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Mechanism of the Paal-Knorr Reaction: The Importance of Water Mediated Hemialcohol Pathway

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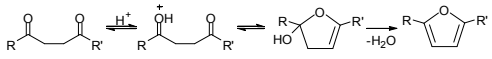
The Paal-Knorr synthesis of furan, pyrrole and thiophene rings is one of the most important methods of generating these very important heterocycles, but the mechanism of this reaction is not well understood. Though several mechanistic paths are suggested, the exact energy requirements of this reaction, the structural features of transition states associated with the cyclization step, have not been established, especially for furan and thiophene synthesis. In this work, we explore the mechanism of the Paal-Knorr method and establish the energy requirements, using quantum chemical methods. The Paal-Knorr reaction to give furans is endergonic by 3.7 kcal/mol whereas the same reaction is exergonic for pyrrole and thiophene generation by 16.4 and 15.9 kcal/mol, using G2MP2 method. The cyclization step is associated with high energy barrier, however, explicit water participation reduces the barrier significantly. For example, under the neutral condition two water mediated pathways – (i) monoenol and (ii) hemiketal, are possible on the reaction leading to furan. The cyclization step in these two pathways require 28.9 and 27.1 kcal/mol, respectively. The ring formation step becomes highly favorable in the presence of H_3O^+ with a barrier of only 11.5 kcal/mol (solvent phase) from the monoenol to dihydrofuran derivative and 5.5 kcal/mol (solvent phase) from hemiketal to dihydroxy dihydrofuran derivative. Similarly, a water mediated pathway involving the intermediacy of hemialcohols has been found to be energetically preferred mechanism for pyrrole and thiophene also.

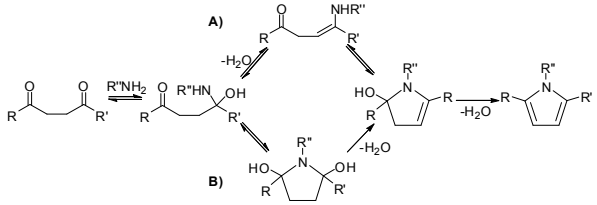
Introduction

Organic compounds containing five membered heterocyclic rings are extremely important in chemistry.[1-3] Especially systems with furan, pyrrole and thiophene ring containing species have found extensive applications in generating pharmacologically important species using bioisosteric replacement. The pharmacophoric as well as the toxicophoric features originating from these rings were extensively explored in drug design and drug metabolism.[4] Establishing synthetic procedures to generate polyfunctional furan, pyrrole and thiophene derivatives is an active research endeavour for organic and medicinal chemists. One common reaction to generate these three derivatives is the Paal-Knorr method[5,6] (Schemes 1-3), even though many alternative methods are reported in recent years,[7-9] the importance of this method in the synthesis of polysubstituted heterocycles continues to be high.

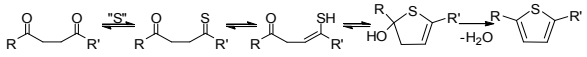
The Paal-Knorr synthesis of furan was first reported in the year 1884[5,6] later it was modified for the synthesis of pyrrole and thiophene and its importance has been established over a period of time. Some of the recent applications of the Paal-Knorr synthesis include (i) synthesis of Tri and Tetrasubstituted furans by Stauffer and Neier[10] (ii) synthesis of 1,2,3,5-tetrasubstituted pyrroles by Braun et al.[11] (iii) carrying out the reaction under deep eutectic solvents by Handy and Lavender[12] (iv) utilizing sulfamic acid as a catalyst by Luo et al.[13] (v) utilizing MgI_2 etherate under solvent-free conditions as a catalyst to perform unique chemoselective Paal-Knorr reaction by Zhang et al.[14] (vi) synthesis of conjugated C3 symmetric aryl tripyrroles and aryl bipyrroles by Saroukou et al.[15] (vii) synthesis of substituted furans by successively recycled waste as a catalyst by Chen et al.[16] (viii) synthesis of fully substituted symmetrical thiophenes via chemoselective Paal-Knorr approach by Ramulu et al.[17] etc. Microwave assisted five membered heterocyclic



Scheme 1. Reported pathway for the Paal-Knorr synthesis of furans.



Scheme 2. Reported pathways for the Paal-Knorr synthesis of pyrroles -- A) the enamine pathway and B) the hemiaminal pathway.



Scheme 3. Reported pathway for the Paal-Knorr synthesis of thiophenes.

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ring synthesis using the Paal-Knorr reagents is also being reported.[18,19] Ionic liquids are also being adopted for the Paal-Knorr synthesis under green conditions.[20-22] Many articles are appearing where transition metal catalysts are being employed in reactions involving the Paal-Knorr method for five membered ring generation.[23-30] Use of nano catalysts[31-33] and organo-catalysts[34,35] is also being practised for the Paal-Knorr synthesis. Green chemistry methods employing nanomagnetically modified sulfuric acid[36] and water[37] catalysts for the Paal-Knorr pyrrole synthesis were also reported. Very recently, catalyst and solvent-free conditions have been employed to synthesize underivatized and N-substituted pyrroles by Cho et al.[38] The importance of this synthetic reaction is highlighted in the synthesis of the drugs Atorvastatin (anti-triglyceride),[39-41] Aloracetam (anti-Alzheimer's),[42] Prodiogiosin (anti-bacterial, anti-fungal and anti-malarial)[43,44] and Roseophilin (anti-tumour) (Figure 1).[43,45-47] For example, innovative strategies are being developed for the economically viable, eco-friendly and easy bulk production of Atorvastatin using second generation synthetic procedures, which also involve the Paal-Knorr method.[48,49]

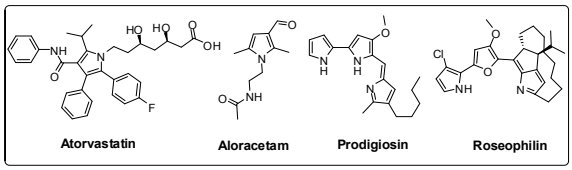

Figure 1: Drugs synthesized using the Paal-Knorr method.

Though the importance of the Paal-Knorr synthetic procedure was clear, very few studies were carried out to explore the mechanism of this reaction. A commonly accepted mechanism for the Paal-Knorr furan synthesis involved the ring closure of monoenol[50,51] followed by water elimination. Amarnath and Amarnath challenged this mechanism on the basis of the differences in the reaction rates of diastereomers and proposed a pathway involving protonation of one of the carbonyls followed by the electrophilic attack at the protonated carbonyl by the enol at the carbonyl center (Scheme 1).[52] In the case of pyrrole synthesis the reaction between 1,4-diketone and amine is expected to yield an initial hemiaminal which may (a) get cyclised directly or (b) after the formation of an enamine (Scheme 2).[53,54] Quantum chemical studies on this reaction supported the hemiaminal path on a relative scale.[55] On the thiophene generation path, no studies on the mechanism have been reported, but the generally suggested path (Scheme 3) is quite similar to that of furan synthesis. Clearly, no common theme is being considered for the three reactions. In the synthetic pathways leading to the pyrrole and the thiophene rings, a heteroatom external to 1,4-diketone is involved. In the case of furan ring synthesis also it may be expected that none of the original oxygen atoms of the 1,4-diketone may be a part of the furanic oxygen. However, all the mechanistic paths proposed till now suggested pathways involving one of the oxygens of 1,4-dicarbonyls as a part of final product furan, this leads to many intriguing questions.

Initial quantum chemical free energy studies at G2MP2 level indicated that the Paal-Knorr furan synthesis is an endergonic process by about ~3.7 kcal/mol, whereas the pyrrole and thiophene synthetic processes are exergonic by about ~16.4 and ~15.9 kcal/mol, respectively. What are the barriers of these reactions on the respective potential energy surfaces? Is there any common mechanism? What are the structures and the relative energies of the reactive intermediates? What is the role of protonated environment and what is the role of water in the reaction? These factors were not explored. In this article, we report the energy profiles of these reversible reactions and establish the mechanism using density functional methods.

Results and Discussion

Initially, the overall free energy change in three reactions under gas phase and under implicit solvent phase conditions were estimated using three levels of quantum chemical analysis. It is clear from Table 1 that the furan ring formation is an endergonic process, whereas the pyrrole and thiophene ring forming reactions are exergonic processes. Also, the data indicates that spontaneity of these reactions are in the order furan < pyrrole ≈ thiophene. The M06 data is only marginally different for all the reactions with reference to the G2MP2 data, and hence, the results from M06 method will be used in the manuscript. The overall free energy values of the reactions do not differ much under implicit solvent and under the gas phase conditions.

Table 1. The free energy change (ΔG) values of the Paal-Knorr reactions (under gas phase and implicit water conditions) leading to the formation of furan, pyrrole and thiophene, estimated using various levels of quantum chemical analysis.

