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ROLE OF FLUORINE ON THERMAL REARRANGEMENT OF BROMO AND CARBETHOXY-2-PYRONES-EVIDENCES FROM DFT

Akilandeswari Lakshminarayanan* & Kalaiselvan Anbarasan**
* Department of Chemistry, Sri Sarada College for Women (Autonomous), Salem, Tamilnadu
** Department of Chemistry, University College of Engineering, Thirukkuvalai, Tamilnadu

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Abstract:

The thermal rearrangement of 2-pyrones are tandem reactions involving reversible electrocyclic ring opening (ERO), rotation, [1,5]-sigmatropic, rotation and electrocyclic ring closing (ERC). Experimentally thermal rearrangements of 2-pyrone with different substituents such as methyl, bromine, methoxy, acetoxy, carbethoxy groups at 3 & 5 –positions have been carried out at elevated temperatures. With methyl, bromine, acetoxy & methoxy substituents, an equilibrium mixture of 3,5-substituted isomers have been obtained in each case while with 3-Carbethoxy-2-pyrone, only 5-substituted isomer is obtained with >99% conversion. In order to understand and reason out the above experimental observations, thermal rearrangement of 2-pyrone and 6-Fluoro-2-pyrone with bromine and carbethoxy substituents has been modeled at B3LYP/6-31G(d) level with 30% exact exchange as it has been found to give good results with MP2 accuracy. Computed results are in good agreement with the experimentally observed percentage of conversion. In both the reactions, rotation is found to be rate determining step. Substitution of fluorine at the 6th position alters the reaction profile significantly.

Key Words: 2-Pyrone, Thermal Rearrangement, B3LYP Calculations, Becke's Parameter Set, Substituent Effect & Sigmatropic Shift

Introduction:

2-pyrone and their derivatives are recognized as one of the potential synthons in the field of synthetic and medicinal chemistry[1-2] due to its unique features and universal pharmacological properties[3-4]. The unique structural features of 2-pyrone makes it amenable to a wide variety of chemical reactions such as substitution, ring transformation, photochemical and thermal rearrangements and cycloaddition reactions[5-9]. Pyrone and pyran-2-thiones undergo thermal rearrangement during gas phase pyrolysis by sequence of reactions involving reversible electrocyclic ring opening, rotation and [1, 5]-sigmatropic rearrangement and as a result substituents switch between 3 and 5 positions[10-11]. This rearrangement is feasible only in the presence of a group at the 6th position with greater migratory aptitude such as H/D[12]. Halogens are good migrating groups and known to undergo [1,5]-sigmatropic shifts[13-14]. We have reported the halogen effect on the thermal rearrangement of 2-pyrone and found that halogen substitution drastically altered the potential energy landscape and the electrocyclic ring opening transition state and the corresponding intermediate are resolved in the PES upon halogen substitution[15]. Pirkle et al[11-12] have investigated the thermal rearrangement of certain substituted 2-pyrones and found that pyrones bearing hydrogen at the 6th position and having bromine, methyl, methoxy or acetoxy at 3rd or 5th position rearrange readily to give an equilibrium mixture of 3 & 5 substituted isomers. But 3-Carbethoxy-2-pyrone rearranges to 5-Carbethoxy-2-pyrones to >99% and reverse does not occur presumably because the equilibrium favour for the 5-carbethoxy-2- pyrone greatly[12]. These observations have motivated us to model this thermal rearrangement and examine in more detail, with the following questions in mind; (i) Why the thermal rearrangement of 5-Bromo-2-pyrone gives an equilibrium mixture while the 3-Carbethoxy substituent favours a single isomer? (ii) the effect of fluorine substitution on the rearrangement?

Computational Details:

All calculations have been performed with Gaussian 98W program[16]. B3LYP[17-18] calculations have been performed with different percentages of exact exchange through the variation of Becke's for the 6-fluoro-2-pyrone. It has been found that calculations with 30% exact exchange yield the results with MP2 accuracy and therefore this modified functional has been used throughout this study. Vibrational harmonic frequencies have been computed for all the stationary points in order to ascertain whether they are minima or saddle points. Transition states have a single imaginary frequency while minima have all real frequencies.

