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Electrophilic hexa(methoxycarbonyl)cycloheptatrienyl anion in the synthesis of electron-deficient 5-hydroxyisoquinolones

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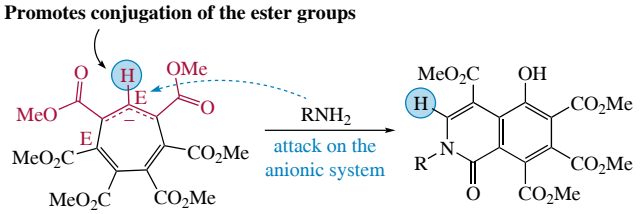
The reaction of hexa(methoxycarbonyl)cycloheptatrienyl anion with amines affords 5-hydroxyisoquinolones bearing four 4,6,7,8-positioned methoxycarbonyl groups and having unsubstituted C^{3}H unit. The reaction is selective due to better steric availability and both charge and orbital distribution within the seven-membered ring and may proceed through a nucleophilic attack on the allyl-anionic moiety.



Keywords: cycloheptatriene, cycloheptatrienyl anion, 8π-electrocyclic ring-opening, dritterion, 5-hydroxyisoquinolones, large Stokes-shift, fluorescent dyes.

Cycloheptatrienyl anions with multiple withdrawing groups can form bench-stable salts with pK_a (DMSO) values down to 8.[1,2] Theoretical heptacyanocycloheptatriene has a pK_a value of –10 and retains a highly antiaromatic character.[1] In addition to their fundamental importance, these anions have shown versatile ambiphilic reactivity. For instance, hepta(methoxycarbonyl)-cycloheptatrienyl anion **1** has demonstrated nucleophilic reactivity towards alkyl halides, halogens, tropylium and aryldiazonium ions and azides.[3] Conversely, the nucleophilic addition of amines to hepta(methoxycarbonyl)cycloheptatrienyl anion initiates a cascade reaction resulting in the formation of 5-hydroxyisoquinolones.[4] Additionally, we observed anti-aromatic nucleophilic substitution reactions in cycloheptatrienyl-anion zwitterions. In these cases, the cycloheptatrienyl-anion moiety does not directly react with nucleophiles but instead eliminates either pyridine or triphenylphosphine initially forming a Möbius-aromatic cycloheptatetraene intermediate.[5] The most practically interesting results include superphotoacidity-induced[6] large Stokes-shift fluorescence in the abovementioned 5-hydroxyisoquinolones.[7] However, these phenomena are specific to the very anion **1**, whereas other cycloheptatrienes and their anions with up to five electron-withdrawing groups[8] do not exhibit such a reactivity. Moreover, other methods for the synthesis of isoquinoline derivatives afford different substitution patterns and mainly give electron-abundant derivatives.[9–20] Therefore, herein we present our investigation into the reactivity of hexa(methoxycarbonyl)cycloheptatrienyl anion **2** toward amines. Additionally, we explore the mechanistic details of this reaction.

According to X-ray data,[21] anion **1** represented a nearly planar pentadienylic anionic system with a double bond fragment extending out of the plane. In a recent study,[1] we discovered that the most stable conformers in solutions of both **1** and **2**, as well as most other cycloheptatrienyl anions, were distorted to an allylic anionic system with a diene fragment twisted over the former. Our prior research indicated that the reaction of **1** with amines proceeded through a nucleophilic addition to the separated double bond of the diallylic conformer (Figure 1, left). Taking into consideration our data concerning the anions' geometry in solutions, we investigated the possibility of direct nucleophilic addition to the most stable conformers of **1** and **2**, without a conformational transition into the diallylic conformer. Thus, we propose that amines may attack either the center of the allylic anionic fragment (the *ipso*-position, see Figure 1) or the β-position. This suggestion is substantiated by the charge distribution in species **1** where the *ipso*-position possesses a slightly positive charge (Table 1), whereas the negative charge is localized at the α- and γ-positions; and by the LUMO shapes