S. No.	Method	ΔG_{furan}[b] (kcal/mol)		$\Delta G_{pyrrole}$[b] (kcal/mol)		$\Delta G_{thiophene}$[b] (kcal/mol)	
		Gas	Solvent	Gas	Solvent	Gas	Solvent
1	B3LYP[a]	0.4	1.3	-18.5	-18.8	-17.7	-17.6
2	M06[a]	4.4	4.6	-15.1	-15.7	-12.4	-13.0
3	G2MP2	3.5	3.7	-15.2	-16.4	-15.1	-15.9

[a] The 6-311+G(2df,3pd) basis set is employed at all levels. [b] The overall free energy changes reported are for (i) furan w.r.t. 1,4-diketone; (ii) pyrrole w.r.t. ketone-imine and (iii) thiophene w.r.t. 1-keto,4-thioketone. See supporting information for the ΔG value for pyrrole w.r.t. 1,4-diketone + amine.

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Mechanism of Furan generation from 1,4-diketones

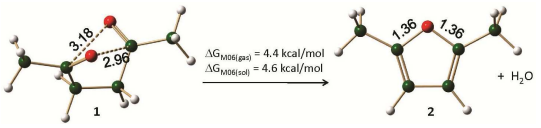

Figure 2. The Paal-Knorr reaction for the synthesis of 2,5-dimethylfuran. The distances are given in Å (refer Table 1 for energies).

To analyse the electronic structure and reactivity of 1,4-diketones, 2,5-dimethyl-1,4-diketone (**1**) has been taken as a model system. The 3D structure of the most stable conformer of compound **1** is given in Figure 2. Compound **1** is characterised by two weak intramolecular electrostatic interactions (~3.0 Å and ~3.2 Å) between the oxygen atom at one carbonyl center and the carbon atom at the other carbonyl center. These weak interactions are originating from the electron deficient p orbital of the carbon centers and the electron rich oxygen atoms. As can be expected, the 2,5-dimethylfuran (**2**) is a flat molecule with 6 π electron delocalisation.

The free energy required for the formation of furan **2** from diketone **1** after the release of a water molecule is about 4.4 kcal/mol (under gas phase) and 4.6 (under solvent phase) at M06 level of theory. Thus this reaction is endergonic reaction, surprisingly, no report till now established the endergonic character of this synthetic pathway. Considering that this reaction is being frequently reported, the endergonic character is not generally expected, this fact leads to several queries regarding the driving force for this reaction. Based on physical organic chemistry analysis a few proposed pathways are available in literature,[52] which need to be elaborated to obtain atomic level details of the reaction mechanism. Six different pathways can be envisaged for the ring closure of 1,4-diketones to yield the furan ring – Three pathways based on the initial monoenol formation (Scheme 4) and three more based on the initial hemiketal formation (Scheme 5) – (i) conversion of one of the keto groups to enol followed by cylization, (ii) water assisted ring closure of the monoenol isomer, (iii) ring closure in proton catalysis conditions, (iv) ring closure after the initial formation of hemiketal derivative (v) water mediated hemiketal pathway and (vi) ring closure after the initial formation of hemiketal derivative in proton catalysis conditions. The potential energy surfaces of these pathways were explored in detail, the results are discussed in the following sections.

Monoenol pathway: Ketones are known to exist in keto-enol equilibrium. The monoenol tautomer **3** of compound **1** is characterized by intramolecular hydrogen bond interaction with a bond length of 1.87 Å (Figure S1, supporting information). The energy difference between acetaldehyde and vinylalcohol is reported to be of the order of 16 kcal/mol,[56] it is generally considered that any keto-enol pair whose energy difference is less than 16 kcal/mol is a feasible tautomerisation process.[57-59] In compound **1**, the keto-enol energy difference (i.e. Δ*G* between **1** and **3**) is estimated to be 11.3 kcal/mol, thus indicating that keto-enol tautomersim is an accessible process in 1,4-diketones.

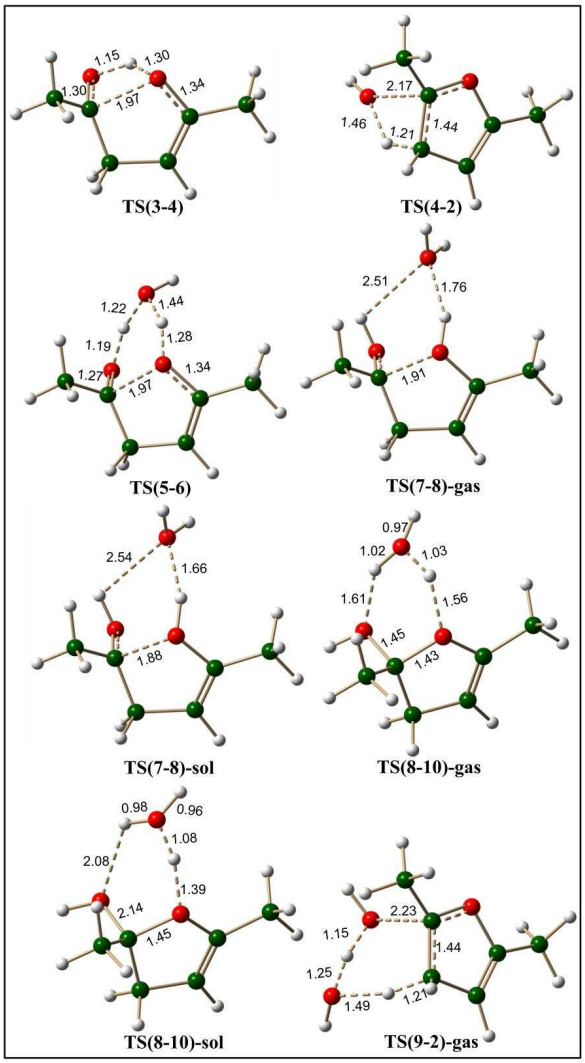

Figure 3. The 3D structures of the transition states on the potential energy surface of the monoenol pathways for the Paal-Knorr synthesis of furan. The distances are given in Å.

The monoenol **3** can give the cyclized intermediate **4** through a transition state **TS(3-4)**, which involves (i) transfer of proton from the enolic oxygen to the carbonyl oxygen and (ii) the attack of enolic oxygen at the carbonyl carbon. The energy barrier for this cyclization reaction (pathway A(O), Scheme 4) is about ~40.0 kcal/mol. The C…O bond length is 1.97 Å and the O…H(O) bond

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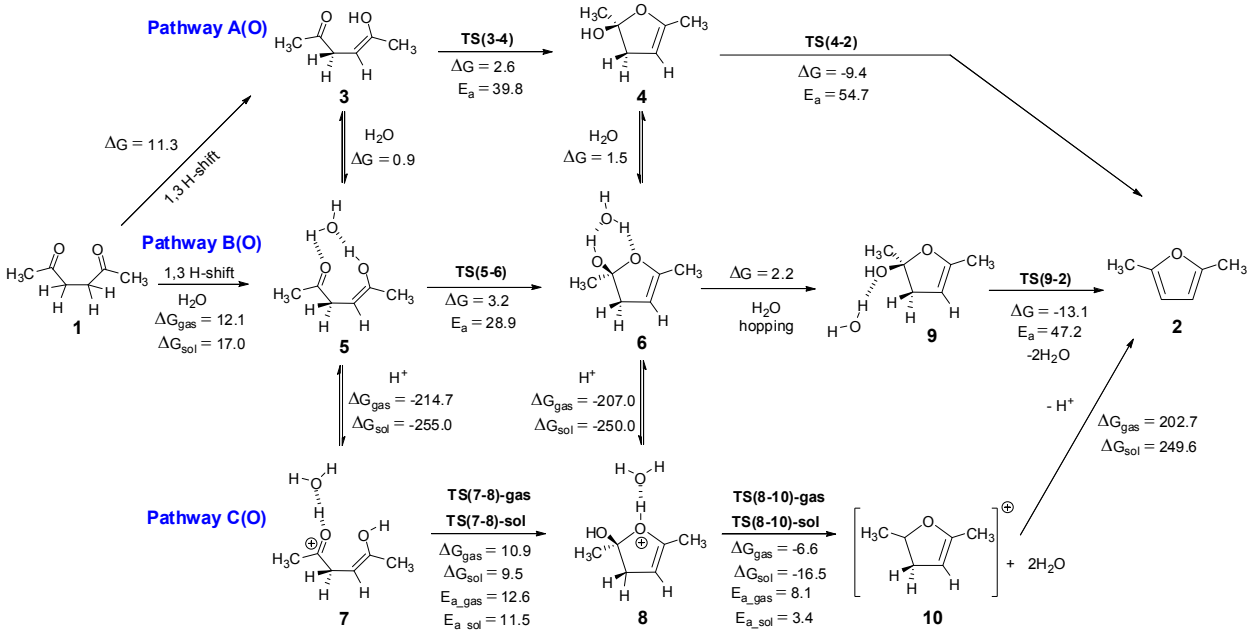

Scheme 4. Monoenol pathways for the Paal-Knorr synthesis of furan -- pathway A(O) without explicit water, pathway B(O) with explicit water and pathway C(O) under proton catalysis condition. The energy values (kcal/mol) are obtained using M06 method. The corresponding values obtained using B3LYP method are given in supporting information. The 3D structures of the transition states are given in Figure 3.

length is 1.30 Å in **TS(3-4)** (Figure 3). The simultaneous hydrogen transfer and oxygen attack from the enolic OH group is a highly strained process, hence, it can be envisaged that such a process can be assisted by the participation of a water molecule. Calculations along pathway B(O) (Scheme 4) indicated that the proton transfer through a water molecule reduces the barrier to ~29.0 kcal/mol via the transition state **TS(5-6)** (Figure 3). **TS(5-6)** is characterized by a C…O bond length of 1.97 Å, elongated H-O bonds of water and a network of hydrogen bonds through water molecule, which clearly facilitates the proton transfer as well as the oxygen attack. Thus it can be concluded that the participation of a water molecule is essential for the reaction.