Results and Discussion:

Scheme 1 represents various sequential steps involved in the thermal rearrangement of 2-pyrone. When the thermal rearrangement of 2-pyrones was modeled at B3LYP/6-31G(d) level, all the species could not be located on the PES of rearrangement (Electrocyclic ring-opening TS (ETS) and its intermediate (EInt) were not located). This is due to the reason that the electrocyclic ring opening takes place along with the simultaneous rotation of C-C bond to form rotational intermediate (RotInt). Our efforts to locate the ETS and EInt of this rearrangement have not been successful as reported by Birney [19] and Reva et al[20].

Scheme 1 Here

Calculations with 30% exact exchange (PS4) relatively performs well (Table 1) in 6-Fluoro-2-pyrone rearrangement by giving near MP2 accuracy at a fractional cost. Therefore the effect of bromo and carbethoxy substitution on thermal rearrangement of 2-pyrone (2P) and 6-Fluoro-2-pyrone (6FP) has been studied at this level.

Table 1 Here

Figure 1 Here

Thermal rearrangement of 3-Carbethoxy-2-pyrone (3CE2P):

Free energy profile of thermal rearrangement of 3-Carbethoxy-2-pyrone (3CE2P) is shown in Figure 1. 3-Carbethoxy-2-pyrone to 5-Carbethoxy-2-pyrone (3CE2P → 5CE2P) rearrangement is a tandem process involving five steps in that the activation barrier for the formation of RotInt1 from 3CE2P is 28.8 kcal/mol. The high activation barrier is observed since both the electrocyclic ring opening (ERO) and the rotation of C-C bond occurs simultaneously to form RotInt1. This is in consistent with experiment[12] that a very high temperature (550°C) is required to precede the thermal rearrangement of 3-Carbethoxy-2-pyrone. In this reaction, the ERO step could not be resolved and hence the electrocyclic ring opening transition state (ETS1) and the corresponding intermediate (EInt1) could not be located. In the thermal rearrangement of 3CE2P→5CE2P, the forward process is thermodynamically and kinetically controlled. i.e., the activation barrier for the forward reaction is 28.8 kcal/mol that leads to a thermodynamically stable 5CE2P. Therefore the reverse process is relatively not favourable by both thermodynamically and kinetically. This is the reason why the 3CE2P undergoes rearrangement to 5CE2P with >99% conversion. Computed % of rearrangement listed in Table 2 is in good agreement with the experimental observations. In both reverse and forward processes, rotation is found to be the rate determining step.

Figure 2 Here

Table 2 Here

Thermal rearrangement of 5-Bromo-2-pyrone (5Br2P):

Free energy profile of 5-Bromo-2-pyrone (5Br2P) rearrangement at PS4 level is shown in Figure 2. 5Br2P→3Br2P rearrangement yields an almost equilibrium mixture of 5Br2P and 3Br2P products[15]. This may be due to the reason that the thermal stability of both 5Br2P and 3Br2P are almost same. Calculations predict that the reactant and product isomers exist in 34:66 ratios. This is consistent with the experimental and calculated % of the reaction[12]. 5Br2P→3Br2P rearrangement is a tandem process with rotational step being the rate determining step in both forward and reverse process.

Figure 3 Here

The Effect of Fluorine:

In this section, the effect of fluorine on the thermal rearrangement of 3CE2P and 5Br2P has been discussed and their respective free energy profiles are presented in Figure 3 and Figure 4. Two major effects have been found upon substitution of fluorine at the 6th position of 3CE2P and 5Br2P. (i) It is interesting to find that substitution of fluorine at the 6th position of 3CE2P and 5Br2P resolves the ERO step and introduces a small barrier (3.9 kcal/mol and 6.2 kcal/mol) to the electrocyclic ring opening (ERO) step and hence the electrocyclic ring opening transition state and the corresponding intermediate could be located. This is consistent with earlier reports[15]. It is also interesting to note that the ERC step could not be resolved for these reactions for both 3CE6F2P→5CE6F2P and 5Br6F2P→3Br6F2P. Due to this effect, sigmatropic shift is found to be the rate determining step for the forward process while rotational step is found to be rate determining step for reverse process. Hence, fluorine substitution is helpful to locate the transition state for ERO step and EInt1 and alter the rate determining step of thermal rearrangement. But, in simple 2-pyrones, fluorine substitution introduces barriers to both ERO and ERC steps[15].