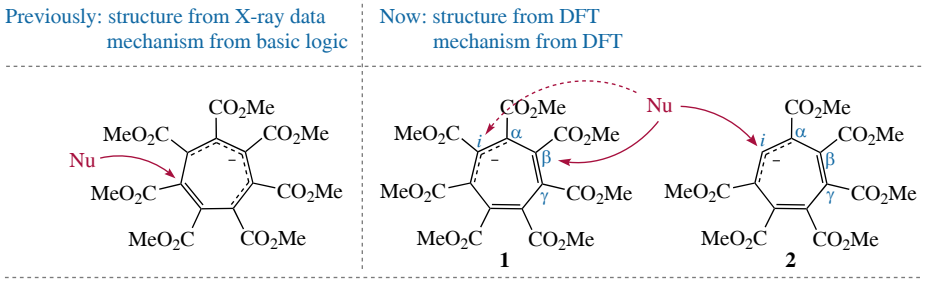


Figure 1 Previous and new understanding of the nucleophilic attack onto cycloheptatrienyl anions **1** and **2**.

Table 1 Atomic charges and Fukui function indices at cyclic carbon atoms in cycloheptatrienyl anions **1** and **2**.

Anion	Charge[a]				f^+ index[b]	
	i	α	β	γ	*i*	β
1	0.111	–0.240	0.007	–0.120	0.203	0.126
2	0.033	–0.251	0.075	–0.141	0.200	0.166

[a] Charges were obtained *via* revDSD-PBEP86(D4)/aug-cc-pVTZ//r^{2}SCAN-3c/CPCM(DMSO) level of theory. [b] Fukui function indices were obtained *via* PBE0/def2-TZVP//r^{2}SCAN-3c/CPCM(DMSO) level of theory.

[Figure 2(*a*),(*b*)]. Moreover, we conducted an analysis of the Fukui function indices (f^+) at different positions of the ring. This function is determined as the change in the electron density when the number of electrons changes from $n+1$ (radical anion) to n (neutral molecule).[22] These indices indicate which parts of a molecule are most likely to be attacked. Our analysis of the Fukui function indices in species **1** indicates that both *ipso*- and β-positions are electrophilic, but the Fukui function index at the *ipso*-position is almost twice as large [Table 1, Figure 2(*c*),(*d*)].

In the most stable conformer of species **2**, the allyl-anionic fragment is positioned so that the hydrogen atom is attached to the middle carbon atom thereof (at the *ipso*-position), promoting coplanarity of the α-positioned ester groups with the anionic system. Consequently, the charge distribution in **2** is similar to that in **1**; however, the absence of one ester group shifts the positive charge from the *ipso*-position to the β one. Conversely, the Fukui function indices remain similar to those of **1**, with the most electrophilic carbon atom at the *ipso*-position. Therefore, owing to this and better steric availability, the *ipso*-position in anion **2** is most likely to be attacked by a nucleophile.

In this investigation, cycloheptatrienyl anion **2** is generated *in situ* from cycloheptatrienehexacarboxylate **3** (Scheme 1), which, in turn, was formed through the cascade reaction of dimethyl glutaconate with dimethyl bromomaleate and pyridine.[2] It can be obtained as a single isomer that is not the most stable but is the least soluble (see Online Supplementary Materials). Anion **2** possesses four distinct electrophilic centers within the cycle potentially leading to totally seven subsequent electrocyclic ring-opening pathways. Among these pathways, five can result in various isomeric 5-hydroxyisoquinolones (mechanistic details will be discussed below). Nevertheless, our investigations into the reactivity of **2** towards amines revealed the formation of a single isomer of 5-hydroxyisoquinolones **4a–d**, with the yields being generally lower than those from **1**.[7] The position of the hydrogen atom in the heterocycle was determined from a NOESY spectrum of benzylated derivative **4c** (see Scheme 1).

