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Cocondensation reactions of heterocyclic aromatic compounds with lithium, calcium and magnesium atoms at 77 K

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Abstract

Calcium and magnesium atoms were cocondensed with aromatic heterocycles containing five- and six-membered rings in the presence of THF at 77 K. In the case of calcium the cocondensation with five-membered heterocyclic compounds resulted in C–H bond activations and led to the corresponding aryl calcium compounds, while magnesium did not show comparable reactions. When six-membered heterocyclic compounds, e.g., pyridine and 4-methylpyridine (4-picoline) were cocondensed with calcium, magnesium and lithium atoms, all reactions led to the formation of non-metallated aromatic products and the formation of metal hydride. DFT calculations at the B3LYP/6-31G** level of theory were carried out in order to interpret the pathways of the cocondensation reactions using calcium atoms and identify the possible intermediates involved. In all reactions π- and σ-complexes between calcium atoms and the heterocyclic aromatic reactant were found as stable intermediates on the energy hypersurface.

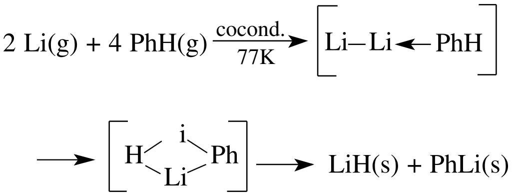
Keywords: Lithium atoms; Calcium atoms; Magnesium atoms; Metal vapour synthesis; CH activation; DFT calculations

1. Introduction

The activation of carbon-hydrogen bonds has been a major topic of research for the last thirty years [1–3]. Earlier reports involving lithium atoms [4–6] showed that they are able to activate aromatic hydrocarbons in the presence of THF selectively under cocondensation conditions at 77 K. This resulted in the direct synthesis of aryl lithium compounds on a synthetic scale.

$$8\mathrm{Li(g)} + 4\mathrm{PhH(g)} + 4\mathrm{THF(g)} \overset{\text{cocond.}}{\underset{77\,\mathrm{K}}{\rightarrow}} [\mathrm{PhLi\cdot THF}]_4 + 4\mathrm{LiH(s)}$$

One of the key intermediates in this reaction is a Li_2-benzene π-complex. This complex is capable of undergoing a two-electron transfer from the Li_2 to the LUMO of the aromatic ring, resulting in the activation of the aromatic C–H bond.



The work has been expanded to +I substituted (CMe_3, $SiMe_3$, *o*- and *m*-xylene) and donor substituted (OMe, NMe_2, SMe) benzene derivatives [7] as well as five-membered heterocycles [8] and nitrogen-containing heterocycles [9]. In the case of anisole a selective C–H bond activation was found to occur in the absence of THF as well; its reaction mechanism was calculated in detail in a recent DFT study [10]. The aim of this paper is to present cocondensation experiments of heterocycles and calcium or

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magnesium atoms and to compare them with the analogues lithium cocondensation reactions. In addition, theoretical studies are carried out to understand the reaction mechanisms of the calcium experiments.

2. Results

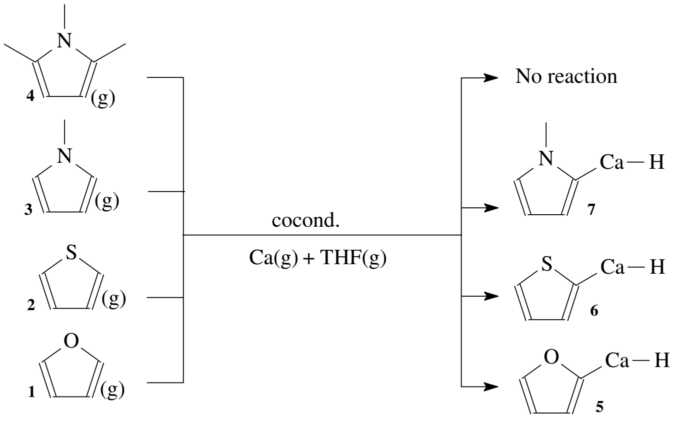
2.1. Experimental study

Previous reports have shown successful cocondensation [8] reactions of lithium atoms and five-membered heterocycles. When the heterocycle used was furan (**1**) or thiophene (**2**), the reaction led to a monolithiated species. The reaction was identified as a C–H activation and the lithium was found in an ortho position with respect to the oxygen and sulphur respectively. When the same cocondensation experiment was carried out using 1-methyl pyrrole (**3**) or 1,2,5-trimethyl pyrrole (**4**) the reaction failed.