The Paal-Knorr synthesis is known to take place in mild acidic conditions.[1-3,60] The mechanisms considered by Amarnath and Amarnath were all in the protonated enolic state. Hence, the quantum chemical calculations were repeated under the H^+ and H_3O^+ conditions (pathway C(O), Scheme 4). The pathway C(O) involves proton catalysis, hence, it was explored under both gas phase and under implicit solvent (water, ε = 80.4) conditions. Compound **4** with H^+ on furan ring oxygen does not lead to any stable structure under gas phase conditions (presumably owing to a very shallow potential well associated with this intermediate). Under the H_3O^+ conditions, however, the cationic species (**8**) is stable, and hence, the barrier for its formation from **7** could be estimated through the transition state **TS(7-8)-gas** (under gas phase conditions) and **TS(7-8)-sol** (under solvent phase conditions). On the pathway C(O), under gas phase conditions, the cyclization step is an endergonic process involving 10.9 kcal/mol, with a barrier of 12.6 kcal/mol via transition state **TS(7-8)-gas**. The same cyclization step under implicit water phase conditions was also observed to be an endergonic process by 9.5 kcal/mol, with an energy barrier of 11.5 kcal/mol via transition state **TS(7-8)-sol**. During the cyclization, it is observed that the water molecule migrates from the carbonyl OH^+ center to the enolic OH center. In the transition states **TS(7-8)-gas** and **TS(7-8)-sol**, the water molecule bridges the two OH groups (Figure 3). Clearly the cyclization step along pathway C(O) under solvent phase conditions is more favorable than in gas phase conditions, also it requires very small barrier (11.5 kcal/mol), much less than the other two neutral monoenol pathways (39.8 and 28.9 kcal/mol along pathways A(O) and B(O), respectively). The 3D structures of **TS(5-6)** and **TS(7-8)** (Figure 3), clearly demonstrate that the role of water molecule is to stabilize a conformation for the cyclization process. The 3D structures of **5** and **7** further support this particular observation. The above mentioned observations clearly establish the importance of explicit water as well as the importance of protonated environment under solvent phase conditions in the Paal-Knorr synthesis of furan.

The neutral paths, pathway A(O) and B(O), lead to intermediates **4** and **9** respectively, which need to undergo water

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elimination. Intermediate **4** can undergo cis water elimination via **TS(4-2)** with a very high energy barrier of 54.7 kcal/mol. A water assisted cis water elimination from the intermediate **9** was found to require an energy barrier of 47.2 kcal/mol (**TS(9-2)**), comparatively lower to the direct water elimination step. Alternatively, dehydration process can take place with proton catalysis (pathway C(O)), as it has been reported that the Paal-Knorr furan synthesis is normally carried out under aqueous acidic conditions with protic acids such as aqueous sulfuric or hydrochloric acid, or anhydrous conditions with a Lewis acid or dehydrating agent.[1-3,60,61] The cyclized protonated intermediate **8** can undergo water assisted dehydration to give an intermediate **10**. This step is exergonic under both gas phase and implicit solvent phase conditions, involving the energy barriers of 8.1 (**TS(8-10)-gas**) and 3.4 (**TS(8-10)-sol**) kcal/mol, respectively. The overall reaction free energy from **7** to **10** is endergonic by 4.3 kcal/mol under gas phase conditions, but it is exergonic (highly favorable) by 7.0 kcal/mol under implicit solvent conditions. This clearly establishes that the polar environment (low dielectric constant medium) facilitates the cyclization and the water elimination steps and this stabilizing force could be the driving force for the furan ring formation, though the overall reaction is endergonic.The intermediate **10** can further loose a proton to give furan **2**. This step is endergonic by 202.7 kcal/mol under gas phase condition (249.6 kcal/mol under implicit solvent phase condition). Initially, during H^+ addition (**5** → **7** reaction step), the system gains 214.7 kcal/mol under gas phase condition (255.0 kcal/mol under implicit solvent phase condition) and towards the end the system loses 202.7 kcal/mol. Hence, there is a balancing act. Overall the reaction is endergonic by only 4.4 kcal/mol (4.6 kcal/mol under solvent phase conditions).

***Hemiketal pathway*:** Considering that the pyrrole and the thiophene synthetic procedures using the Paal-Knorr method involve the participation of external substrates, it may be considered that external water molecule probably is participating in the case of furan also (surprisingly such a mechanism was not considered till now). This can happen through the formation of a hemiketal intermediate, Scheme 5 shows the possible reaction pathways from **1**. Addition of a water molecule to 1,4-diketone leads to the formation of a hemiketal **11** with an endergonic value of 7.3 kcal/mol and energy barrier of 32.7 kcal/mol via **TS(1-11)** (Figure 4). Hemiketal **11** can have an orientation of $-CH_3$ and -OH groups such that after cyclization it can lead to tetrahydrofuran **12** having cis or trans orientation w.r.t. -OH groups. Keeping this stereochemistry aspect in mind all the calculations were carried out maintaining the cis orientation (both the -OH groups on the same side of the plane, stabilizing the molecule via an intramolecular H-bond). The results of the corresponding trans orientation are given in supporting information. Cyclization of **11** leads to the 2,5-dihydroxy derivative of tetrahydrofuran **12**, with an endergonic value of 1.2 kcal/mol and with a barrier of 40.9 kcal/mol (through the transition state **TS(11-12)**, Figure 4). Alternatively, this path also may be facilitated by the direct participation of one water molecule (pathway E(O)). On this pathway, formation of the hemiketal is an endergonic process (by 9.6 kcal/mol), the cyclization is an exergonic process (-0.6 kcal/mol) and the activation energy of the cyclization is 27.1 kcal/mol (through the transition state **TS(13-14)**), leading to an intermediate **14**. This data clearly indicates that the water participation facilitates the cyclization in hemiketal pathway also. Hemiketal pathway involving proton catalysis (pathway F(O)) under gas phase conditions and solvent conditions was also explored. Under proton catalysis conditions the cationic species **15** (with H_3O^+) can cyclise to give **16**. The energy barrier for the cyclization process was calculated to be 5.3 kcal/mol under gas phase conditions and 5.5 kcal/mol under solvent phase conditions. Clearly cyclization step is quite feasible under proton catalysis conditions in comparison to the corresponding neutral conditions.

The neutral hemiketal pathway D(O) lead to an intermediate **4**, after cis water elimination from **12**. This step requires a high energy barrier of 59.0 kcal/mol via **TS(12-4)**. Pathway E(O) involves water mediated cis water elimination from **17** leading to an intermediate **9**, having an energy barrier of 37.3 kcal/mol. The water mediation significantly reduced the energy barrier for the dehydration step. Intermediates **4** and **9** can further undergo water elimination very similar to in monoenol pathway. On the proton catalysis pathway F(O), the cyclized protonated intermediate **16** can undergo water assisted dehydration to give an intermediate **18**. This step is exergonic under both gas phase and implicit solvent phase conditions, involving the energy barriers of 8.4 (**TS(16-18)-gas**) and 5.6 (**TS(16-18)-sol**) kcal/mol, respectively. This intermediate **18** can further loose a proton in the form of H_3O^+ to give **4**. Species **4** can further lead to **8** under H_3O^+ conditions. The cyclized protonated intermediate **8** can undergo water assisted dehydration to give an intermediate **10** which can further loose a proton to give furan **2**. Hence, pathway F(O) is the most energetically favorable path for the formation of furan from 1,4-diketones.

From the above analysis of six different pathways for the Paal-Knorr synthesis of furan, it can be concluded that the ring cyclization step is quite favorable under proton catalysis conditions, pathway C(O) and pathway F(O). The proton catalysed hemiketal path under solvent conditions, pathway F(O) requires an energy barrier of only 5.5 kcal/mol for the ring cyclization step. Whereas, the energy barrier for the cyclization step in the proton catalysed monoenol pathway under solvent phase conditions (pathway C(O)) was calculated to be 11.5 kcal/mol. This suggests that pathway involving hemiketal formation needs to be considered extensively in all future studies. It is worth experimentally exploring the possibility of external water molecule supplying the oxygen atom of the furan molecule on the Paal-Knorr furan synthetic process.