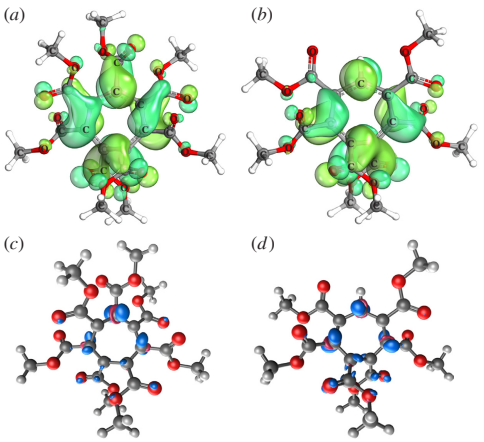
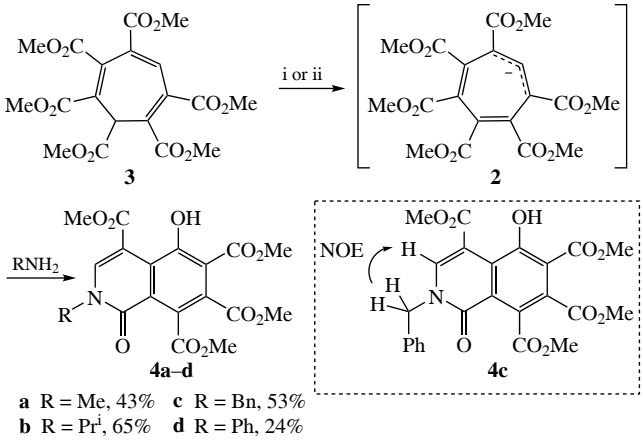


Figure 2 (*a*), (*b*) Visualizations of the LUMO shapes obtained *via* r^{2}SCAN-3c/CPCM(DMSO). (*c*), (*d*) The Fukui function f^+ obtained *via* PBE0/def2-TZVP/CPCM(DMSO) for anions **1** and **2**, respectively.



Scheme 1 *Reagents and conditions*: i, RNH_2, K_2CO_3, DMF, 60 °C, 8 h (for **4a–c**); ii, $PhNH_2$, Et_3N, DMF, 80 °C, 72 h (for **4d**).

This corresponds to a nucleophilic attack on the *ipso*-position, as shown in Figure 1, which is consistent with the Fukui function indices presented in Table 1.

In our previous investigations,[7] we presented an overview of the mechanism postulating the formation of cycloheptadienyl anion **5** from **1** and its subsequent electrocyclic ring-opening into **6** at the initial stages. To delve deeper, we employed quantum chemical calculations to explore the initial addition of methylamine to cycloheptatrienyl anions **1** and **2** (Scheme 2, Figure 3). This addition stage was found to be rate-limiting in both cases, with a notably lower barrier in the case of anion **2** (25 kcal mol^{-1} *vs.* 32 kcal mol^{-1}). This stage led to the formation of species **7**, which contained a cycloheptadienediyl dianionic fragment — a local minimum as per quantum chemical calculations. The two anionic allylic fragments in these dritterions are separated by a single bond (1.45–1.49 Å) indicating minimal or no conjugation between them.

Transition states were identified by considering the reverse stages of methylamine elimination from dritterions **7**, as this allows the reaction direction to be set through increasing the CH-bond length. Notably, the dritterion formed from **1** (X = CO_2Me) afforded the allylic conformer of **1** with amine close to its β-position according to its geometry, whereas the dritterion formed from **2** (X = H) yielded the conformer of anion **2** corresponding precisely to an attack at the center of the anionic fragment (the *ipso*-position), as suggested above. It is important to note that these results do not necessarily preclude a nucleophilic attack on the *ipso*-position in **1** as well as onto other conformers, since quantum chemical calculations in these systems are hindered by huge conformational ensembles.