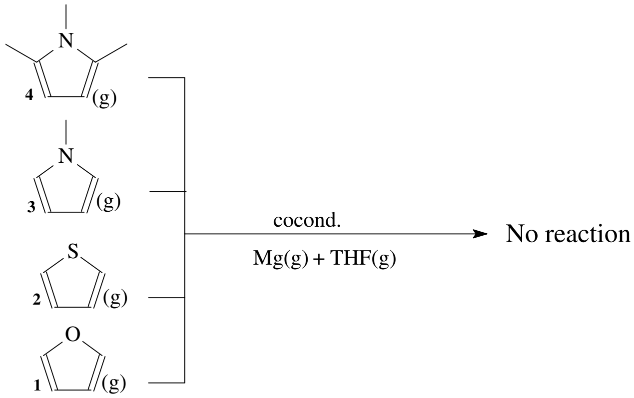
The cocondensation reaction of calcium atoms with furan (**1**), thiophene (**2**), 1-methyl pyrrole (**3**) and 1,2,5-trimethyl pyrrole (**4**) in THF was carried out at 77 K. When **1**, **2** and **3** were cocondensed a reaction was observed and the product was identified as the corresponding calcium compound. However, when **4** was cocondensed, no product could be obtained. The products of these reactions were monocalcium compounds (**5**–**7**) where the heterocyclic ring showed a C–H activation in the ortho position as shown in Scheme 1. In the case of furan, thiophene and methyl pyrrole the yields were 18%, 23% and 8%, respectively.

In order to identify the position of the calcium on the aromatic ring, a derivatisation reaction with Me_3SiCl was carried out yielding air stable products. The TMS substituted compounds were identified by comparing with literature-known NMR and GC–MS data [11–13].

A similar reaction series was carried out, but this time the metal used was magnesium instead of calcium. Compounds **1**, **2**, **3**, or **4** were reacted with magnesium atoms and THF under the same cocondensation conditions but in any case no reaction was found (Scheme 2).



Scheme 1. Cocondensation reactions of calcium atoms with heterocycles at 77 K.



Scheme 2. Cocondensation reactions of magnesium atoms with heterocycles at 77 K.

Earlier reports showed that lithium atoms are able to [9] dimerise pyridine molecules (**9**) by losing hydrogen in the *para*-position. When lithium atoms were cocondensed with pyridine in a THF solution, the reaction lead to a non-lithiated species. The product was identified as 4,4′-bypyridine (**11**) and lithium hydride as by-product.

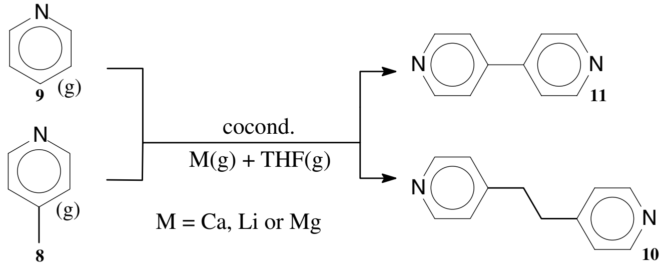
The same cocondensation reaction was carried out using magnesium and calcium atoms. In both cases, as seen in the corresponding lithium reaction earlier, the product was identified as 4,4′-bypyridine [14]. Therefore, lithium, calcium and magnesium atoms are able to activate the C–H bond in the para position forming a dimeric product.

