We acknowledge the use of a VG 70-S mass spectrometer purchased through funding from the National Institutes of Health, S10-RR-02478, and 300-MHz and 360-MHz NMR instruments purchased through funding from the National Science Foundation, NSF CHE-85-16614 and NSF CHE-8206103, respectively. Some mass spectral determinations were made at the Midwest Center for Mass Spectrometry with partial support by the National Science Foundation, Biology Division (Grant No. DIR9017262). We thank Mr. John Miller and Ms. Stacey Johnson for their preliminary efforts on the project described in this manuscript.

Mechanism of the Reaction of Methylene with Benzene: A Study of Kinetic Hydrogen Isotope Effects and Theoretical Calculations

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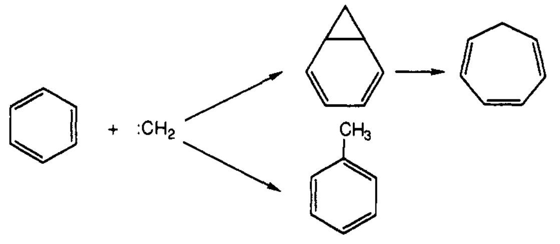
Received February 19, 1991. Revised Manuscript Received November 10, 1992

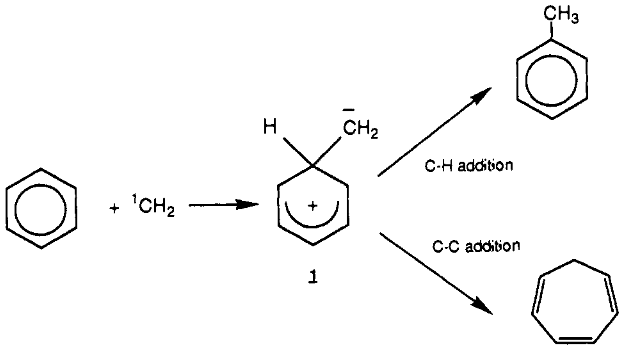
Abstract: The reaction mechanism of singlet and triplet methylene with benzene and related aromatic compounds was investigated by kinetic isotope effects (KIEs), solvent effects, and product studies. The results are further rationalized by a series of ab initio calculations at MP2/6-31G*//RHF/6-31G* and UMP2/6-31G*//UHF/6-31G* levels of theory. The proposed **1c** intermediate for the triplet reaction was found by means of the calculations, whereas no singlet analog **1** could be found.

Introduction

The reaction of diazomethane with aromatic compounds is well-known in organic chemistry.[1] Various ratios of cycloheptatriene (via norcaradiene) and toluene are obtained depending on the reaction conditions. Although the reactivity of benzene with electrophiles and the mechanism of many methylene reactions are well established in the literature,[2] no detailed study of this particular reaction mechanism has been reported so far.



In general, two possible pathways are conceivable for the attack of singlet methylene on the aromatic ring: (i) direct C—H and C=C bond reaction giving products by two independent concerted mechanisms (similar to the singlet methylene reaction with aliphatic and olefinic compounds),[3] and (ii) a multistep reaction mechanism involving a distinct intermediate that subsequently rearranges to the products. The intermediate in the latter path would resemble the Wheland intermediate of the typical electrophilic aromatic substitution mechanism. It can be depicted as a neutral zwitterionic species, **1** (i.e., benzeniummethylide).



The effect of different solvents on the reaction of methylene with a variety of substrates has been studied[4] previously. The changes in product distribution in aromatic and aliphatic solvents were discussed in terms of the formation of complexes between the carbene and the solvent. Schoeller[5] has calculated structures analogous to **1** as possible transition states for the 1,5-walk rearrangement of norcaradienes, but so far no stable intermediate with a comparable structure has been reported. At this point it should be mentioned that the concerted thermal walk rearrangement does not show toluene derivatives as significant side products.[4b] However, experimental evidence for a distinct intermediate was found in pyrolysis studies of norcaradiene[6] and norbornadiene,[7] where toluene was predominantly formed. The pyrolysis reactions carried out at temperatures around 475 °C in the gas phase suggest the presence of a diradical intermediate.[8]

