First innermolecular Diels–Alder reaction of *o*-benzyne inside a molecular container compound

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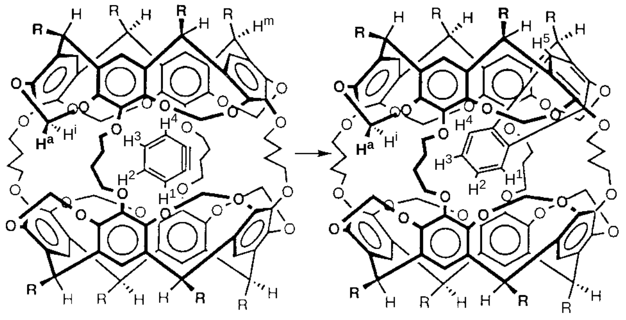
1,2-Didehydrobenzene 1, incarcerated in the inner phase of a hemicarcerand 2, undergoes an innermolecular Diels–Alder reaction with its surrounding host, which is a new type of reaction at the borderline between intra- and intermolecular reactions.

Previously, we reported the successful generation of the highly reactive *o*-benzyne **1** in the inner phase of a molecular container compound.[1] The synthesis and application of molecular container compounds was developed by D. J. Cram.[2] They are particularly suitable for the generation and study of highly reactive species, which cannot be isolated under usual conditions in solution.[3] *o*-Benzyne was generated inside hemicarcerand **2**[4] by UV illumination of incarcerated benzocyclopropenone **3** at 77 K in [$^2H_8$]THF. It was stable enough in solution to determine and fully interpret for the first time its solution ^1H and ^{13}C NMR spectra.[1] However, the high reactivity of **1**, even at low temperature, led to the inner phase reaction of the incarcerated *o*-benzyne with hemicarcerand **2**. This reaction is the first reported reaction[2c,5] where the guest reacts with the surrounding host shell. Now we report the results of a detailed investigation of this reaction.

Incarcerated *o*-benzyne **2**⊙**1** was prepared photochemically from a solution of **2**⊙**3** in [$^2H_8$]THF at 77 K as described previously.[1] During the warming of the sample to room temperature the incarcerated **1** reacts with the host to form the addition product **4** (> 90%) (Scheme 1).† This new compound **4** was isolated and analysed. The elemental analysis, FT-IR spectrum and the FAB-MS, which shows only a single peak at the expected mass of the benzyne hemicarceplex [M + 1] = 2327, are all consistent with a reaction product of *o*-benzyne with the host **2**. In the ^1H NMR spectrum of **4** (Fig. 1) the outward pointing hydrogens H^a of the eight methylene spanners, which are equivalent in **2**⊙**3**,[1] are split into four doublets. Each integrates for two protons. The same is true for the inward pointing methylene protons H^i and the eight methine protons, which give four triplets. The proton signals originating from *o*-benzyne were identified at δ 6.14 (d, 1 H, H^1), 5.21 (t, 1 H, H^2), 4.58 (t, 1 H, H^3) and 3.12 (d, 1 H, H^4). Their relationship was identified by ^1H homonuclear shift correlation experiments. The only reaction that is consistent with the observed ^1H NMR spectrum is the [4 + 2] Diels–Alder reaction illustrated in Scheme 1.



1⊙**2** R = CH_2CH_2Ph **4**

Scheme 1

o-Benzyne (ene component) adds to one of the aryl ether units of **2** (diene component) to give the geminal *para* adduct **4**. In the ^{13}C NMR spectrum of the $^{13}C_6$ labelled Diels–Alder product, obtained from the addition of ^{13}C labelled *o*-benzyne **5** to **2**,[1] the signals for the six carbons originating from **5** appear at δ 149.20, 142.98, 122.38 (C-H^2), 120.85 (C-H^3), 119.34 (C-H^4) and 117.04 (C-H^1). The chemical shifts agree well with the corresponding chemical shifts of benzocyclooctatriene model compounds.[6]