In order to prevent a C–H activation in the para position, a methyl group was placed in that position and the cocondensation reaction was carried out. 4-Picoline (**8**) was reacted with magnesium, calcium and lithium atoms and for all the cases the product was identified as a non-metallated compound. Also a C–H activation took place, but surprisingly, an aryl C–H bond was not activated. In this case an alkyl C–H bond is activated instead and 1,2-di-4-pyridylethane (**10**) (Scheme 3) is formed through loss of hydrogen in an unexpected reaction sequence [15].

In order to facilitate an overview and a comparison of magnesium, lithium and calcium cocondensation reactions, all reactions are summarised in Table 1.

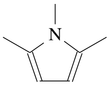
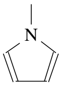
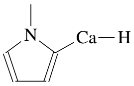
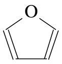
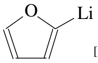
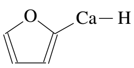
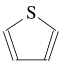
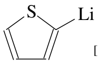
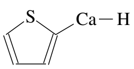
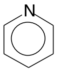
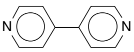
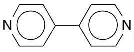
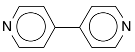
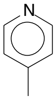
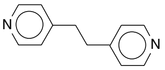
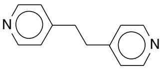
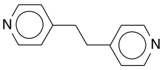
2.2. Theoretical studies

One of the aims of this work was to identify in a theoretical study plausible intermediate species for all these



Scheme 3. Cocondensation reactions of lithium, magnesium and calcium atoms with pyridine **9** and 4-picoline **8** at 77 K.

Table 1
Summary of the reactions of magnesium, lithium and calcium atoms with heterocyclic aromatic compounds in the presence of THF at 77 K

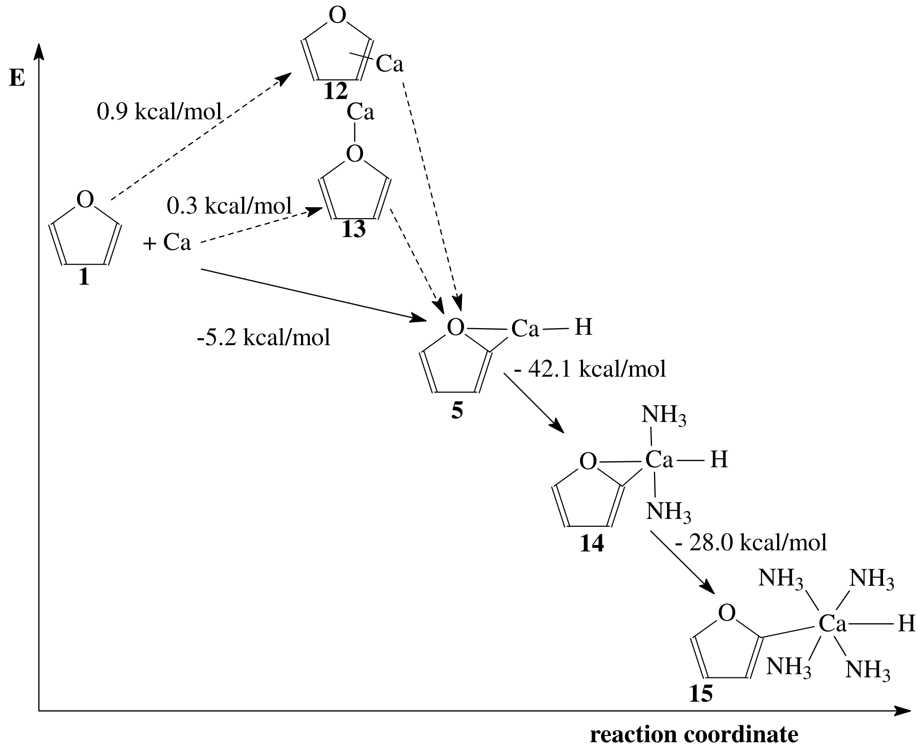
	Mg	Li	Ca
	No reaction	No reaction [8]	No reaction
	No reaction	No reaction [8]	
	No reaction	 [8]	
	No reaction	 [8]	
		 [9]	
			

cocondensation reactions involving calcium atoms and heterocyclic aromatic compounds, and thereby identifying the reaction mechanism for this new type of CH activation. Calculations were performed using GAUSSIAN 98 [16] and the B3LYP DFT functional. As in previous organocalcium theoretical work [17], the basis set combination AKR4/6-31G** was used.