We wish to report now an investigation of the reaction between methylene and benzene as well as some other aromatics. Kinetic isotope effects (KIEs), reaction product ratios for different substrates and spin states, and solvent effects were studied to in-

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(1) (a) Meerwein, H.; Disselnkötter, H.; Rappen, F.; v. Rintelen, H.; van de Vloed, H. *Liebigs Ann. Chem.* **1957**, 151-154. (b) Lemmon, R. M.; Strohmeier, W. *J. Am. Chem. Soc.* **1959**, *81*, 106-108. (c) Doering, W. v. E.; Knox, L. H. *J. Am. Chem. Soc.* **1950**, *72*, 2305-2306. (d) Doering, W. v. E.; Knox, L. H. *J. Am. Chem. Soc.* **1953**, *75*, 297-303.

(2) Lowry, T. H.; Schueller Richardson, K. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; pp 553-562, 623-639.

(3) (a) Doering, W. v. E.; Prinzbach, H. *Tetrahedron* **1959**, *6*, 24-30. (b) Dobson, R. C.; Hayes, D. M.; Hoffmann, R. *J. Am. Chem. Soc.* **1971**, *93*, 6188-6192. (c) Hoffmann, R. *J. Am. Chem. Soc.* **1968**, *90*, 1475-1485. (d) Skell, P. S.; Woodworth, R. C. *J. Am. Chem. Soc.* **1956**, *78*, 4496-4497.

(4) (a) Russell, G. A.; Hendry, D. G. *J. Org. Chem.* **1963**, *28*, 1933-1934. (b) Neugebauer, S. M.; DeLuca, J. P. *Tetrahedron Lett.* **1989**, *30*, 7169-7172. (c) Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* **1985**, *41*, 4987-4993.

(5) Schoeller, W. W. *J. Am. Chem. Soc.* **1975**, *97*, 1978-1980.

(6) Klump, K. N.; Chesick, J. P. *J. Am. Chem. Soc.* **1963**, *85*, 130-132.

(7) Woods, W. G. *J. Org. Chem.* **1958**, *23*, 110-112.

(8) Wentrup, C. *Reaktive Zwischenstufen*; Georg Thieme Verlag: Stuttgart, 1979; Vol. 1, p 55.

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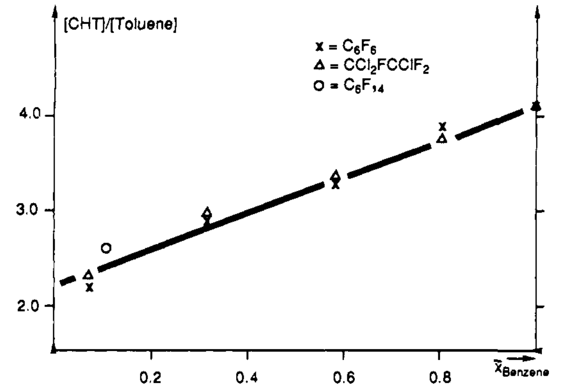


Figure 1. Plot of mole fraction of benzene in different halogenated solvents versus the observed reaction product ratio.

vestigate the existence of a benzeniummethylide intermediate. A series of ab initio calculations were also carried out in order to find structures similar to **1** as stationary points on both the singlet and the triplet surface of the system. On the basis of these results a mechanism is proposed that best fits the available data.

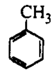
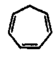
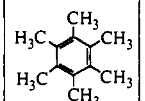
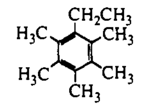
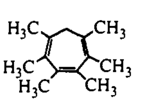
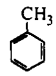
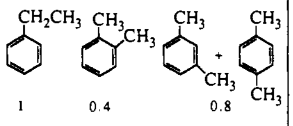
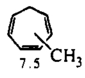
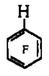
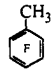
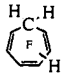
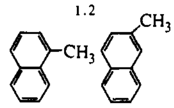
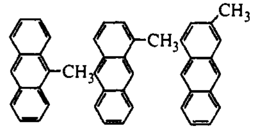
Results and Discussion