Figure 4 & 5 Here

Secondly, substitution of fluorine on the 6th position of 3CE2P and 5Br2P reduces the reaction barrier approximately 15-20 kcal/mol compared with unsubstituted one. The activation barrier for (5CE6F2P→3CE6F2P) is lower (16.5 kcal/mol) than the reverse reaction of 3CE2P→5CE2P (33.7 kcal/mol) and this indicates a slight competition for the reverse process in the case of the former. This leads to slight reduction in the % of conversion is observed (Table 2). The fluorine substitution at the 6th position introduces a small barrier (6.2 kcal/mol) for the ERO step and not for the ERC as in the case of 5-bromo-6-fluoropyrone. The activation barrier for reverse process (3Br6F2P→5Br6F2P) is relatively very high (21.5 kcal/mol). [i.e., electrocyclic ring opening and rotation takes place simultaneously]. Therefore, the reversibility of 5Br6F2P→3Br6F2P rearrangement is reduced and the % of reaction is increased to 84.1%. No experimental reports are available for comparison.

Conclusions:

Thermal rearrangement of 3-carbethoxy and 3-bromo-2-pyrone and 6-fluoropyrone has been modeled using the B3LYP functional with 30% Becke's exchange functional. Calculations reveal that, i) For the 3CE6F2P→5CE6F2P reaction, computed barrier and free energies of activation predict that the forward reaction is favoured while the reverse reaction is not favoured and therefore it is >99% rearranged. ii) 5Br2P→3Br2P rearrangement gives almost an equilibrium mixture since the stabilities of 5Br2P and 3Br2P are almost same. iii) In both carbethoxy and bromo substituted thermal rearrangement, electrocyclic ring opening/closure (ERO/ERC) along with the rotation of C-C bond is the rate determining step. iv) Comparison of fluorine substitution on carbethoxy and bromine substituted pyrone rearrangement with simple pyrone rearrangement reveals that the fluorine substitution alters the potential energy surface drastically by introducing a small barrier to ERO and not for ERC step. In fluorine substituted rearrangements, Sigmatropic shift is the rate determining step for the forward process and rotation for the reverse process. v) Fluorine substitution also reduces the % reversibility of the rearrangement.

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Table 1: Relative free energies (kcal/mol) of the species along the thermal rearrangement pathway of 6-Fluoro-2-pyrone (6F2P) obtained at the B3LYP/6-31G(d) with different parameter sets (PS) and at MP2/6-31G(d) level.

PS[a]	a_0	a_x	a_c	ETS	EInt	Rot TS	Rot Int	Sig TS
1	0.200	0.720	0.810	--	--	19.5	9.19	19.40
2	0.100	0.900	0.900	--	--	17.49	6.98	15.68
3	0.200	0.800	0.800	--	--	17.82	7.33	18.72
4	0.300	0.700	0.700	6.59	5.62	18.21	8.52	21.69
5	0.400	0.600	0.600	7.97	6.32	18.69	9.31	24.56
6	0.500	0.500	0.500	9.21	7.73	19.13	10.08	27.84
7	0.600	0.400	0.400	10.37	8.81	19.52	10.86	29.87
8	0.700	0.300	0.300	11.44	9.76	19.95	11.64	32.31
9	0.800	0.200	0.200	12.43	10.62	21.08	12.40	34.60
10	0.900	0.100	0.100	13.33	11.40	21.97	13.16	36.75
MP2				6.82	5.11	15.89	7.78	21.01

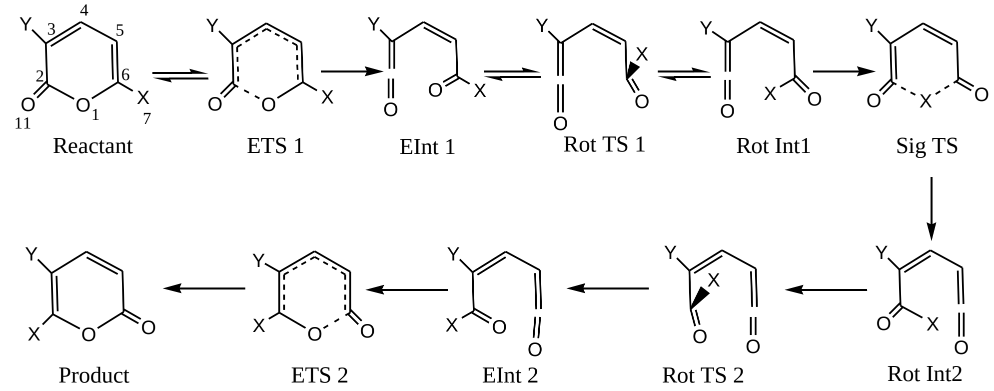
[a] PS=parameter set, a_c=a_x , a_x=1- a_o, except for PS1 where a_o =0.200, a_x=0.72 and a_c=0.81, the default values for Becke functional in B3LYP calculations.