Previous theoretical studies performed with lithium atoms and five-membered heterocycles, showed that the C–H activation reaction involves at least two steps, the coordination of the lithium atom with the aromatic compound and then the insertion of the metal atom into the C–H bond by a double electron transfer via the aromatic system [4,5].

When the same calculations are performed using calcium atoms and furan (Scheme 4), two possibilities are found for the first intermediate. The first possibility is the coordination of one calcium atom to the aromatic system to form a π-complex, and the second possibility is η^1-coordination of the calcium atom to the oxygen in the ring. Both structures are found as stable intermediates, since they are minima on the energy hypersurface. However, their formation is found to be an energetically neutral step with a reaction enthalpy of less than +1 kcal/mol, which is well within the error margin of the applied theoretical method. Please note that in some cases the lines on the diagrams only have topological significance.

Then the formation of the furyl calcium hydride is calculated to be a slightly exothermic step (−5.2 kcal/mol) with respect to the parent compounds. In the next steps solvent molecules fill the coordination sphere of the calcium centre; NH_3 instead of THF molecules were used in these calculations for simplification. When two ammonia molecules are



Scheme 4. Calculated reaction mechanism for the cocondensation of calcium atoms with furan. Calculations were performed using NH_3 instead of THF for simplification.

considered, the reaction leads to a furyl calcium hydride with coordination number 4 with $\Delta H = -42.1$ kcal/mol (Scheme 4), while another two NH_3 molecules fill-up to coordination number 6 in a further exothermic reaction step releasing another 28.0 kcal/mol.

When comparing the structures **5**, **14** and **15**, it can be seen that calcium oxygen interactions are found in some cases. The calculated structure **5** and **14** show a Ca–O bond (231.4 and 242.4 pm, respectively), however when four molecules of solvent are considered (**15**), this Ca–O interaction is lost (d_{CaO}: 326.2 pm). This is due to the coordination number 6 at the calcium centre; now the intramolecular donor furyl cannot compete against the solvent molecules.

Only the formation of monomeric aryl calcium hydride species has been considered, while, as previous reports showed, the formation of oligomeric products is also possible [17].