We studied *o*-benzyne and its reactivity in the inner phase of **2** by ^1H NMR spectroscopy in the temperature range between −75 and −108 °C in [$^2H_8$]THF. In this temperature range, we noticed an upfield shift of the signal assigned to the protons H^1 and H^4 and a downfield shift of the signal of the protons H^2 and H^3 with increasing temperature [Fig. 2(*a*)]. These shift differences seem to be too large to be just a temperature effect, since the downfield shift of the guest protons of **2**⊙benzene ($\Delta\delta$ 0.033 ppm) is only 8% of the shift of H^1 and H^4. We believe that upon lowering the temperature the two cavitands of **2** are squeezed together more tightly to increase the number of van der Waals contacts. As a consequence, the shape of the inner cavity, which is characterized by the ratio of the length of the polar axis l_{pa} and the equatorial axis l_{ea}, will change, leading to a smaller l_{pa}/l_{ea} ratio at lower temperature [Fig. 2(*b*)].

Due to its shape, *o*-benzyne **1** will be more likely located inside **2** with its C_2 axis parallel to the polar axis of **2** at low temperature [orientation **I** in Fig. 2(*b*)]. This leads to a stronger shielding of H^2 and H^3, which would be located in the polar region of **2**. Upon increasing the temperature, orientation **II** in Fig. 2(*b*) will be more populated, resulting in an enhanced shielding of H^1 and H^4 and a deshielding of H^2 and H^3. Orientation **I** would explain the high tendency of **1** to undergo a reaction with **2** even at very low temperatures, since in this orientation the reactive triple bond of **1** is facing into one of the polar regions of **2**. It would also explain why incarcerated *o*-benzyne does not react with water in the bulk solvent even though H_2O is small enough to pass through the equatorial portals of **2**.

The course of the Diels–Alder reaction was followed by the decrease of the signal assigned to the *o*-benzyne protons H^1 and H^4.[1] At all temperatures we observed first-order kinetics for the reaction of **1** with **2**.

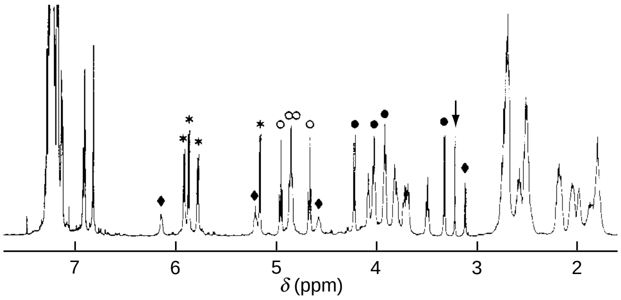


Fig. 1 ^1H NMR spectrum (500.113 MHz; $CDCl_3$; 25 °C) of **4**: (*) outward pointing methylene bridge protons, (●) inward pointing methylene bridge protons, (○) methine protons, and (◇) protons originating from *o*-benzyne. Arrow indicates the proton H5.

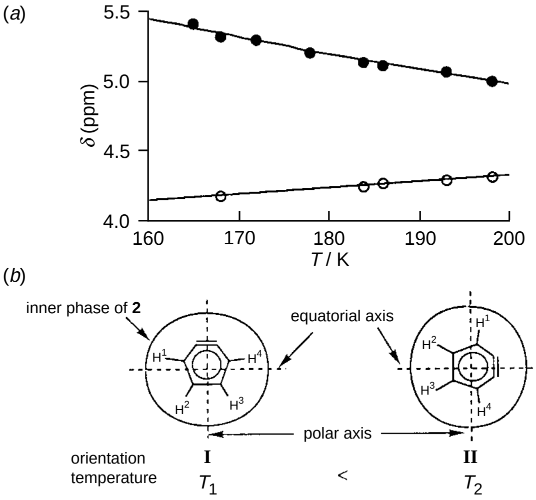


Fig. 2 (*a*) ^{1}H NMR chemical shifts of the *o*-benzyne protons (●) H^1 and H^4 and (○) H^2 and H^3 in [${}^2H_8$]THF as function of the temperature. (*b*) Simplified representation of the orientation of **1** in the inner phase of **2** at different temperatures.