Table 2: Free energy of reaction and percentage of conversion for the rearrangement of 3 and 5 substituted pyrones at 298K. [a]computed at PS4 level.; [b]Ref 16.

Reactant Product	ΔG_r (kcal/mol)	% rearrangement	
		Computed[a]	Experimental[b]
3CE2P → 5CE2P	-4.87	99.97	[>99]
3CE6F2P → 5CE6F2P	-2.06	96.90	-
5Br2P → 3Br2P	1.09	33.30	53-54
5Br6F2P → 3Br6F2P	-1.09	84.10	-

Figure Captions:

1. Scheme 1. The pathway of rearrangement of 2-pyrones.
2. Fig. 1. Deviation of free energy activation (of Electrocyclic ring-opening, rotation of C6-F7, sigmatropic shift) computed at PS4-10/6-31G(d) from their corresponding MP2/6-31G(d) values.
3. Fig. 2. Relative Free energy profile for the 3CE2P → 5CE2P rearrangement
4. Fig. 3. Relative Free energy profile for the 5Br2P → 3Br2P rearrangement
5. Fig. 4. Relative Free energy profile for the 3CE6FP → 5CE6FP rearrangement
6. Fig. 5. Relative Free energy profile for the 5Br6F2P → 3Br6F2P rearrangement