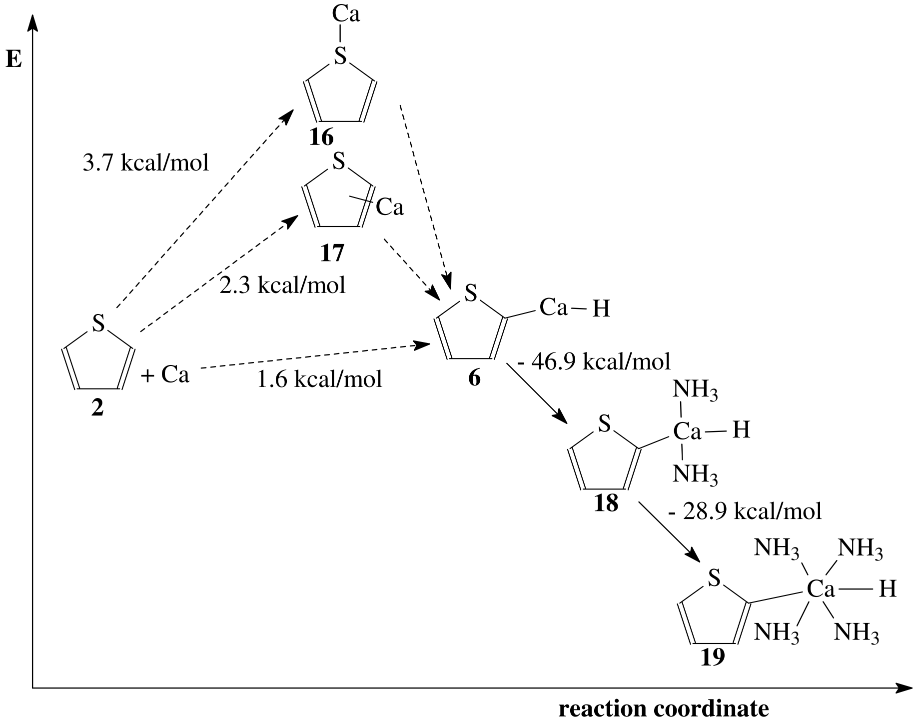
In the thiophene calculations, which are shown in Scheme 5, the formation of the first intermediate is found to be slightly endothermic in both cases of the π- and σ-complexes (+3.7 and +2.3 kcal/mol, respectively). Also the insertion of calcium atoms into the CH bond of thiophene is found to be a slightly endothermic process of +1.6 kcal/mol. However, as it was found in furan, once the solvent is considered in the coordination sphere of the calcium atom, the structures are stabilized. Solvated thiophenyl calcium hydride is formed in two clearly exothermic reaction steps releasing −46.9 and −28.9 kcal/mol when two or four solvent molecules of ammonia, which is used instead of THF to simplify the calculations, are allowed to coordinate. Unlike the furan case, there is no pre-coordination of the calcium centre by sulfur in any of the calculated structures involving thiophene.

The *N*-methyl pyrrole case shows that the formation of the π-complex intermediate (**20**) is found to be slightly exothermic (−1.5 kcal/mol), while the formation of *N*-methyl pyrrolyl calcium hydride **7** from calcium atoms and **3** is slightly endothermic (+1.9 kcal/mol), respectively. The corresponding σ-complex is not found as a stable intermediate, since there is no lone pair available for coordination. However, as in previous cases, once the solvent interaction is considered, the reaction is driven to energetically very stable products. When two ammonia molecules are allowed to coordinate the reaction enthalpy is found to be −41.9 kcal/mol. Another two NH_3 molecules are filling the coordination sphere of calcium completely and release further 28.2 kcal/mol; all results are summarised in Scheme 6.

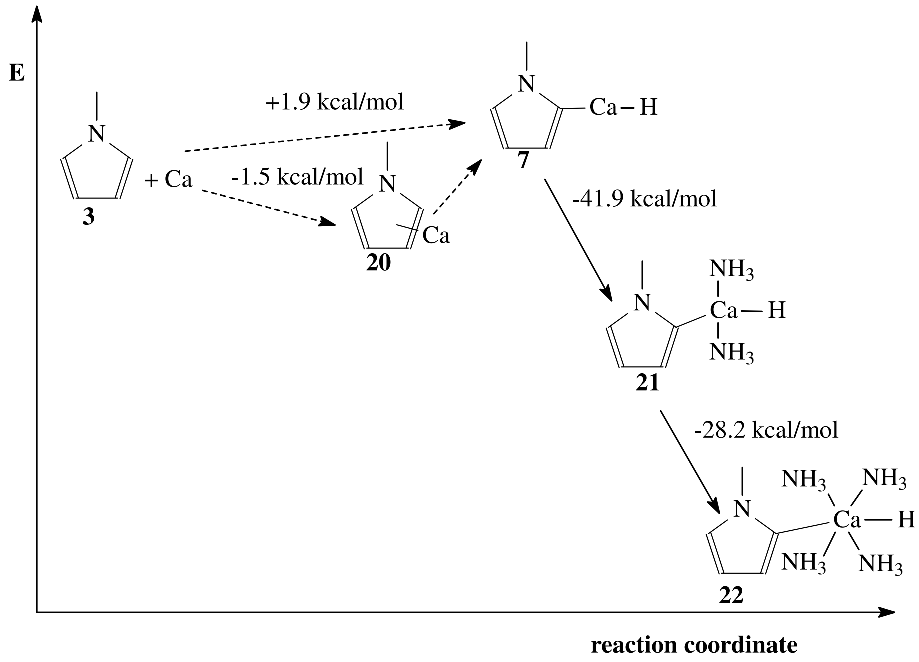
In all calculations involving **1**, **2** and **3** their corresponding π- and σ-complexes with calcium **12**, **13**, **16**, **17** and **20** were calculated as triplet and singlet states; in all the cases singlet states were found to be energetically favoured.