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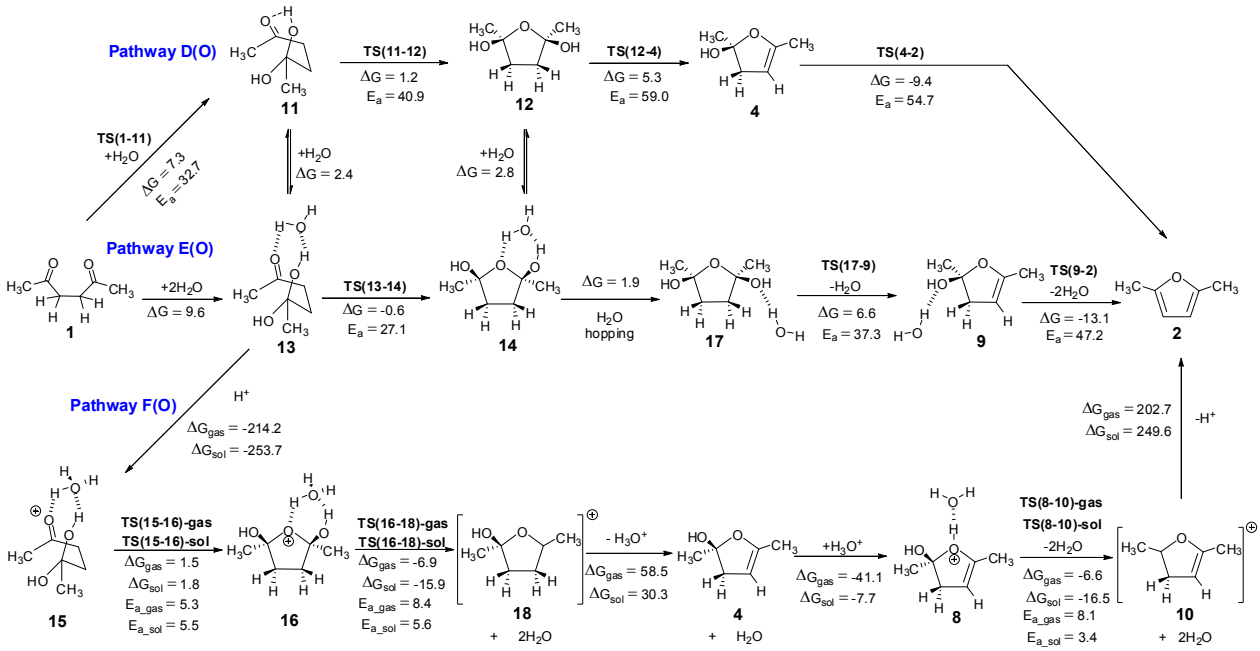

Scheme 5. Hemiketal pathways for the Paal-Knorr furan synthesis – (i) Pathway D(O) without explicit water, (ii) Pathway E(O) with explicit water and (iii) Pathway F(O) under proton catalysis conditions. The energy values (kcal/mol) are obtained using M06 method. The corresponding values obtained using B3LYP method are given in supporting information. The 3D structures of the transition states are given in Figure 4. Structures **12**, **14**, **16** and **17** with cis arrangement of -OH groups are employed in this scheme. The corresponding reaction pathways for the trans arrangement are given in supporting information.

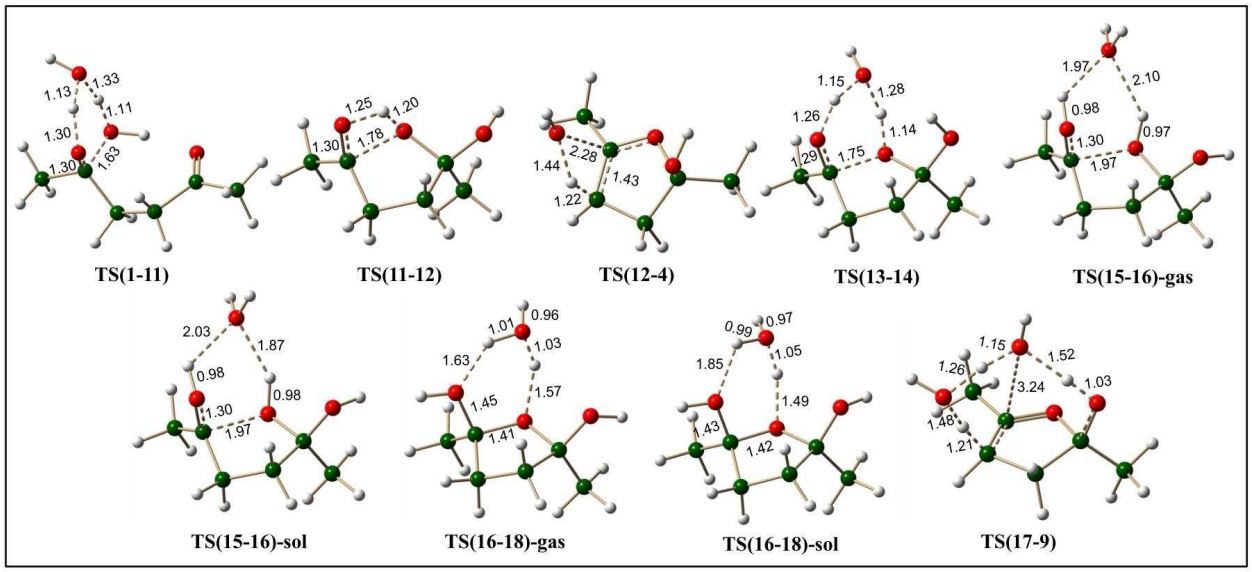

Figure 4. The 3D structures of the transition states on the potential energy surface of the hemiketal pathways for the Paal-Knorr synthesis of furan. The distances are given in Å.

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Mechanism of pyrrole generation from 1,4-diketones

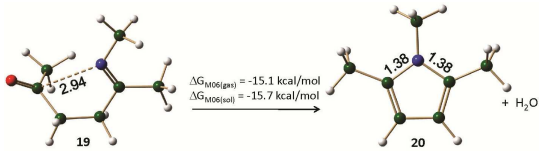

Figure 5. The Paal-Knorr reaction for the synthesis of 1,3,5-trimethylpyrrole. The distances are given in Å (refer Table 1 for energies).

The reaction between 1,4-diketones and amines lead to the formation of imine (**19**), the overall energy of the reaction for the formation of pyrrole **20** from imine **19** is found to be exergonic by 15.1 kcal/mol (under gas phase conditions) and 15.7 kcal/mol (under implicit solvent phase conditions) at M06 level (Table 1, Figure 5). The overall energy of the reaction between 1,4-diketones (**1**) and methylamine to give pyrrole **20** was also found to be highly exergonic (Table S1, supporting information). Experimental and theoretical studies (with no explicit water mediation) on the reaction supported a mechanism involving hemiaminal formation.[53-55] Six different pathways can be envisaged for the Paal-Knorr synthesis of pyrroles (pathways A(N), B(N), C(N), D(N), E(N) and F(N)).

The role of water in the cyclization step of the reaction was not explored in the previous studies, thus the cyclization barriers reported were quite high for a highly spontaneous reaction exergonic by 15.7 kcal/mol. Encouraged by a significant decrease in the barrier for the furan generation in the presence of water, detailed studies on the water participation in pyrrole generation have been taken up. The Paal-Knorr reaction to give pyrrole is not reported under proton catalysis conditions. Such a possibility was recently suggested by Akbaşlar and coworkers, though they did not employ explicit acidic medium in the reaction.[37] Considering the basic nature of the imine and enamine intermediates, this pathway is a challenging process, which is supported by the difficulties encountered during the computational analysis. The six distinct processes of cyclization studied are (i) cyclization of an enamine intermediate directly (pathway A(N)) (ii) cyclization of an enamine intermediate with the help of water (pathway B(N)), (iii) cyclization of an enamine intermediate with proton catalysis (pathway C(N)), (iv) direct hemiaminal cyclization (pathway D(N)), (v) water assisted cyclization of hemiaminal (pathway E(N)) and (vi) cylclization of hemiaminal derivative in proton catalysis conditions (pathway F(N)).

***Enamine pathway*:** The reaction between ketone and amine is known to give imine, in the case of 1,4-diketone, single water elimination can lead to the formation of an imine **19** (formation of **19** may be happening through an initial formation of hemiaminal, **21**). Imine **19** is 6.5 kcal/mol less stable than the two starting materials **1** and methylamine. Scheme 6 shows the possible mechanism along the pathways A(N), B(N) and C(N), starting from imine **19**. Imine-enamine tautomerism in imine **19** to give enamine **22** is marginally endergonic by about 1.6 kcal/mol. For comparison, the imine-enamine tautomer energy difference in methylamine is ~3.9 kcal/mol in favor of imine.[57,62] In the enamine **22**, the intramolecular hydrogen bond (~2.1 Å) stabilizes the tautomer. The enamine **22** can cyclize directly (pathway A(N)) to give **23**, which is about 1.2 kcal/mol less stable. The energy barrier for the cyclization is estimated to be about 39.2 kcal/mol via **TS(22-23)** (Figure 6), the transition state involves an attack of lone pair of electrons from the -NHR center at the carbonyl carbon of the enamine **22**. This pathway is also associated with a transfer of hydrogen from the -NHR center to the oxygen atom of the carbonyl group. This barrier is very high because of the two simultaneous processes, leading through a strained four membered cyclic transition state. Structure **22** is not readily suitable for cyclization. Water can assist this process and release strain significantly. As shown in pathway B(N), the cyclization step demands only 25.3 kcal/mol barrier in the presence of water, thus facilitating the formation of the C-N bond, leading to a less stable (by 4.1 kcal/mol) intermediate **25**.