Isotope effects were measured by photolysis of diazomethane in equimolar solutions of deuteriated and nondeuteriated solvents at 25 °C (see Experimental Section for details). Diazomethane was generated by hydrolysis of *N*-nitroso-*N*-methylurea and subsequently dried over KOH pellets. Triplet methylene was generated by photolysis of diazomethane with 313-nm light in the presence of benzophenone as sensitizer. The quantitative measurement of the isotope effects as well as the product ratios was made by integration of the GC peaks. The response factors for the correctly labeled and unlabeled toluene were determined with independently obtained reference compounds. In the reaction of benzene with methylene, the kinetic isotope effect (k_H/k_D) for toluene was measured to be 1.34 ± 0.04. For the formation of cycloheptatriene (CHT), the k_H/k_D was 1.05 ± 0.04. Investigation of the isotope effects for the reaction of methylene with toluene gave the following results: k_H/k_D(ethylbenzene) = 1.31 ± 0.04, k_H/k_D(*o*-xylene) = 1.16 ± 0.04, k_H/k_D(*m*,*p*-xylenes) = 1.46 ± 0.04, and k_H/k_D(methylated cycloheptatriene) = 1.02 ± 0.04.

The kinetic isotope effect for the formation of cycloheptatriene from benzene is not conclusive since none of the C–H bonds need to be broken. The observed effect can thus only be secondary in nature. Assuming that the formation of **1** occurs in the rate-determining step, the isotope effect would be secondary for the formation of toluene. However, previous investigations suggest that the transformation of a trigonal carbon into a tetrahedral center in the transition state should lead to a reverse kinetic isotope effect.[9] This is not observed in this case. The relatively small value of the measured primary isotope effect can be rationalized in terms of an unsymmetrical nonlinear transition state due to the high reactivity of methylene. Comparably small primary KIEs were already reported for methylene reactions with substrates that are not able to form distinct intermediates.[10] The rate-determining formation of a single intermediate from singlet methylene and benzene can be further excluded since two different isotope effects are being observed for the two products.

The effect of different solvents on the reaction was investigated by measuring the product ratio ([CHT]/[toluene]) as a function of the benzene concentration in different halogenated solvents.

Table I. Product Ratios of Singlet Methylene Reaction with Different Aromatic Substrates

Substrate	C-H addition product	C=C addition product
	 1	 4.1
	 1	 3.2
	 1 0.4 0.8	 7.5
	 1.2	 1
	 1 12.8	C=C addition 2.7
	 1 2.5 11.0	C=C addition <<1

Rather inert perhalogenated solvents such as C_6F_6, CCl_2FCClF_2, and C_6F_{14}[11] are known to lengthen the lifetime of methylene and therefore favor intersystem crossing (ISC).[12] The results, as shown in Figure 1, indicate that the formation of toluene increases at low benzene concentrations. Since different halogenated solvents give nearly identical plots, the effect should be attributed to the spin states of methylene rather than the stabilization of an intermediate or transition state. Triplet methylene was subsequently generated selectively by benzophenone-sensitized photolysis of diazomethane in benzene.[12] The product ratio ([CHT]/[toluene]) was measured to be 0.6, which is in accordance with the previous experiments. The KIE for CHT was found to be 1.06 ± 0.04, and a very large isotope effect of 12.1 ± 1.0 was measured for toluene. The reaction mechanism apparently changes from the singlet to the triplet species. Triplet methylene seems to give C–H insertion products preferentially, whereas singlet methylene adds more readily to the aromatic ring. An alternate mechanism for the formation of toluene by an isomerization of cycloheptatriene can be clearly ruled out, as it occurs only at high temperatures.[6]

Different aromatic substrates were further investigated to measure the regioselectivity of the singlet methylene reaction (Table I). Naphthalene and anthracene are expected to give preferentially the 1-methyl and 9-methyl regioisomers, respectively, in the presence of an areniummethylide. However, steric factors seem to determine the reaction products, and in both cases the 2-methyl isomer is formed more readily. Electron-rich aromatic systems favor ring expansion, whereas electron-withdrawing substituents lead to more C–H addition products. Steric effects can again modify the ratio, as in the case of hexamethylbenzene. These results indicate that a common areniummethylide intermediate is not involved in the reaction of singlet methylene with aromatics.