3. Discussion

Previous research in this area showed that five-membered heterocycles react with lithium atoms in the presence of THF under cocondensation conditions [8]. The isolated products were identified as lithiated aromatic compounds. However when the heteroatom in the ring was nitrogen, as seen in pyrroles, the reactions failed so far. Therefore



Scheme 5. Calculated reaction mechanism for the cocondensation of calcium atoms with thiophene. Calculations were performed using NH_3 instead of THF for simplification.



Scheme 6. Calculated reaction mechanism for the cocondensation of calcium atoms with *N*-methyl pyrrole. Calculations were performed using NH_3 instead of THF for simplification.

this study examines the effect of changing the metal to magnesium and calcium for which the analogues reactions are carried out.

As previous reports show [8], a delicate balance between enhancing complex formation ability and lowering LUMO energy, which allows reductive cleavage of the aromatic C–H bond, is needed for a successful C–H activation. The formation of a π- or η^1-complexes was found as the first step in these reactions when lithium metal was used. This is followed by the C–H activation leading to the metallated product. The formation of this intermediate was found to be an exothermic step in all the cases.

However, when the same calculations are performed using calcium atoms, the reactions show an endothermic step for the formation of this intermediate. In the case of thiophene, even the formation of the metallated species **7** is found to be slightly endothermic.

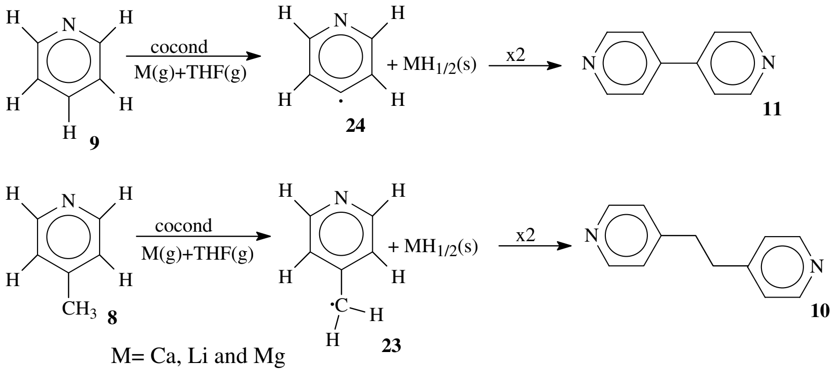
The positive reaction enthalpy can be assumed to be incorrect, since the solvent sphere was omitted. The coordination of the calcium atoms with the THF solvent would stabilise the molecules leading to structures of lower energy. This effect can be seen in the calculated structures of fourfold **14**, **18**, **21**, and sixfold **15**, **19**, **22** coordinated species, which show energetically lowered structures when the solvent is included. Also this coordination effect is observed if the organocalcium species **5** and **6** are compared. Intermediate **6**, which exhibits coordination number two at the calcium centre, is reached in an endothermic reaction step. However, intermediate **5**, with is stabilised by an extra Ca–O coordination is available via an exothermic reaction step.

From such a π- or η^1-complex to furan, thiophene or *N*-methyl pyrrole calcium atoms would be able to transfer electron-density to the aromatic ring. The LUMO energy of the aromatic compound has been interpreted as the key to these reactions [10]. During the C–H activation reaction, the metal atoms will transfer electron density to the aromatic ring in order to form the metallated species. Therefore, high LUMO energy would make electron transfer impossible and thereby preventing the CH activation reaction occurring.