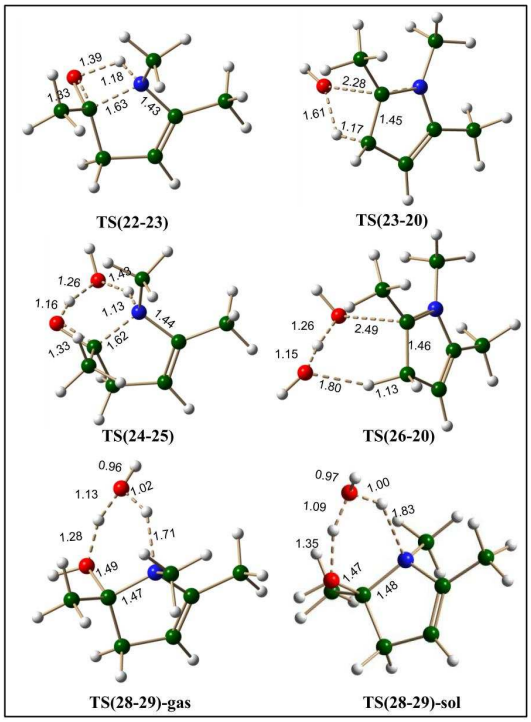

Figure 6. The 3D structures of the transition states on the potential energy surface of the enamine pathways for the Paal-Knorr synthesis of pyrrole. The distances are given in Å.

RSC Advances

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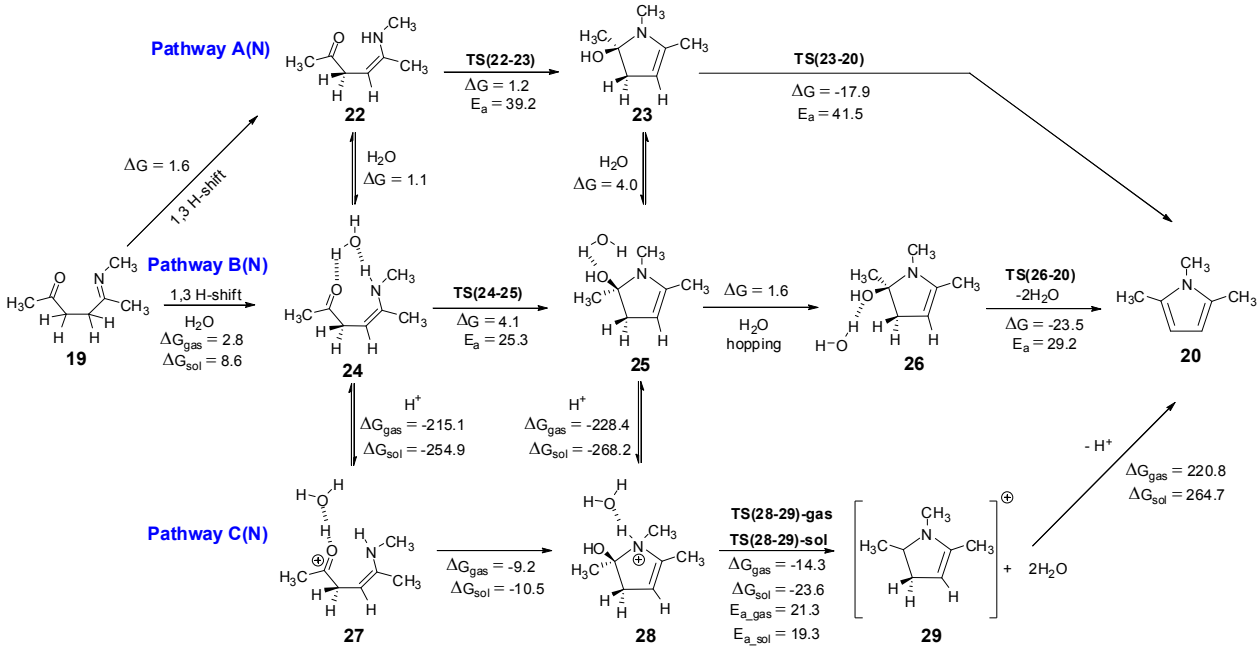

Scheme 6. Enamine cyclization pathways for the Paal-Knorr pyrrole synthesis -- Pathway A(N) without explicit water, Pathway B(N) with explicit water and Pathway C(N) under proton catalysis conditions. The energy values (kcal/mol) are obtained using M06 method. The 3D structures of transition states are given in Figure 6. The corresponding values obtained using B3LYP method are given in the supporting information.

On the pathway A(N), the cyclized intermediate **23** can undergo cis water elimination via **TS(23-20)**, to give pyrrole **20**. This step involves a high energy barrier of 41.5 kcal/mol. The intermediate **25** on the pathway B(N), leads to **26** which can lose water (cis elimination, with the help of an external water molecule) to give the pyrrole with an energy barrier of 29.2 kcal/mol. Water assistance significantly reduces the energy barrier for the dehydration step very similar to furan pathways.

The Paal-Knorr pyrrole formation pathway was also considered under proton catalysis conditions (pathway C(N)). The cationic specie (**27**) under H_3O^+ condition can cyclize to form **28**. On the pathway C(N), the cyclization step is an exergonic process (contrary to pathway C(O) for furan formation) by 9.2 and 10.5 kcal/mol, under gas phase and implicit solvent phase conditions, respectively. All attempts to identify transition state for the cyclization step (on the potential energy surface) under proton catalysis condition failed, leading to the intermediate **28**. Due to the highly exergonic nature of the cyclization step under proton catalysis conditions, this process can be considered to be spontaneous. The cyclized protonated intermediate **28** can undergo water assisted dehydration to give an intermediate **29**. This step is exergonic under both gas phase and implicit solvent phase conditions, involving the energy barriers of 21.3 (**TS(28-29)-gas**)and 19.3 (**TS(28-29)-sol**) kcal/mol, respectively (Figure 6). The activation barrier for this step is reasonably high as compared to **TS(8-10)** (furan synthetic pathway C(O)) under both gas phase and implicit solvent phase conditions. The reason for this can be attributed to over-pyramidalization in case of **TS(28-29)** (pyrrole synthesis) as compared to **TS(8-10)** (furan synthesis) (Figure S3, supporting information). The overall reaction free energy from **27** to **29** is exergonic by 23.5 and 34.1 kcal/mol under gas phase and implicit solvent conditions, respectively. The intermediate **29** can further loose a proton to give pyrrole **20**.

***Hemiaminal pathway*:** The hemiaminal (**21**) may be generated in a reaction between 1,4-diketone and methylamine directly (involving a free energy barrier of 26.4 kcal/mol via **TS(1-21)**, Scheme 7, Figure 7), rather than the hydrolysis of the imine (involving a barrier of 29.5 kcal/mol, Scheme S4, supporting information). Mothana and Boyd supported a mechanism involving the direct cyclization of hemiaminal for the Paal-Knorr pyrrole synthesis.[55] Using quantum chemical analysis, they reported a barrier of 35.0 kcal/mol (enthalpy, using B3LYP method) for the cyclization reaction of hemiaminal **21** The barrier estimated for this process in the current work is 34.2 kcal/mol (Scheme 7), very close to the value reported earlier. The cyclization is triggered by the intramolecular nucleophilic attack of the lone pair of electrons on nitrogen atom at the electron deficient carbon center of the carbonyl group in **21**.

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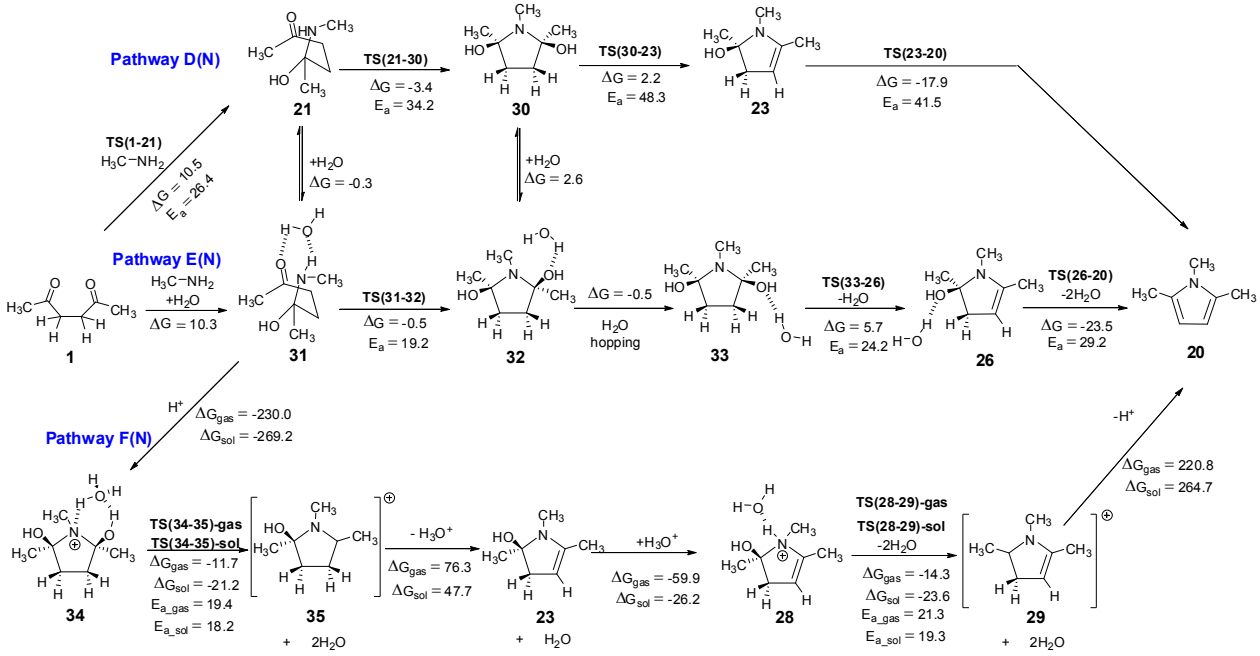

