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Addition of benzyne to thiophene—a DFT study

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ABSTRACT: The literature reports the $2+2$- and $4+2$-cycloadditions of benzyne and thiophene and provides several reaction paths accounting for the observed products: 1-naphthyl and 2-naphthyl phenyl sulfides. A DFT study of these paths shows that some presumed reaction intermediates are, in fact, not stable entities. A new reaction path adapting a portion of the literature paths but with a lower activation free energy is described. Copyright © 2004 John Wiley & Sons, Ltd.
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KEYWORDS: cycloaddition; pericyclic reaction; heterocycle; rearrangement

INTRODUCTION

Although kinetic studies at multiple temperatures allow one to calculate transition structure energies, knowledge of structural details and electronic characteristics can only be acquired by theoretical calculations. Houk, *et al.*[1] presented a detailed discussion and application of theoretical calculations to those pericyclic reactions related to the Woodward–Hoffmann Rules. They concluded the discussion with a summary of generalized transition structures and average bond lengths calculated for these reactions.

Given its known aromatic character, thiophene has proven a reluctant partner in pericylic Diels–Alder reactions. An exception to this statement was provided when it was shown that tetrafluorobenzyne reacted readily with thiophene, producing tetrafluoronaphthalene as the main product (40%).[2] Subsequently, Reinecke and co-workers[3] published a detailed study of the reaction of benzyne with thiophene. Diphenyliodonium-2-carboxylate was used as the benzyne source in their study;[3c] side reactions were minimal with this reagent. Reactions were run without solvent at temperatures of 185–200 °C. Again, naphthalene was the major product (29%) with the α- and β-naphthyl phenyl sulfides formed in 9% and 6% yields, respectively. The mechanism of the formation of these products is the item of major interest in the study reported here.

COMPUTATIONAL METHODS

Calculations at the B3LYP/6–31G* level were employed throughout, although lower level calculations were occasionally used as starting points (this level has been established as satisfactory for calculations on related systems[4]). All structures were optimized with Gaussian 98.[5]

The union of benzyne with thiophene poses a potential error due to basis set superposition. Benzyne and thiophene were optimized as separate entities. The combined structures were then optimized while separated by 6 Å. A counterpoise calculation on the combined structures indicated a BSSE correction of only $0.05\,\text{kcal mol}^{-1}$ ($1\,\text{kcal} = 4.184\,\text{kJ}$), an error in energy considerably below those expected ($\pm 2\,\text{kcal mol}^{-1}$) from single-method calculations at this level. The energies for all structures subsequently reported here belonged to either a $C_{10}H_8S$ or $C_{16}H_{13}S$ series, so that the number of molecular orbitals and electrons were the same within each series.

Synchronous transit-guided quasi-Newton methods (QST2 or QST3)[6] were used to obtain approximate transition structures. These were refined and tested by frequency calculations. Structures, vibrations and ESP charges were examined visually by Gaussview (Gaussian, Pittsburgh, PA, USA). Each transition structure gave a single imaginary frequency consistent with a valid reaction coordinate. Thermal corrections to 473 K were carried as part of the frequency calculations yielding free energies at this temperature.

RESULTS AND DISCUSSION

Based on product analysis, the known chemistry of benzyne and from various precedents in the literature, Del Mazza and Reinecke[3e] postulated two mechanistic schemes that are adapted here as Schemes 1 and 2 (see also Figs 1 and 2). To facilitate the discussion, the structures have been renumbered from the originals. The free energies pertinent to this study are given in Table 1.