This reaction barrier depends on the metal used. Metals with lower ionisation potentials will activate aromatic rings with higher LUMO energy. In Table 2 are listed the aromatic compounds used in this project, their LUMO energies and the reactions that occurred. For example, magnesium metal would need an aromatic compound with a very low LUMO energy to be able to transfer its two electrons to the aromatic ring; therefore the five-membered heterocycles used make it impossible to see the activation reaction. However, lithium and calcium atoms, which have lower ionisation potentials, are able to activate C–H bonds in these aromatic rings, although, there is a limit for both metals. Lithium atoms do not react with the pyrrole derivatives used and calcium atoms will only react with some of them as summarised in Table 2.

Table 2
Calculated LUMO energies of selected reactants using B3LYP/6-31G** compared with their reactivity in selected cocondensation experiments

	LUMO (eV)	Reaction		
		Mg	Li	Ca
1,2,5-Trimethyl pyrrole	1.44	No	No	No
1-Methyl pyrrole	1.27	No	No	Yes
Furan	0.51	No	Yes	Yes
Thiophene	−0.22	No	Yes	Yes



Scheme 7. Proposed mechanism for the cocondensation of calcium, lithium and magnesium atoms with pyridine and 4-picoline.

All these reactions show a C–H activation process, which is always taking place in the ortho position with respect to the heteroatom. Therefore, the cocondensation reaction of aromatic heterocycles and metal atoms can be considered as an important tool for direct ortho metallation of aromatic rings, which has its counterpart in the directed ortho metallation in solution chemistry [18].

This different behaviour of calcium, lithium and magnesium cannot be seen in the cocondensation reactions with pyridine or 4-picoline. In these cases the three metals lead to the same product: the formation of an organic dimer by loss of hydrogen and the formation of a new C-C bond. The formation of a metallated pyridine [19] or picoline is not found in any case.

It seems that the reaction proceeds through a radical intermediate (**23**,**24**) where the aromatic ring has been dehydrogenated and solid metal hydride is formed as well (Scheme 7).

4. Conclusions

When aromatic five-membered heterocycles are cocondensed with lithium, magnesium or calcium atoms in the presence of THF, ortho-metallated products are formed in highly selective C–H activation reactions. However the reaction does not take place in all cases and the LUMO energy of the aromatic ring is interpreted as the main barrier of the reactions. Considerably high LUMO energies will prohibit the carbon hydrogen activation reaction. However the limit in the LUMO of the aromatic compound highly depends on the metal used and there is a clear difference among the three metals.

Lithium atoms are able to activate C–H bonds in aromatic compounds as furan or thiophene, but fail to activate pyrrole derivatives **3** and **4** due to their high LUMO energy. Calcium metal has a higher potential to activate aromatic species and it can react with *N*-methyl pyrrole despite its high LUMO energy. Nevertheless, even calcium atoms fail to activate 1,2,5-trimethyl pyrrole, which has the highest LUMO energy of all compounds used in this project. On the other hand, magnesium needs a very low LUMO barrier and it is not able to activate any the 5-membered heterocyclic compounds **1**–**4**.

When pyridine and 4-picoline are cocondensed with lithium, magnesium or calcium atoms in the presence of THF, the reaction changes towards the formation of aromatic dimers via the formation of a C–C bond and metal hydride is found as a by-product. Here a C–H activation reaction is found in a ring position in the case of pyridine, while 4-picoline shows an unexpected dimerisation via the formation of a C–C bond in the methyl groups.

5. Experimental section

5.1. General

All experimental procedures were performed using standard Schlenk techniques under an atmosphere of dry argon. THF was dried and distilled from sodium benzophenone ketyl under an atmosphere of argon. Furan, thiophene, 1-methyl pyrrole, 1,2,5-trimethyl pyrrole, pyridine and 4-picoline were dried and distilled from calcium dihydride under an atmosphere of argon. All solvents were then degassed by three freeze–pump–thaw cycles. Celite was stored in an oven at 120 °C overnight and was dried under vacuum for three hours before use. For each filtration a plug of approximately 6 cm of celite was used and each filtration was performed under the vigorous exclusion of air and moisture. ^{1}H and ^{13}C NMR spectra were obtained using either a Varian 300 MHz or a Varian 500 MHz NMR machine. All chemical shifts are reported in ppm and are referenced to TMS. All GC–MS samples were run as liquid samples in ethylacetate using a Finnigan Trace GC–MS, equipped with a RTX-5MS 15 m column.