Scheme 7: Hemiaminal pathways for the Paal-Knorr pyrrole synthesis -- Pathway D(N) without explicit water, Pathway E(N) with explicit water and Pathway F(N) under proton catalysis conditions. The energy values (kcal/mol) are obtained using M06 method. The corresponding values obtained using B3LYP method are given in the supporting information. The 3D structures of transition states are given in Figure 7. The cis tautomer with reference to -OH group of structures **30**, **32**, **33** and **34** are used to study the reaction pathway. The corresponding reaction pathways for the trans arrangement are given in supporting information.

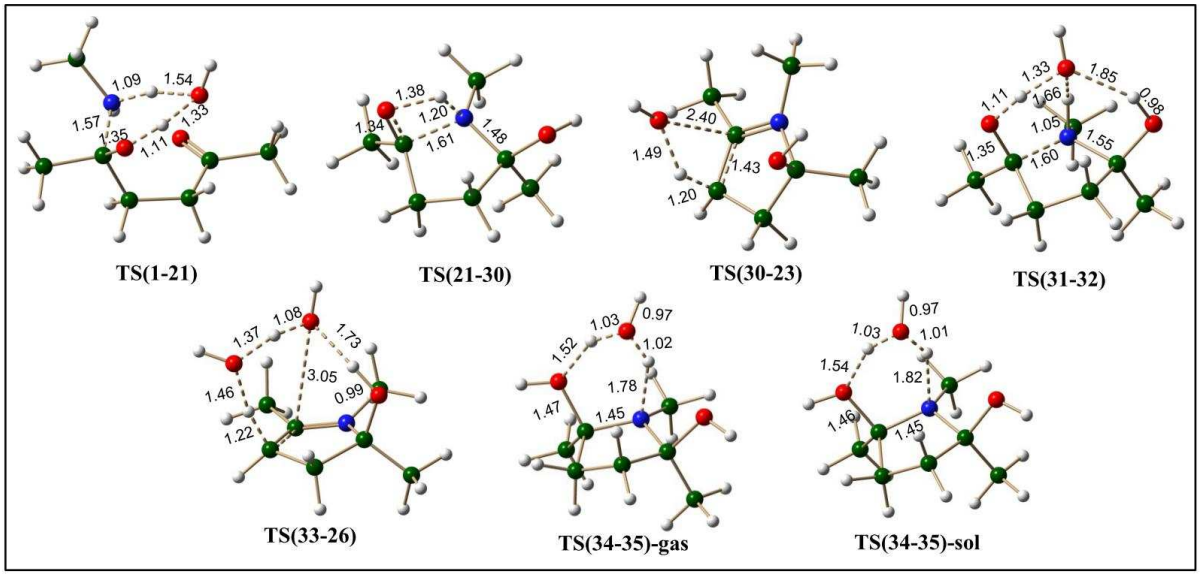

Figure 7. The 3D structures of the transition states on the potential energy surface of the hemiaminal pathways for the Paal-Knorr synthesis of pyrrole. The distances are given in Å.

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PAPER

The transition state **TS(21-30)** is associated with a strained four membered ring. Water greatly reduces the strain in **TS(31-32)** (through a six membered ring), thus facilitating the cyclization process. The free energy barrier for the C-N bond formation leading to cyclization (via **TS(31-32)**) is 19.2 kcal/mol much less than that via **TS(21-30)** (~34.2 kcal/mol). A comparison between pathway B(N) (overall barrier for cyclization -- 34.6 kcal/mol (6.5 + 2.8 + 25.3 kcal/mol)) and pathway E(N) (overall barrier for cyclization -- 29.5 kcal/mol (10.3 + 19.2 kcal/mol)), indicates that the hemiaminal pathway under explicit water conditions is relatively more favorable. On the hemiaminal pathway D(N) the cyclized intermediate **30** can undergo direct cis water elimination (via **TS(30-23**, Figure 7) to form **23**, involving an energy barrier of 48.3 kcal/mol . The cyclized intermediate **32**, on the pathway E(N) lead to an intermediate **33** which can undergo water assisted cis water elimination (via **TS(33-26**, Figure 7) to give **26**. This step involves comparatively low energy barrier of 24.2 kcal/mol. Intermediates **23** and **26** can further lose a water molecule very similar to enamine pathways.

On pathway F(N), compound **31** under H_3O^+ conditions does not lead to a stable structure (presumably owing to a very shallow potential well associated with this intermediate), instead it directly gets converted to the cyclized intermediate **34** during optimization process (pathway F(N), Scheme 7). On this pathway, the cyclized protonated intermediate **34** can undergo water assisted dehydration to give an intermediate **35**. This step is exergonic under both gas phase and implicit solvent phase conditions, involving the energy barriers of 19.4 (**TS(34-35)-gas**) and 18.2 (**TS(34-35)-sol**) kcal/mol, respectively. This intermediate **35** can further loose a proton in the form of H_3O^+ to give **23**. Species **23** can further lead to **28** under H_3O^+ conditions. The cyclized protonated intermediate **28** can undergo water assisted dehydration to give an intermediate **29** which can further loose a proton to give pyrrole **20**. Hence, pyrrole formation pathways (pathway C(N) and pathway F(N) under proton catalysis conditions are the energetically favorable paths for the formation of pyrrole from 1,4-diketones.

Mechanism of thiophene generation from 1,4-diketones

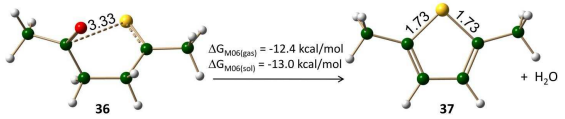

Figure 8. The Paal-Knorr reaction for the synthesis of 2,5-dimethyl thiophene. The distances are given in Å (refer Table 1 for energies).

The Paal-Knorr synthesis of thiophene from 1,4-diketones is expected to take place after the initial formation of 1-keto-4-thioketo (**36**) derivative from the reaction of 1,4-diketone and P_4S_{10}/Lawesson's reagent.[1,2,63] The cyclization of 1-keto-4-thioketone (**36**) to give 2,5-dimethylthiophene is an exergonic reaction by 12.4 kcal/mol (gas phase) and by 13.0 kcal/mol (solvent phase) at M06 level (Table 1) (Figure 8).

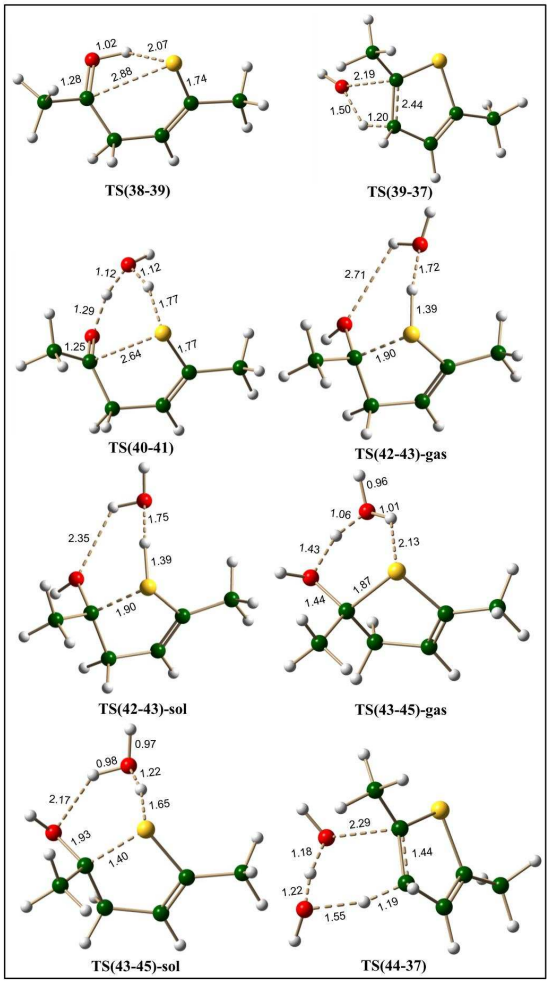

Figure 9. The 3D structures of the transition states on the potential energy surface of the thiol pathways for the Paal-Knorr synthesis of thiophene. The distances are given in Å.