A series of ab initio calculations were carried out to investigate benzeniummethylide structure **1** as a possible intermediate on the pathway to toluene. Both singlet and triplet wave functions were

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(9) (a) Streitwieser, A., Jr.; Jagow, R. H.; Fahey, R. C.; Suzuki, S. *J. Am. Chem. Soc.* **1958**, *80*, 2326–2332. (b) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 240–248.

(10) (a) Cheswick, J. P. *J. Am. Chem. Soc.* **1962**, *84*, 2448. (b) Kirmse, W. *Carbene Chemistry*; Academic Press: New York, 1964; Vol. 1, p 23. (c) Seyferth, D.; Cheng, Y. M. *J. Am. Chem. Soc.* **1973**, *95*, 6763–6770. (d) Su, D. T. T.; Thornton, E. R. *J. Am. Chem. Soc.* **1978**, *100*, 1872–1875. (e) Barcus, R. L.; Hadel, L. M.; Johnston, L. J.; Platz, M. S.; Savino, T. G.; Scaiano, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3928–3937. (f) Hadel, L. M.; Platz, M. S.; Scaiano, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 283–287.

(11) Methylene addition products with the halogenated solvents could not be identified above our GC detection limits.

(12) Turro, N. J.; Cha, Y.; Gould, I. R. *J. Am. Chem. Soc.* **1987**, *109*, 2101–2107.

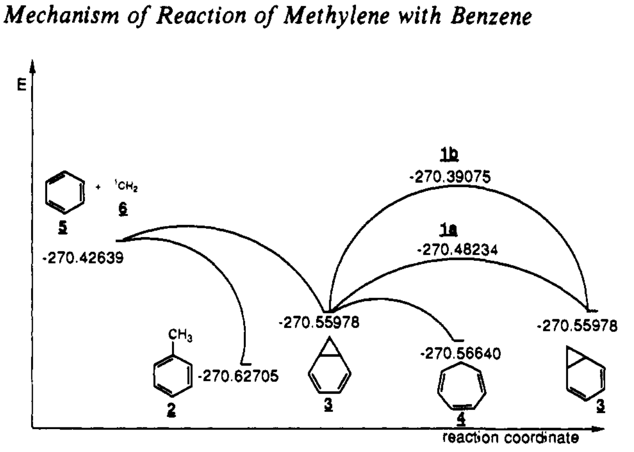


Figure 2. Energetics (in hartrees) of the reaction of singlet methylene with benzene based on MP2/6-31G*//RHF/6-31G* calculations.

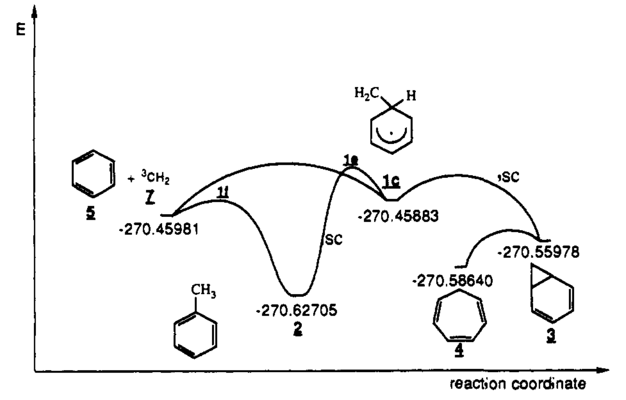
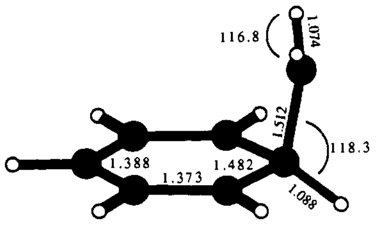


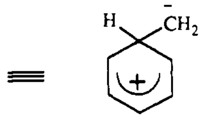
Figure 3. Energetics (in hartrees) of the reaction of triplet methylene with benzene based on UMP2/6-31G*//UHF/6-31G* (**5**, **7**, **1c**) and MP2/6-31G*//RHF/6-31G* (**2**–**4**) calculations.