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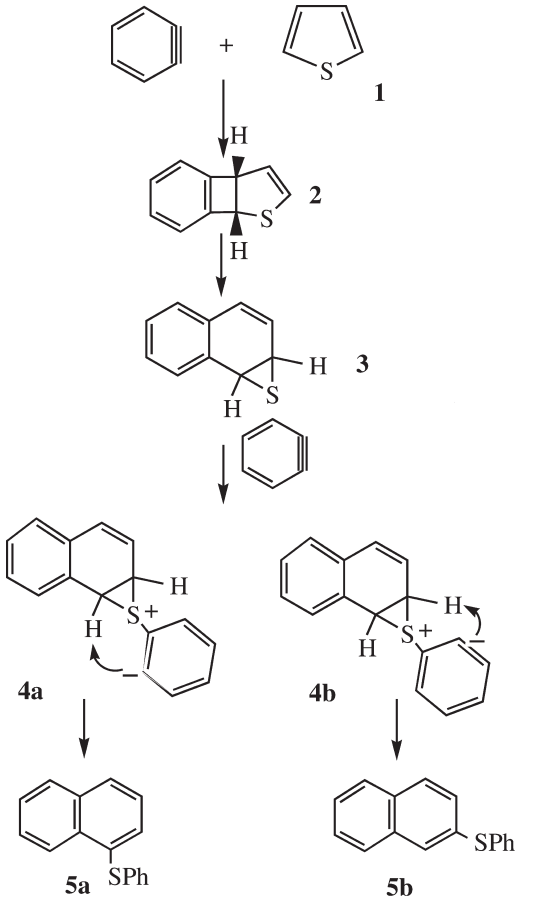
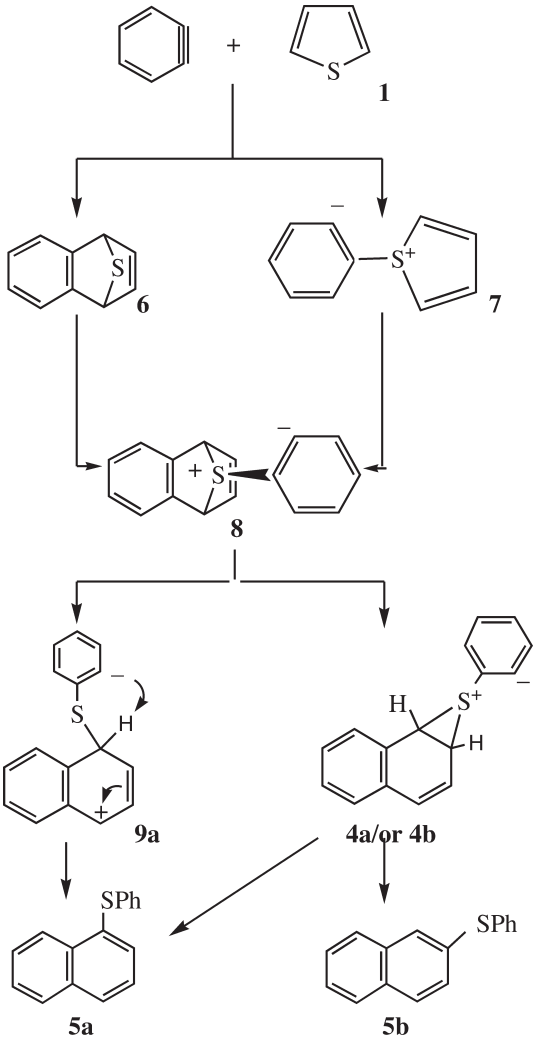


Scheme 1. Postulated steps in the 2 + 2-cycloaddition of benzyne to thiophene[3e]



Scheme 2. Two possible routes to products **5a** and **5b**[3e]

The reported yields (GC–MS) of the observed α- and β-napthyl phenyl sulfides (9% and 6%, respectively) reasonably means the both are formed to the same degree within experimental error. The same can be said of the free energies of formation for these products (-143.4 and $-145.8\,\text{kcal mol}^{-1}$, respectively). Since both products may hypothetically be formed from either of the postulated mechanistic paths in Schemes 1 and 2, the yields and energies cannot be used to discriminate between the two schemes. Although one may feel intuitively that formation of the four-membered ring in **2** would be unfavorable compared with the 4 + 2-cycloaddition product, it is now known that thiophene, in contrast to other five-membered ring heterocycles, does undergos 2 + 2-cycloaddition readily.

Before examining the details of the two reaction schemes, two simplifications will be considered. Ostensibly structure **7** (Scheme 2) was offered as a stable intermediate, and the AM1 structure for **7** had a reasonable benzyne–S bond length of 2.437 Å. However, the B3LYP optimization of this structure exhibited a progressive lengthening of this bond and decreasing values of the energy. Optimization was achieved at 3.673 Å, a length well beyond that expected for a stable benzyne–S covalent bond. Furthermore, the bonds in the two ring components exhibited the bond lengths of the free structures, suggesting that dissociation was essentially complete. Although the proposed structure for **7** is not a stable entity, the energy value for **7** (Table 1) may be approximated from a B3LYP/6–31G*/AM1 calculation.

In a similar fashion, structure **8** was presumed to be a stable structure, and so it is at the AM1 level. However, B3LYP optimization of **8** led to an exothermic rearrangement ($-179.1\,\text{kcal mol}^{-1}$) to **10**. Since **10** is not a reported reaction product, one must assume that both branches of Scheme 2 stop at this point.

As shown in Scheme 1, the 2 + 2-cycloaddition of benzene to thiophene forms the tricyclic structure **2** with an activation free energy of $21.0\,\text{kcal mol}^{-1}$. The strained four-membered ring in **2** undergoes an exothermic ring opening ($-23.4\,\text{kcal mol}^{-1}$) to **3** with an activation free energy of $33.2\,\text{kcal mol}^{-1}$.