5.2. A typical cocondensation experiment

Approximately 0.3 g of magnesium, 0.5 g of lithium or 0.2 g of calcium metal are vapourised from an alumina crucible over 90 min and cocondensed with a mixture of 10 ml of the aromatic compound and 80 ml of THF. In the case of lithium metal, a stainless steel inlet protects the crucible to react with lithium metal. The pressure that what measured at the button of the cocondensation vessel was kept below 10^{-5} mbar to avoid gas phase reactions of the metal atoms and reactants. The apparatus used was described previously [4]. At the end of the experiment, the frozen matrix was allowed to warm-up under argon. The molten mixture flowed through an internal drain into a Schlenk tube. The solution was filtered through a plug of celite in order to remove the solid metal-hydride by-product and unreacted metal. After removal of the solvent mixture in vacuo, a solid was isolated and washed with 20 ml of THF. The lithiated aromatic compound was identified by derivatisation with Me_3SiCl.

5.3. A typical derivatisation of the metallated aromatic with Me_3SiCl

To a room temperature solution of the metallated aromatic compound in 20 ml of THF, Me_3SiCl in THF solution was added dropwise with vigorous stirring. The reaction was judged finished when a colour-change from dark red-yellow to pale yellow occurred. This solution was filtered and the solvent was removed under reduced pressure, which gave the trimethylsilyl derivative. GC–MS as well as ^1H and ^{13}C NMR spectroscopy was used to identify the product.

5.4. Theoretical methods used in this study

DFT calculations were performed using B3LYP and the basis set combination AKR4/6-31G**, where 6-31G** is applied to C, H, N, O and S and AKR4 is used for calcium atoms. This combination has proved to give reasonable geometries without greatly increasing the calculation time. In order to reach reasonable calculation times, ammonia was used as a model of solvent instead of THF, which is the solvent of choice used for the cocondensation reactions.

For this purpose the program GAUSSIAN 98 [16] was used on a Dell workstation running Red Hat Linux. Harmonic vibrational frequencies, calculated at the same level, characterised stationary points and gave the zero-point energy. The difference in the sum of the electronic and the zero-point energies were interpreted as reaction enthalpies at 0 K. LUMO energies for each aromatic compound were obtained from geometry optimised structures using B3LYP/6-31G**.

5.5. 2-Trimethylsilyl furan

The general procedure applied to furan with calcium metal gave 2-furyl calcium hydride (red colour) in 18% yield (2.4 g), which was identified as its TMS derivative [11] by NMR and GC–MS.

5.6. 2-Trimethylsilyl thiophene

The general procedure applied to thiophene with calcium metal gave 2-thiophenyl calcium hydride (red colour) in 23% yield (2.7 g), which was identified as its TMS derivative [12] by NMR and GC–MS.

5.7. N-methyl-2-trimethylsilyl pyrrole

The general procedure applied to *N*-methyl pyrrole with calcium metal gave 2-(*N*-methyl pyrrolyl) calcium hydride (dark yellow colour) in 8% yield (1.5 g), which was identified as its TMS derivative [13] by NMR and GC–MS.

5.8. 4,4′-Bypyridine

The general procedure applied to pyridine with calcium and magnesium metal gave 4,4′-bypyridine in 7% and 17%, respectively [14], which was identified by NMR and GC–MS.

5.9. 1,2-Di-4-pyridylethane

The general procedure applied to 4-picoline with calcium, lithium and magnesium metal gave 1,2-di-4-pyridylethane in 5%, 18% and 19%, respectively [15], which was identified by NMR and GC–MS.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2005.11.022.

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