H(10C)···O(3)	2.705 A^o (130.09^o)
13.	C-H(13A)···O(5)	2.367 A^o (173.13^o)
14.	C-H(15A)···O(1)	2.514 A^o (134.08^o)
15.	C-H(4) ···O(5)	2.367 A^o (173.13^o)
16.	C-H(20) ···N(2)	2.575 A^o (127.16^o)
17.	C-H(5) ···O(5)	3.207 A^o (11.58^o)

Optimized stereochemistry is different than crystal stereochemistry and plane formed by different ring have different angle with respect to each other, there are three rings in molecule and three planes are formed by these rings and angle formed by these planes are 79.21°, 87.69°, 84.76° between 9 membered bicyclic ring and 6 member ring in crystal and optimized E, Z structure, angle between 9 membered bicyclic ring and 5 member ring is 66.96°, 74.84°, 61.65° respectively and angle between 6 and 5 membered rings are 32.0°, 38.97°, 35.40° respectively. These angles represent that weak interactions are present in this molecule due to which the actual stereochemistry of **3** is different than stereochemistry of both optimized structures, so we can conclude by this optimized structure that in this compound non covalent interactions play an important role in its stereochemistry. The optimized structures of **3** were shown in Figure 4.



a **b** **c**

Figure 4. Optimized structures of **3** in both conformations **a.** E-conformer **b.** Z-conformer and **c** represents ball and stick view of crystal of **3**.

Conclusions

We have reported the existence of two conformational isomers in **3**. The results were supported by single crystal X-ray studies and DFT calculations for solid state and VT ^{1}H NMR for solution state. The molecular assembly was controlled mainly by C-H···O and C-H···π networks.

Experimental Section

Synthesis of 5-(3-Bromo-propoxy)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid methyl ester (2). Anhydrous K_2CO_3 (1.78 g, 0.0129 mol) and **1** (3 g, 0.0129 mol) were added in 20 ml DMF and stirred for 30 minutes. 1, 3-Dibromopropane (1.31 ml, 0.0645 mol) was added and stirred at room temperature for 30 hours. TLC checked and reaction mixture was worked up. Pure **2** was obtained by column loaded with SiO_2 in $CHCl_3$. Eluant used was pure chloroform.
2. (3.32 g, 72.73 %) was obtained as fluorescent green coloured oily liquid. ^{1}H NMR δ 2.143-2.223 (pentet, *J* = 6.0, 6.0, 6.0, 6.0 Hz, 2H), 2.470 (s, 3H), 3.372-3.414 (t, *J* = 6.3, 6.3 Hz,2H), 3.874 (s, 3H), 4.298-4.336 (t, J = 5.7, 5.7 Hz, 2H), 7.264-7.620 (m, 5H).
Synthesis of 5-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propoxy]-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid methyl ester (3). Phthalimide (0.20 g, 0.0014 mol) and anhydrous K_2CO_3 (0.19 g, 0.0014 mol) were dissolved in 15 ml DMF for 10 minutes at room temperature and compound **2** (0.5 g, 0.0014 mol) was added. The reaction mixture was stirred at room temperature for 24 h. Completion of reaction was confirmed by TLC. Solvent was removed under pressure and the product was extracted with $CHCl_3$/ H_2O (20/ 20 X 2 ml) layers. The $CHCl_3$ layer was dried with anhydrous Na_2SO_4 and filtered. $CHCl_3$ was evaporated and **3** (0.22 g, 37.06 %) was obtained as colourless crystals from 2% ethyl acetate and hexane mixture. mp= 74 ^{o}C; Element analysis: Found: %C, 66.266; %H, 5.144; %N, 10.159; %O, 18.432. $C_{23}H_{21}N_3O_5$ requires %C, 65.87; %H, 5.01; %N, 10.02; %O, 19.09); ^{1}H NMR δ 2.021-2.111 (pentet, *J* = 6.6, 6.9, 6.9, 6.6 Hz, 2H), 2.456 (s, 3H), 3.705-3.753 (t, *J* = 6.9, 7.5 Hz, 2H), 3.821 (s, 3H), 4.234-4.275 (t, *J* = 6.6, 6.3 Hz, 2H), 7.262-7.844(m, 9H); ^{13}C NMR δ 15.262, 28.894, 34.811, 51.014, 73.563, 99.285, 123.194, 127.505, 129.029, 132.021, 133.021, 137.461, 150.960, 155.081, 163.364, 168.111.

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