The first reaction in Scheme 2 is the 4 + 2-cycloaddition of **1** forming **6**. The reaction to **6** is exothermic by $-36.5\,\text{kcal mol}^{-1}$; whereas the activation free energy is $34.1\,\text{kcal mol}^{-1}$. Kinetically, the 2 + 2-cycloaddition is faster than the 4 + 2-addition. The original authors[3]

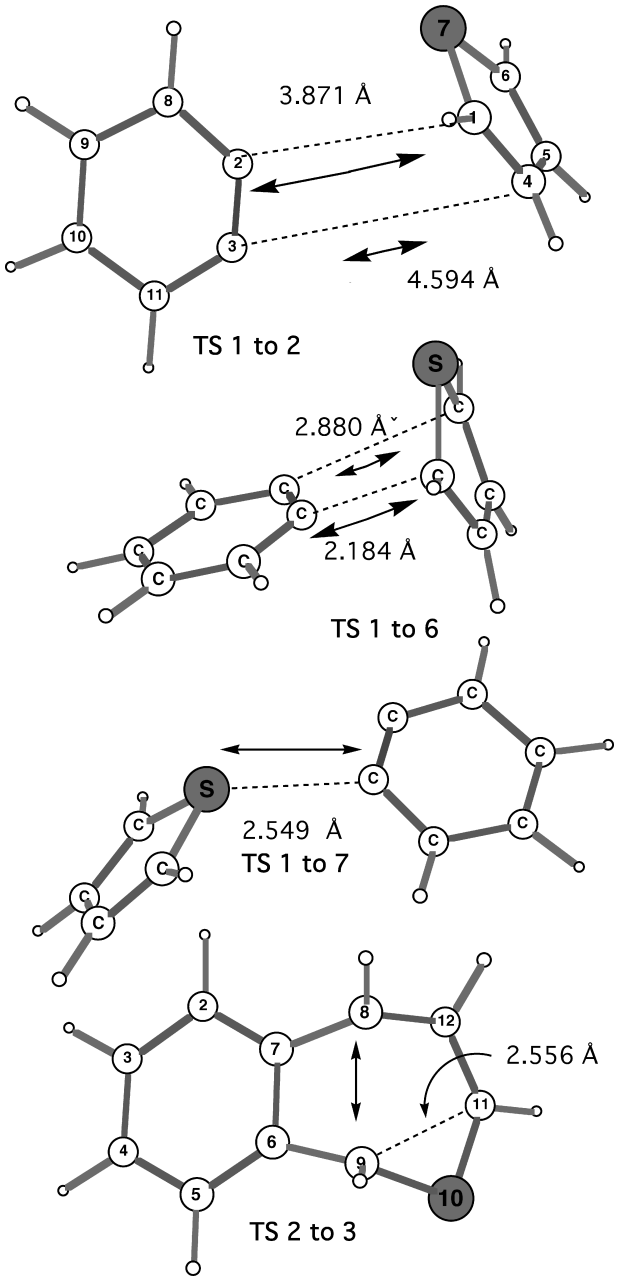


Figure 1. The four transition structures required for Schemes 1 and 2. The arrows indicate the direction and magnitude of the bond vibrations

postulated conversion of **6** to **8** is now an established dead end. There is a path, however, not considered by the original authors, namely the allylic rearrangement of **6** to **3** (Fig. 3). Such thermal allylic rearrangements are known.[7] According to this thinking, Scheme 2 joins Scheme 1 at structure **3**. The reactions of **2** to **3** and of **1** to **6** are the rate-determining steps for each path.

Subsequent reaction of **3** with a second benzyne produces structure **4**. Initial optimization of **4** places the pendant $C_6H_4^-$ perpendicular to the plane of the incipient naphthalene ring. The two rotamers shown as **4a** and **4b** were found by PM3 calculations to fall at 20.2 and 20.0 kcal mol^{-1} higher energies referenced to this equilibrium structure.