The mechanism for this reaction is expected to follow a pathway similar to that of the cyclization of 1,4-diketone to give furan. The initial tautomerisation of **36** to give **38** is a favorable process (ΔG = 3.9 kcal/mol in favor of thione). Schemes 8 and 9 show the possible mechanistic pathways (A(S), B(S), C(S),D(S), E(S) and F(S)) along with the necessary energies on the pathways. The direct cyclization in thiol pathways via **TS(38-39)** requires 33.0 kcal/mol, but water participation reduces the barrier to 23.7 kcal/mol (via **TS(40-41)**) (Scheme 8, Figure 9). The alternative

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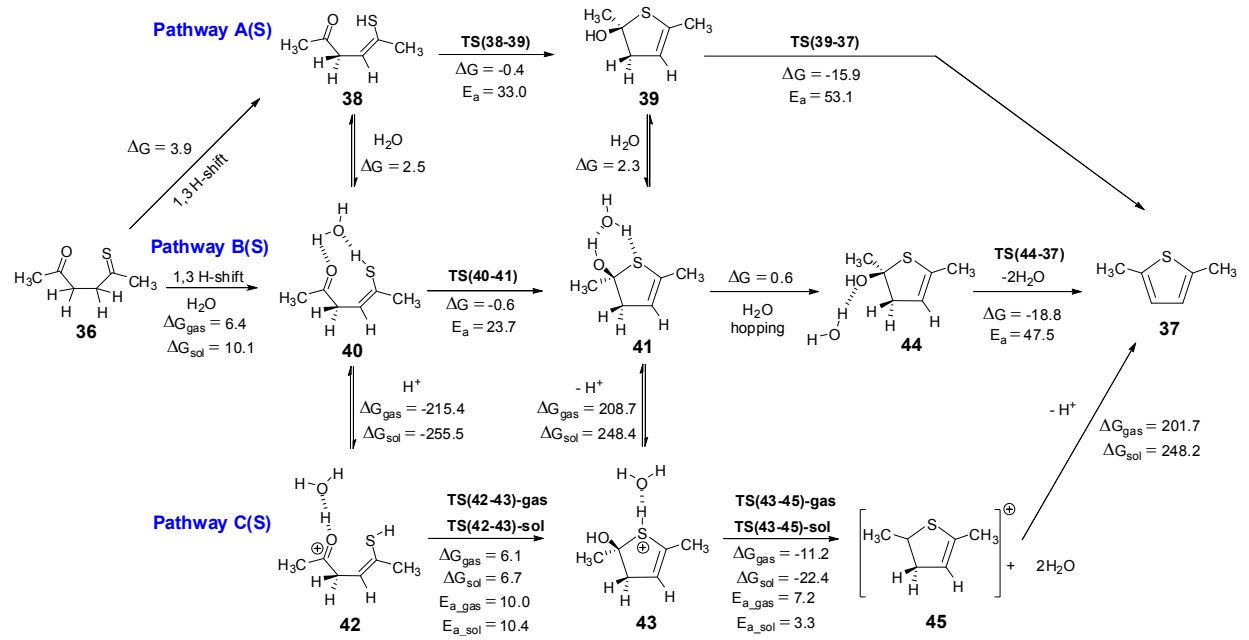
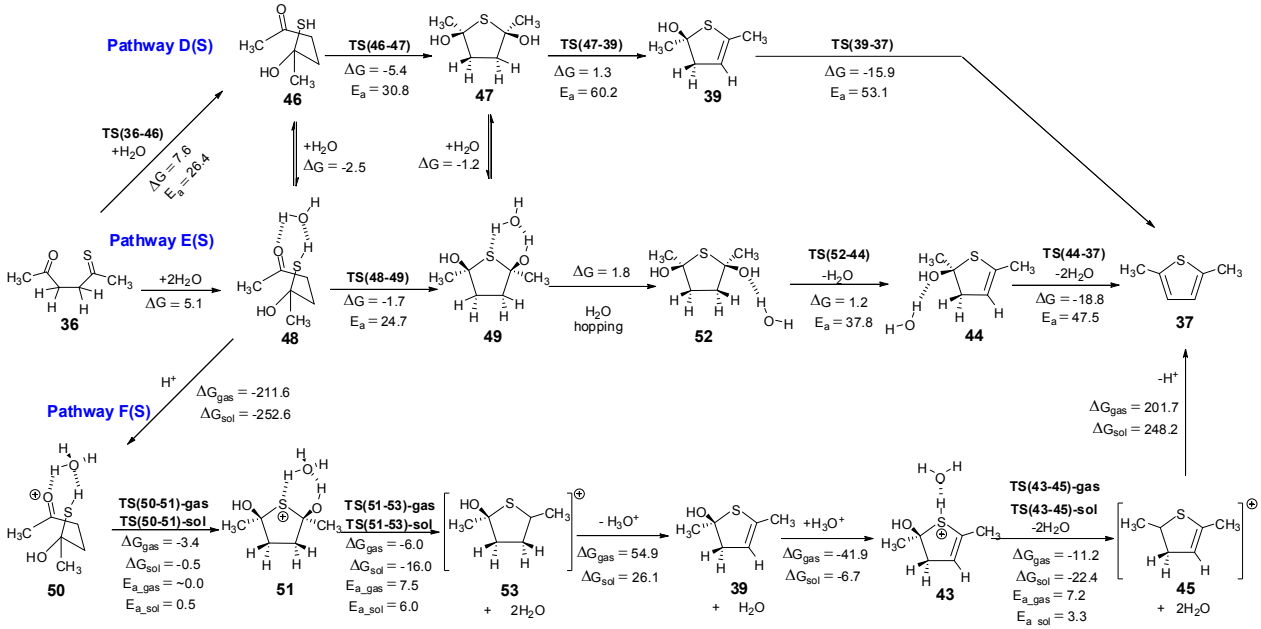


Scheme 8. Thiol pathways for the Paal-Knorr synthesis of furan -- pathway A(S) without explicit water, pathway B(S) with explicit water and pathway C(S) under proton catalysis. The energy values (kcal/mol) are obtained using M06 method. The corresponding values obtained using B3LYP method are given in supporting information. The 3D structures of the transition states are given in Figure 9. The distances are given in Å.



Scheme 9. Hemithioketal pathways for the Paal-Knorr thiophene synthesis – (i) Pathway D(S) without explicit water, (ii) Pathway E(S) with explicit water and (iii) Pathway F(S) under proton catalysis. The energy values (kcal/mol) are obtained using M06 method. The corresponding values obtained using B3LYP method are given in supporting information. The 3D structures of the transition states are given in Figure 10. Structures **47**, **49**, **51** and **52** with cis arrangement of -OH groups are employed in this scheme. The corresponding reaction pathways for the trans arrangement are given in supporting information.

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PAPER

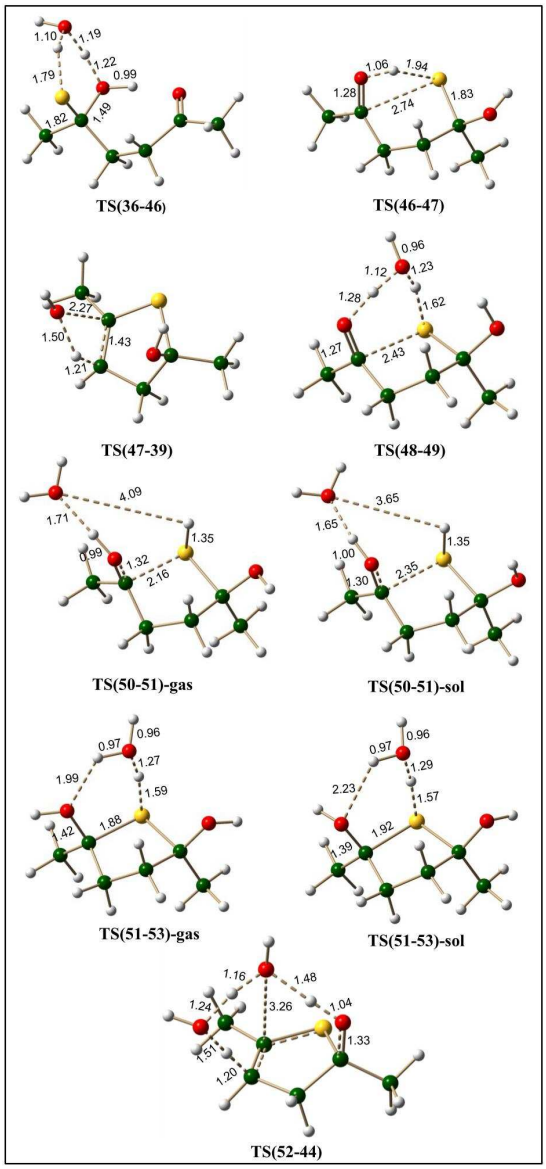

Figure 10. The 3D structures of the transition states on the potential energy surface of the hemithioketal pathways for the Paal-Knorr synthesis of thiophene.

hemithioketal path also is benefitted by the participation of water in the reaction as it shows a decrease of ~6.1 kcal/mol (~30.8 kcal/mol for reaction via **TS(46-47)** vs. ~24.7 kcal/mol for reaction via **TS(48-49)**) (Scheme 9, Figure 10). In this case also the participation of proton in the reaction is suggested,[63,64] hence the thiol and hemithioketal pathways with proton catalysis were also studied. The energy barrier for the cyclization with proton catalysis in pathway C(S) was found to be 10.0 kcal/mol and 10.4 kcal/mol under gas phase and solvent phase conditions, respectively (Scheme 8, Figure 9). The energy barrier for cyclization step was significantly reduced in hemithioketal pathway under proton catalysis conditions. The reaction barrier for this step in pathway F(S) was found to be 0.5 kcal/mol under solvent phase conditions (Scheme 9, Figure 10). On the pathway F(S)-gas phase, location of transition state became tricky, presumably due to the flat potential energy surface.