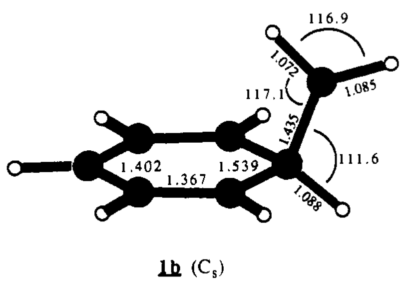
considered using the restricted and unrestricted Hartree–Fock formalisms, respectively. Geometries were typically optimized with the 3-21G basis set and subsequently further improved at the (U)HF/6-31G* level. Electron correlation was taken into account with second-order perturbation theory using (U)HF/6-31G* optimized geometries ((U)MP2/6-31G*//(U)HF/6-31G*). Stationary points were characterized as minima or transition states with frequency calculations at the (U)HF/3-21G level. Table II summarizes the energies of all structures involved in this study.

Two stationary points were located for the singlet system at RHF/6-31G* (**1a** and **1b**). Both turned out to be the two possible transition states for the 1,5-walk rearrangement in norcaradiene and are not involved in the reaction of methylene with benzene.



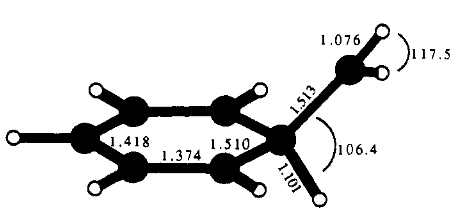
1a (C_s)



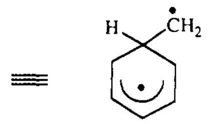


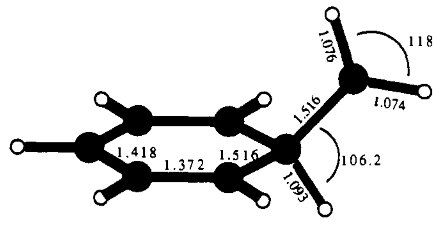
1b (C_s)

However, a minimum structure was found at the UHF/6-31G* level for the triplet system **1c**. The $\langle S^2\rangle$ expectation value of 2.108 at this level indicates some spin contamination. A second triplet structure, **1d**, was located as the transition state for the rotation of the CH_2 group in **1c**.



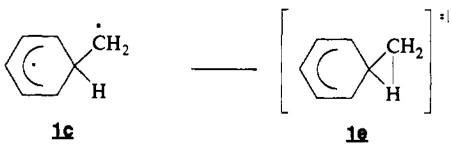
1c (C_s)



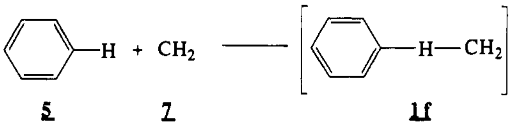


1d (C_s)

The structure **1c** is slightly destabilized compared to the reactants (0.6 kcal/mol) at the UMP2/6-31G*//UHF/6-31G* level. If **1c** was involved in the C–H addition mechanism and its formation is not rate limiting, then the 1,2 H-shift from the ring to the methylene carbon is responsible for the measured isotope effect. In order to estimate the theoretical kinetic isotope effect for this process (eq 1) as well as for the alternative abstraction–



(1)



(2)

recombination mechanism (eq 2), the corresponding transition states (**1e**, **1f**) were calculated at the UHF/3-21G//UHF/3-21G level and the frequencies were determined at the same level for the deuteriated and unlabeled isotopomers.

All frequencies were subsequently scaled by a factor of 0.9 to correct the systematic error at this level of theory.[13] The kinetic isotope effects were then calculated to be 3.81 for the H-shift reaction and 8.97 for the H-abstraction step in the alternate mechanism.[14] The involvement of **1c** is therefore supported neither by the calculated isotope effect nor by the lower energy of the transition state for the H-abstraction (**1f**) compared to the

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(13) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986; pp 228–261.