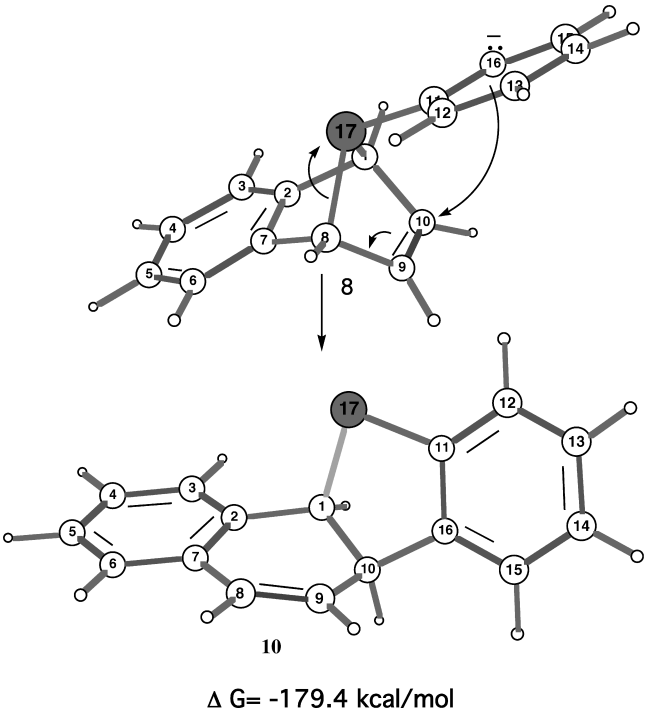


Figure 2. The rearrangement of **8** to **10**

Hydrogen atom transfer and ring-opening rearrangement then leads to products **5a** and **5b**.

In conclusion, although portions of the originally proposed reaction schemes[3e] meet the criteria of

Table 1. Free energies of structures in Schemes 1 and 3[a]

Structure	E_h (hartree)	ΔG (kcal mol^{-1})
Scheme 1		
Benzyne	−230.884348	—
Thiophene	−552.984722	—
Benzyne + thiophene (**1**)	−783.86907	—
2 (**1** → **2**)[b]	−783.92699	−36.4
3 (**2** → **3**)	−783.96424	−23.4
3 + benzyne	−1014.84859	—
4 (**3** → **4**)	−1014.79989	−29.2
5a (**1** → **5a**)	−1014.98197	−143.4
5b (**1** → **5b**)	−1014.98578	−145.8
Scheme 2		
6 (**1** → **6**)	−783.92722	−36.5
7[c] (**1** → **7**)	−783.89692	−17.5
8[c] (**6** → **8**)	−1014.75624	34.7
9 (**8** → **9**)	−1014.83792	−51.3
Figure 2		
8 to **10** rearrangement	−1015.04156	−179.4
Various TSs	$E_h^{\ddagger}$ (hartree)	$\Delta G^{\ddagger}$ (kcal mol^{-1})
1 to **2**	−783.83563	21.0
2 to **3**	−783.87401	33.2
1 to **6**	−783.81470	34.1
1 to **7**	−783.82017	30.7
6 to **3**	−783.88895	24.0

[a] Energies were determined at the B3LYP/6–31G* level and a thermal correction to 200 °C was applied.
[b] The numbers in parentheses represent the differences in energies reflected in the last column.
[c] B3LYP/6–31G*//AM1.

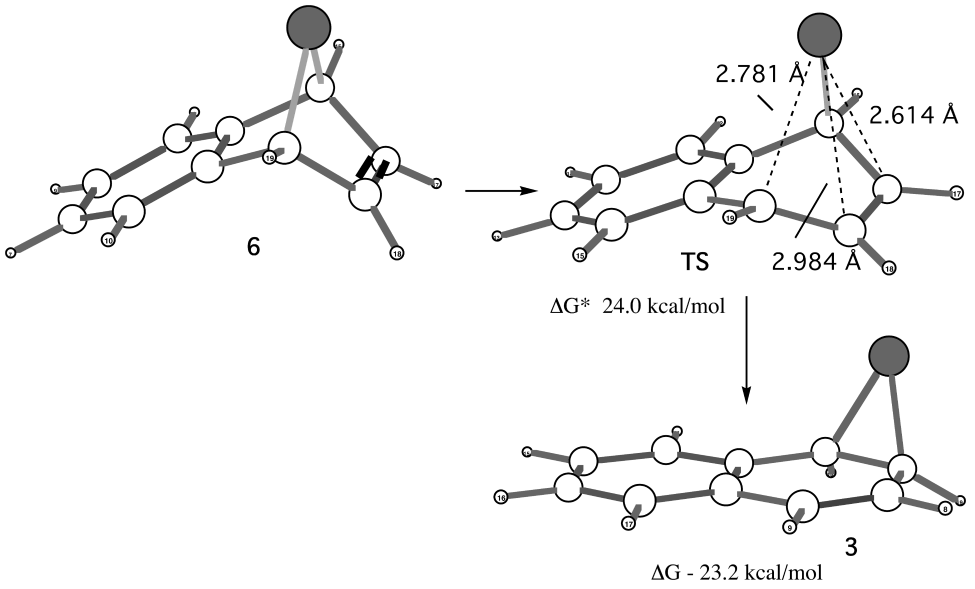


Figure 3. The pathway from **6** to **3**

computational stability and rational energetics, the instability of structures **7** and **8** requires modification of the initial proposal. The $4+2$ path then crosses over from **6** and joins the $2+2$ path with structure **3**. The possible paths appear to proceed by both $2+2$- and $2+4$-additions with approximately equal facility.

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