Scheme 1

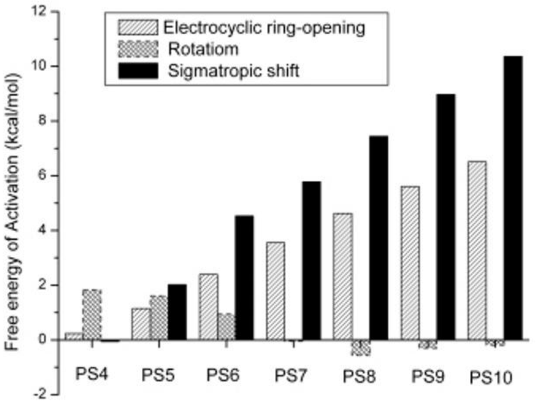


Figure 1

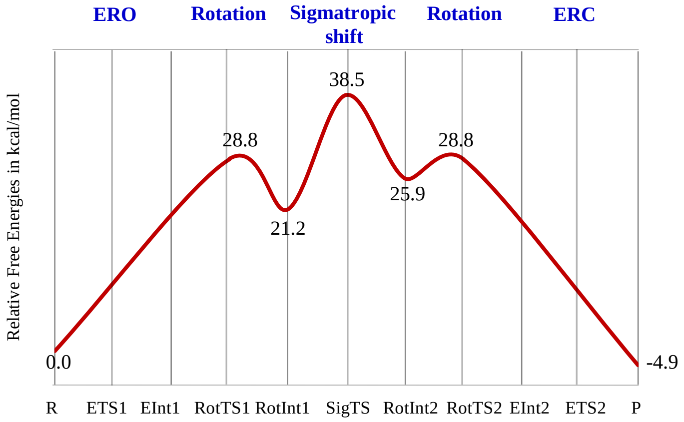


Figure 2

Figure 3

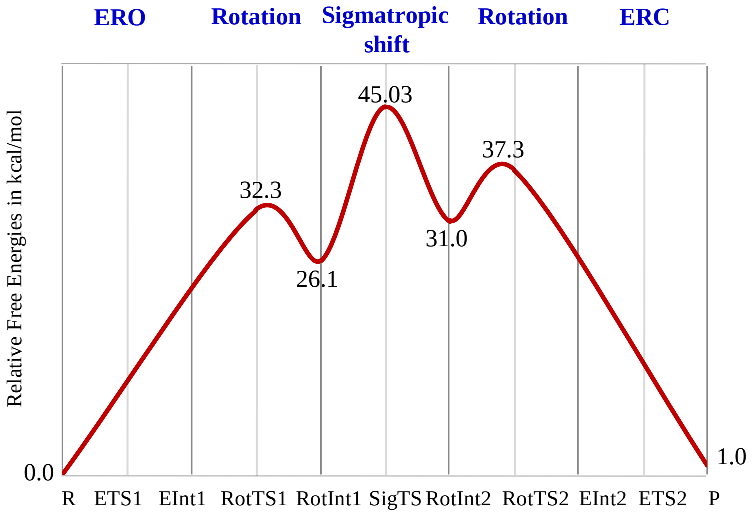


Figure 4

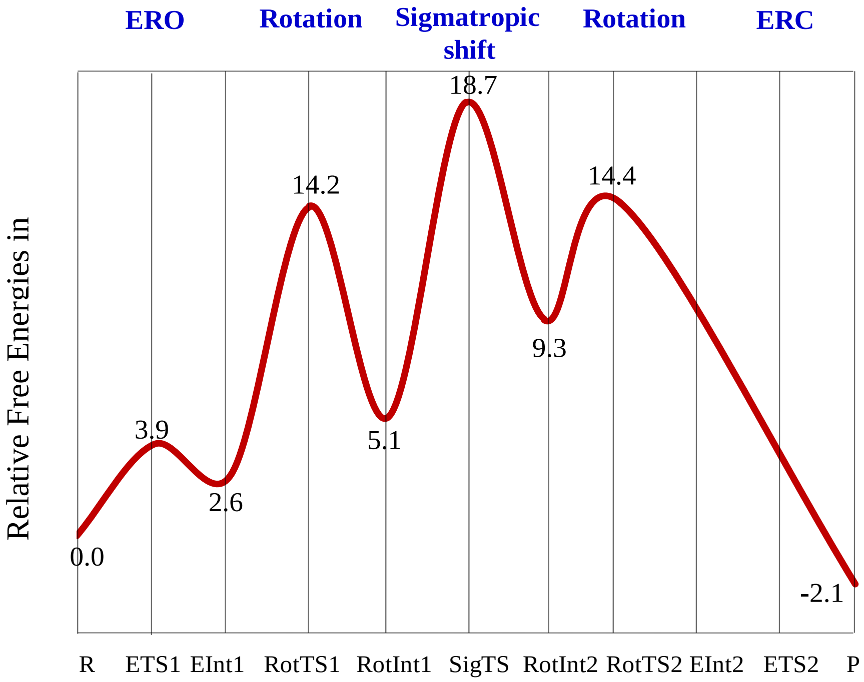
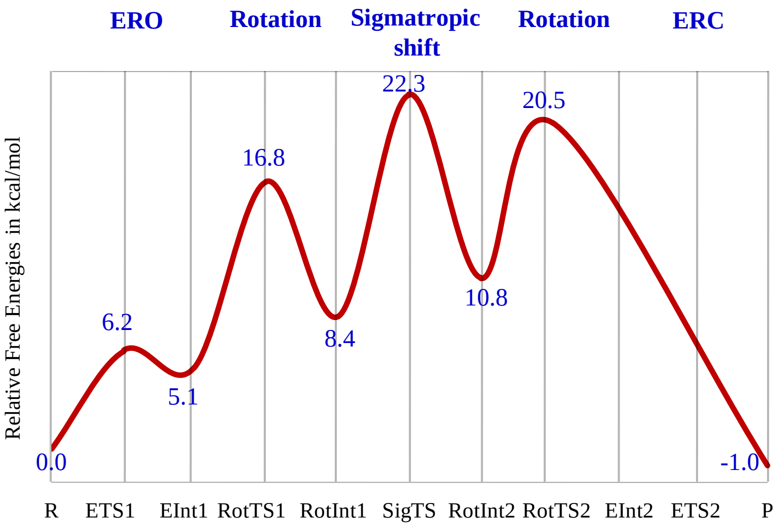


Figure 5



Graphical Abstract:

Role of Fluorine on Thermal Rearrangement of Bromo and Carbethoxy-2-pyrones-Evidences from DFT

Thermal rearrangement of bromo and carbethoxy substituted 2-pyrones have been modeled with B3LYP/6-31G(d) level with 30% exact exchange as it gives result with MP2 accuracy. Fluorine substitution alters the reaction profile by introducing a small barrier and resolves the ERO step.