(14) A semiclassical rate ratio of the form

$$\frac{k_H}{k_D} = \exp\left\{-\frac{hc}{2kT}\left[\sum_i^{3N^{\#}-7}(\nu^{\#}_{i(H)} - \nu^{\#}_{i(D)}) - \sum_i^{3N-6}(\nu_{i(H)} - \nu_{i(D)})\right]\right\}$$

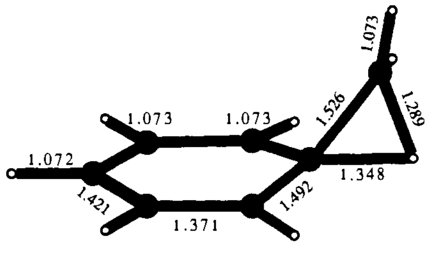
was used to estimate the theoretical isotope effect. The calculated values are lower limits since thermal excitation and tunneling are not taken into account. Including thermal excitation, the isotope effect for reaction 1 at 298 K does not exceed 4.30: Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; John Wiley & Sons: New York, 1980; p 27.

Table II. Total Energies, Zero Point Vibrational Energies (ZPE), Point Groups (PG), and $\langle S^2 \rangle$ Values for Structures **1**–**7**[a]

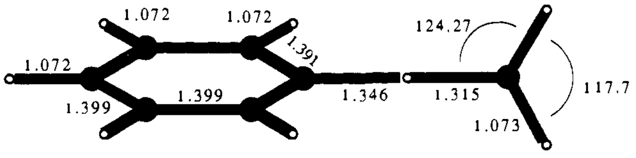
compd	PG	(U)HF/3-31G// (U)HF/3-31G (ZPE)	(U)HF/6-21G*// (U)HF/6-31G*	(U)MP2/6-31G*// (U)HF/6-31G* ($\langle S^2 \rangle$)
1a	C_s	−268.063 09 (84.5)	−269.563 25	−270.482 34
1b	C_s	−267.998 73 (84.8)	−269.501 14	−270.390 75
1c	C_s	−268.153 96 (80.9)	−269.653 90	−270.458 83 (2.108)
1d	C_s	−268.153 57 (80.8)	−269.652 87	−270.458 37 (2.101)
1e	C_s	−268.049 45 (78.5)	−269.556 96[b]	−270.382 72[b] (2.112)
1f	C_s	−268.093 16 (75.7)	−269.587 68[b]	−270.392 11[b] (2.297)
2	C_s	−268.241 07 (86.6)	−269.740 13	−270.627 05
3	C_s	−268.163 77 (86.9)	−269.672 09	−270.559 78
4	C_s	−268.181 46 (86.8)	−269.682 33	−270.566 40
5	D_{6h}	−229.419 46 (68.3)	−230.703 14	−231.456 50
6	C_{2v}	−38.651 85 (11.0)	−38.872 37	−38.872 37
7	C_{2v}	−38.709 07 (11.4)	−38.921 50	−39.003 31 (2.000)

[a] Molecules **1c**–**f**, and **7** were treated as triplets with the unrestricted Hartree–Fock formalism. [b] Based on UHF/3-21G* optimized structure.

H-shift transition state (**1e**) ($\Delta E_{\text{UMP2/6-31G*//UHF/3-21G*}}$ = 5.9 kcal/mol.



1e



1f

On the basis of these results, the singlet and triplet C═C and C—H bond reaction mechanisms can be rationalized with the diagrams shown in Figures 2 and 3.

The mechanism for the singlet methylene reaction seems to follow the concerted pathway, giving the products via direct insertion into the bonds. Initial formation of π-complexes cannot be excluded from our results since this process is not rate determining.

An intermediate can be formed in the triplet methylene reaction according to our calculated results. The isotope effects for the formation of toluene suggest, however, that an abstraction mechanism is more likely. The presence of **1c** in the formation of CHT is possible, but the isotope effect suggests again that it is not formed in the rate-limiting step. Pyrolysis studies of norcaradiene and norbornadiene have shown that the formation of a structure similar to **1c** is most probably involved in the formation of toluene at high temperatures.[6,7] It should be noted that facile intersystem crossing between singlet and triplet species can in fact affect the mechanism.