Comparison between the possible mechanisms on the three important Paal-Knorr synthetic reactions.

The most important step along the Paal-Knorr synthetic procedure is the cyclization step. The reactions leading to the preparation of the reagents for cyclization (hemialcohol generation/tautomersim) as well as the dehydration reactions after cyclization are the associated reaction steps. Figure 11 shows a comparative diagram (under neutral conditions) of the energy barriers for the water mediated cyclization along the tautomeric pathways (pathways B(O), B(N) and B(S)) and the water mediated cyclization of the hemialcohols (pathways E(O), E(N) and E(S)).

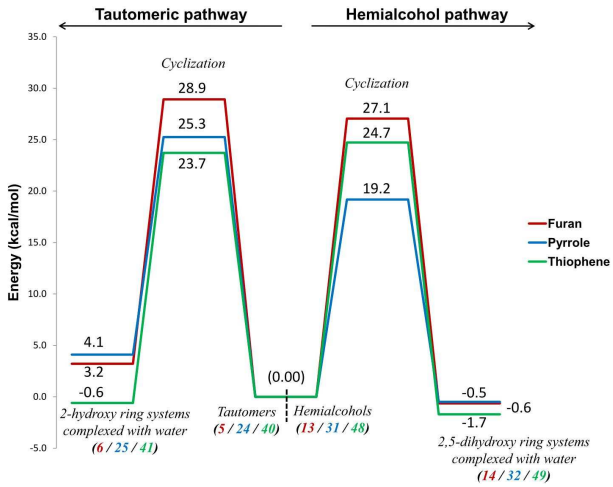

Figure 11. A correlation diagram showing the comparative potential energy surfaces for the cyclization step along the pathways B(O), B(N) and B(S) (water mediated cyclization of tautomers) and pathways E(O), E(N) and E(S) (water mediated cyclization of hemialcohols) for the Paal-Knorr synthesis of furan, pyrrole and thiophene respectively. Energy values are given in kcal/mol.

It can be noticed that these cyclization reactions are marginally favorable (exergonic) on the hemialcohol pathways, but they are marginally unfavorable (endergonic, except in thiophene case) on the tautomeric pathway. Even the energy

RSC Advances

PAPER

barriers are lower for the hemialcohol pathways (except for thiophene). In the case of pyrrole both the ΔG values (4.1 *vs* -0.5 kcal/mol) and the E_a values (25.3 *vs* 19.2 kcal/mol) clearly favor the hemiaminal pathway. In case of furan both the pathways are comparable for the cyclization step, marginally favoring the hemiketal path. In case of thiophene, there is breakeven comparison among the two pathways. Water participation has a marginal influence in stabilizing the intermediates (stabilizing in a few cases but destabilizing in few cases). More significantly, water molecules cause positive conformational changes preparing reactive centers in the intermediates towards cyclization.

Under the proton catalysis conditions, a common mechanism can be considered for the Paal-Knorr synthesis of furan and thiophene (pathways C(O), C(S), F(O) and F(S)), both involve the participation of H_3O^+ in a catalytic role. Figure 12 clearly establishes that the hemialcohol pathways (under both gas and solvent phase conditions) are the favourites both in terms of kinetic and thermodynamic controls. For the pyrrole formation the proton catalysis conditions were not generally used. The transition states and the intermediates on this pathway could not be clearly established on the corresponding potential energy surface. Though, according to free energy estimates this process appears to be highly exergonic.

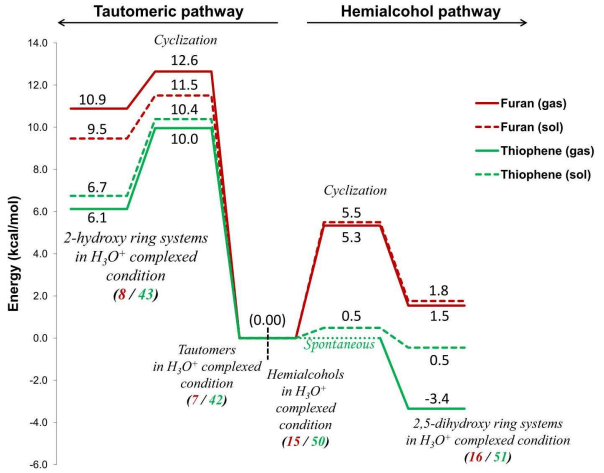

Figure 12. A comparison of the proton catalyzed cyclization step on the potential energy surfaces along the tautomeric pathways C(O) and C(S) and hemialcohol pathways F(O) and F(S) for the Paal-Knorr synthesis of furan and thiophene. Energy values are given in kcal/mol.

The water elimination steps in all the pathways are also important steps. Water elimination requires significant barriers under neutral conditions (24 to 60 kcal/mol). On a relative scale, the barrier for water elimination is low for pyrrole generation as compared to furan and thiophene synthetic pathways. Under proton catalytic conditions the barriers for water elimination step for furan and thiophene generation are in the range of 7.0 to 8.5 kcal/mol (under gas phase conditions) and 3.0 to 6.0 kcal/mol (under implicit solvent (water) conditions). These values are marginally high to the barriers for cyclization along the hemialcohol pathways, but, they are marginally small along the tautomeric pathways.

Conclusions

Quantum chemical studies have been carried out to establish the reaction mechanism for the Paal-Knorr reaction in the generation of furans, pyrroles and thiophenes. Initially three levels of quantum chemical methods (G2MP2, M06 and B3LYP) were employed to calculate overall free energies for the Paal-Knorr synthesis of furan, pyrrole and thiophene. The free energy change along the furan synthetic path is endergonic (by ~3.7 kcal/mol), whereas, the same for the pyrrole and thiophene synthetic paths is exergonic by ~-16.4 and ~-15.9 kcal/mol, respectively. Hemiketal pathway under proton catalysis conditions requiring an overall barrier of ~ 5.5 kcal/mol for the cyclization step is the most preferred pathway for the Paal-Knorr furan synthesis. Similarly, hemiaminal and hemithioketal pathways are favorable for the synthesis of pyrrole and thiophene, respectively. Water participation is quite significant in terms of reducing the energy barriers. The explicit water also specifically participates in dictating the orientation of the reactive centers towards each other by enforcing some specific conformational changes in the intermediates which facilitate the cyclization process. After the crucial cyclization step, water elimination step turned out to be highly energy demanding, explicit water participation is found to be critical at this step also.

This work establishes that a common reaction pathway (hemialcohol pathway) is the preferred mechanistic procedure for the formation of all the three products. All previous studies ignored the role of hemiketal intermediates in the Paal-Knorr furan formation. The current study highlights the importance of this pathway. This needs further experimental exploration, especially due to the fact that Paal-Knorr furan synthesis is an endergonic process on the potential energy surface.

Methods of Calculations

Density functional (DFT)[65] analysis was carried out to explore the mechanism of the Paal-Knorr synthesis of furan, pyrrole and thiophene rings. The GAUSSIAN09 suite of programs[66] was used to carry out the geometry optimization of all the structures on the possible mechanistic paths of the Paal-Knorr synthesis and to estimate the absolute energies. Complete optimizations without any symmetry constraints were performed using M06 method (to incorporate the influence of the dispersion factors into the reaction profile estimation)[67] and Becke–Lee–Yang–Parr (B3LYP),[68-70] with the 6-311+G(2df,3pd) basis set. Frequencies

RSC Advances

PAPER

were computed analytically with the same basis set for all optimized species to characterize stationary points to minima and transition states to first-order saddle points with one imaginary frequency vibrational mode and also to estimate the zero point vibrational energies. Each transition state is a first-order saddle point with only one imaginary vibrational mode on the potential energy surface. The NBO analysis[71,72] using the B3LYP/6-311+G(2df,3pd) and B3LYP/6-311+G(2df,3pd) levels of theory was performed to estimate partial atomic charges. The free energies of overall reactions were also explored using high accuracy G2MP2[73] level.

Acknowledgements

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Keywords: Paal-Knorr reaction • reaction mechanism • density functional calculations • water mediation • proton catalysis

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RSC Advances

PAPER

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Mechanism of the Paal-Knorr Reaction: The Importance of Water Mediated Hemialcohol Pathway

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Quantum chemical methods were employed to explore all the possible pathways for the Paal-Knorr formation of the heterocyclic rings (furan, pyrrole and thiophene). Hydronium ion catalysed hemialcohol pathway has been established as the preferred mechanistic route for the Paal-Knorr formation of furan, pyrrole and thiophene.