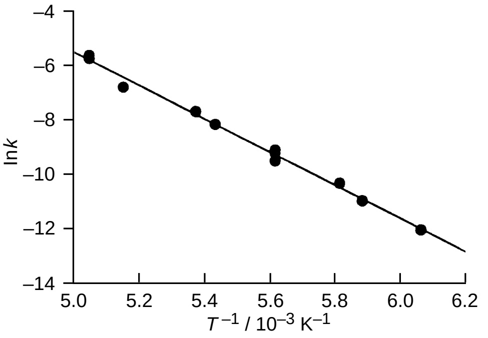
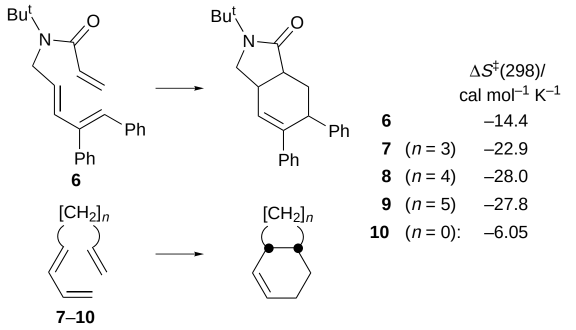


Fig. 3 Arrhenius plot for the reaction of **1** inside **2**



Scheme 2

From an Arrhenius plot (Fig. 3) we determined the activation parameters of this reaction: $\Delta G^\ddagger(298\ \text{K}) = 14.7$ kcal mol^{-1}; $\Delta S^\ddagger(298\ \text{K}) = -10.7$ cal mol^{-1} K^{-1} and $\Delta H^\ddagger(298\ \text{K}) = 11.6$ kcal mol^{-1}, which gives excellent agreement with the calculated $\Delta H^\ddagger$ (298 K) = 10.7 kcal mol^{-1} for the addition of *o*-benzyne to benzene.[7] The enthropy of activation $\Delta S^\ddagger(298\ \text{K})$ is a good measure of the degree of preorganization of this reaction. The measured value is much smaller than the $\Delta S^\ddagger$(298 K) values of intermolecular Diels–Alder reactions [$\Delta S^\ddagger(298\ \text{K}) \approx -40$ cal mol^{-1} K^{-1}][8] and of the intramolecular Diels–Alder reactions of trienes **6**–**9**,[9,10] but much larger than the $\Delta S^\ddagger$(298 K) value of the Cope rearrangement of hexatriene **10** (Scheme 2).[11]

In the present case *o*-benzyne has the possibility of reacting in two different orientations, of which both differ by a 180° rotation of **1** around its C_2 axis, with eight equivalent aryl ether units of **2** to form **4**. This would favour $\Delta S^\ddagger$ by $\Delta\Delta S^\ddagger = R\ln 16 = 5.51$ cal mol^{-1} K^{-1}. Subtracting $\Delta\Delta S^\ddagger$ from the measured $\Delta S^\ddagger$ gives -16.2 cal mol^{-1} K^{-1}, which is between the $\Delta S^\ddagger$ values of the intramolecular Diels–Alder reactions of **6** and **7**.

According to the kinetic parameters, we place the Diels–Alder reaction of **1** with **2** in the category of intramolecular Diels–Alder reactions. Like intramolecular reactions, the reaction of **1** and **2** shows first-order reaction behaviour. However, both reaction partners, **1** and **2**, are not covalently connected but are held together by incarceration. They are separate, individual species, free to rotate in all dimensions. Hence, in this specific case we observed for the first time a bimolecular reaction which, contrary to bimolecular reactions in solution or in the gas phase, obeys first order kinetics. Reactions of this type are only possible if one reactant A is completely encapsulated inside the closed surface of inner phase[3,12] of the second reaction component B and is retained inside B by constrictive binding.[13] Therefore, we would like to introduce the name *innermolecular* reaction for this new type of reaction, which is an intermolecular reaction with a rate law of an intramolecular reaction and which is limited to the *inner phase* of molecular container compounds.[14] Since the inner phase of reactant B is the reaction medium, the course of an innermolecular reaction is expected to be independent of the bulk phase, which might be the solid, the liquid or the gas phase.[3]

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Footnotes and References

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† All new compounds gave C and H elemental analyses within 0.5% of theory, M$^+$ *m/z* signals of substantial intensity in their FAB-MS, and ^{1}H and ^{13}C NMR spectra consistent with their structure.

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