Conclusion

The study of the reaction between methylene and benzene using isotope and solvent effects suggests distinctly different reaction mechanisms for the singlet and the triplet species. The proposed intermediate for the triplet reaction, **1c**, is supported by ab initio UMP2/6-31G*//UHF/6-31G* calculations. No stable singlet analog **1**, however, could be found. These observations are consistent with other carbene addition reactions.[4b,15]

Experimental Section

HPLC grade benzene (Aldrich), benzene-d_6 (Cambridge Isotope Laboratories), HPLC grade toluene (Aldrich), and toluene-d_8 (Aldrich) were used after distillation over sodium.

All ^{13}C- and ^{1}H-NMR spectra were recorded with a Varian (VXR 200) superconducting NMR spectrometer. Chemical shifts were referenced relative to TMS as an internal standard. GC–MS spectra were obtained with an INCOS-50 spectrometer coupled to Varian 3400 GC. Quantitative analysis of the reaction products was exclusively performed on a Varian gas chromatograph (Model 3700) equipped with a quartz silica capillary column coated with DB 5. Solvents (Aldrich) were used exclusively after being dried and purified by following standard procedures. Products were identified by comparison of their retention times with pure samples. Diazomethane generation was carried out in an all-glass apparatus without any ground-glass joints following published procedure[16] with utmost care. The triplet-sensitized photolysis of a solution of diazomethane in benzene was carried out in the presence of benzophenone (0.015 M).

2,3,4,5,6-Pentadeuteriobenzyl Bromide.[17] Perdeuteriobenzene (10.00 g, 119 mmol, 9.50 mL) was added to a mixture of 48% aqueous HBr (22.0 mL) and glacial acetic acid (10 mL), followed by 1,3,5-trioxane (21.41 g, 238 mmol, 2 equiv) and tetradecyltrimethylammonium bromide (0.6 g). The mixture was then stirred rapidly and heated to a gentle reflux for 24 h. After the mixture cooled to 20 °C, the acid was neutralized with $NaHCO_3$, and the organic phases were separated. The aqueous layer was then washed with ether, and the combined organic phases were dried over anhydrous Na_2SO_4. After evaporation of the ether, the product was distilled under vacuum: ^{1}H-NMR ($CDCl_3$) δ 4.46 (s, 2 H); ^{13}C-NMR ($CDCl_3$) δ 137.5, 128.5, 128.2, 127.8, 33.4; MS (50 eV) *m/z* 176 (0.5) [M$^+$], 96 (100) [M − Br], 69 (14), 68 (15), 42 (9).

α,2,3,4,5,6-Hexadeuteriotoluene.[18] 2,3,4,5,6-Pentadeuterio-benzyl bromide (5.00 g, 28.4 mmol) in 5 mL of ether was added to a mixture of $LiAlD_4$ (1.40 g, 28.4 mmol) in 10 mL of ether. After 5 h all starting material was consumed. Ice was added to the cooled solution until hydrogen evolution stopped. After the aluminum hydroxide was dissolved with aqueous sulfuric acid, the organic layer was separated and washed with saturated NaCl solution. The aqueous layer was washed with ether, and the combined organic phases were dried over Na_2SO_4. After evaporation of the ether, the product was distilled twice under vacuum: ^{1}H-NMR ($CDCl_3$) δ 2.40 (t, 2 H); ^{13}C-NMR ($CDCl_3$) δ 137.5, 128.6, 127.7, 124.8, 20.9; MS (50 eV) *m/z* 98 (100) [M$^+$], 96 (97) [M − D], 69 (18), 54 (16), 42 (21).

Typical Experimental Procedure for the Measurement of Isotope as Well as Solvent Effects. (CAUTION! *Diazomethane is extremely hazardous. For proper care for its generation see ref 16*).