Dritterions **7** undergo proton migration to form anions **5** with a significant decrease in free energy. To the best of our knowledge, the transformations of **5** into **6** represent the sole examples of 8π-electrocyclic ring-opening reactions known thus far,[23,24] with

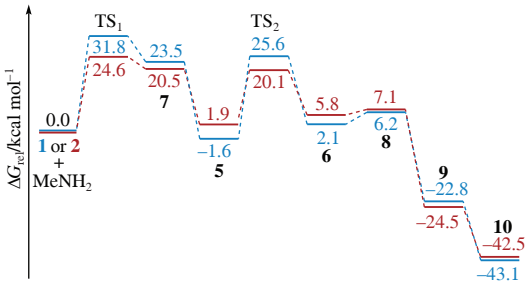
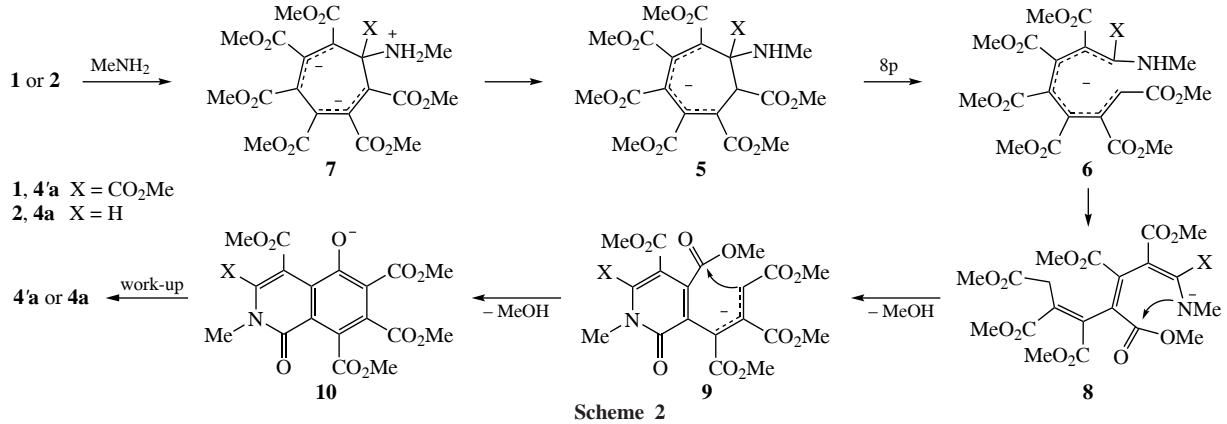


Figure 3 Rationalization of the mechanism for the formation of 5-hydroxyisoquinolone anions **10** from cycloheptatrienyl anions **1** and **2**. The energies were obtained *via* revDSD-PBEP86(D4)/aug-cc-pVTZ/CPCM(DMF)//r^{2}SCAN-3c/CPCM(DMF) level of theory.



Scheme 2

even 6π-electronic ring-opening reactions[25] being exceptional in carbocyclic systems (not ring-expansions).[26–32] The absence of one ester group results in a lower barrier for the ring-opening stage, with both barriers being lower than those of the addition stages. The subsequent stages of the mechanism include proton migration with a conformational transition into **8**, amidation into pyridinone **9** and the Dieckmann condensation to form **10**. The last stages cause a significant decrease in free energy due to the formation of aromatic rings (~30 kcal mol^{-1} for the first and ~20 kcal mol^{-1} for the second rings). Since the modeling of methanol elimination may require consideration of the reaction medium, unlike the rearrangements, the barriers and intermediates of these stages were omitted.

To summarize, we have demonstrated that hexa- and hepta(methoxycarbonyl)cycloheptatrienyl anions have similar reactivity towards nucleophiles. However, the nucleophilic attack in the former case proceeds to the middle atom of the allyl-anionic system, while in the latter case, the separate diene fragment is more likely to be attacked. Despite the presence of four potential reactive sites, the reactivity of hexa(methoxycarbonyl)-cycloheptatrienyl anion is selective because of the better steric availability as well as orbital control. The full mechanism of the formation of 5-hydroxyisoquinolone, including the formation of a dritterion, was established *via* DFT calculations. The compounds obtained seem promising as fluorescent materials.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7616.

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