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KOH/H_2O (40%, 10.0 mL) was added slowly to *N*-nitroso-*N*-methyl urea (1.0 g, 9.6 mmol). The evolving gas was then purged through a column filled with KOH pellets into a Pyrex vessel containing 2 mL of a 1:1 mixture of perdeuteriobenzene and benzene. After all the diazomethane dissolved, the vessel was cooled and irradiated until the color of the solution disappeared (30 min). Control experiments indicate that prolonged irradiation does not alter the product distribution.

Calculations were performed on an ALLIANT FX/40 computer using the GAUSSIAN86[19] and GAUSSIAN90[20] packages of programs.

Acknowledgment. We wish to thank the National Institutes of Health and the National Science Foundation for financial support. Professor C. Foote is thanked for his generosity in allowing us the use of his equipment to carry out photosensitized triplet methylene reactions. N.H. thanks Professor H.-J. Bestmann for his interest and support.

Supplementary Material Available: Tables of calculated Cartesian coordinates and point groups for **1a–f** (5 pages). Ordering information is given on any current masthead page.

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Molecular Self-Assembly through Hydrogen Bonding: Supramolecular Aggregates Based on the Cyanuric Acid·Melamine Lattice

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Received June 8, 1992. Revised Manuscript Received October 7, 1992

Abstract: Reaction of the tris(melamine) derivatives hubM$_3$ (C_6H_3-1,3,5-[$CONHC_6H_4$-3-$N(CH_2C_6H_4$-4-$C(CH_3)_3)COC_6H_3$-2-$NHC_3N_3(NH_2)(NHCH_2CH_2C(CH_3)_3)$-5-Br]$_3$) and flexM$_3$ (C_6H_3-1,3,5-[$CO_2(CH_2)_3OCOC_6H_4$-2-$NHC_3N_3(NH_2)(NHCH_2CH_2(CH_3)_3)$]$_3$) with R′CA (neohexyl isocyanurate) and R″CA (3,3,3-triphenylpropyl isocyanurate) in $CHCl_3$, respectively, yields structurally well-defined supramolecular aggregates hubM$_3$(R′CA)$_3$ and flexM$_3$(R″CA)$_3$. These structures were characterized using ^{1}H NMR, ^{13}C NMR, and UV spectroscopy, gel permeation chromatography, and vapor pressure osmometry. flexM$_3$ is a conformationally flexible analog of hubM$_3$. The greater degree of preorganization that is built into the molecular structure of hubM$_3$ compared to flexM$_3$ makes hubM$_3$(R′CA)$_3$ a more stable aggregate than flexM$_3$(R″CA)$_3$. These self-assembling structures are the first step in a program to design, synthesize, and develop methods to characterize supramolecular complexes that are held together by networks of noncovalent interactions.

Introduction

Molecular self-assembly is the spontaneous association of molecules under equilibrium conditions into stable aggregates, joined by noncovalent bonds, with well-defined composition and structure.[1,2] We are developing a program whose objective is to design, synthesize, and characterize macromolecular aggregates that are the products of molecular self-assembly, using networks of hydrogen bonds to form these aggregates.[3,4] Molecular self-assembly is a principle demonstrated in many biological systems: the hierarchy of interactions in nucleic acids and proteins provides examples.[5] The backbone of tRNA is composed of covalent bonds; secondary structure (the arms of the cloverleaf structure of tRNA), tertiary structure, and interactions between tRNA and proteins rest on noncovalent interactions (hydrogen bonds and van der Waals, hydrophobic, and Coulombic interactions). A feature common to many self-assembled biological structures is cooperativity. An initiation event is followed by subsequent steps that lead to the completed assembly without accumulation of intermediates.[6]

A strategy for forming structure through molecular self-assembly differs fundamentally from that most highly developed in organic synthesis—the formation of covalent bonds—in several important respects. In self-assembly, enthalpy and entropy are approximately balanced and structures are at equilibrium; in covalent synthesis, enthalpy dominates and the structures are formed in irreversible processes.[7]

We limited our initial studies to structures based on hydrogen bonds because these interactions have a strong directional component that should simplify the design of complementary subunits for recognition and binding. Rebek,[8] Lehn,[9] Hamilton,[10] and

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