supplementary publication nos. CCDC-112414 and -112415. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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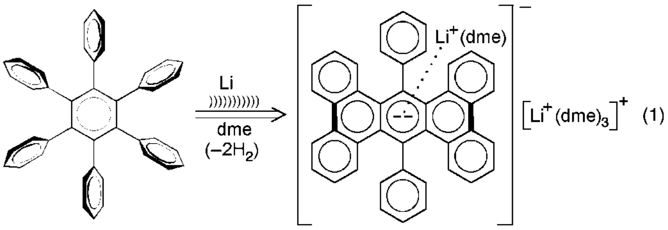
The Li$^+$-Initiated Twofold Dehydrogenation and C–C Bond Formation of Hexaphenylbenzene to the Dilithium Salt of the 9,10-Diphenyltetrabenz[*a*,*c*,*h*,*j*]anthracene Dianion[**]

Hans Bock,[*] Zdenek Havlas,
Katayoun Gharagozloo-Hubmann, and Mark Sievert

Structures of molecular crystals are often a well-suited starting point for hypersurface calculations[1] aiming to reveal essential sections of microscopic reaction pathways. Examples that take into account the energetically important cation solvation[2] are the reductive ring opening of dibenzothiophene to the dimeric sodium sulfide salt[1c] or the reductive C6/C6′ azulene dimerization to the solvent-wrapped contact ion triple $[(\text{diglyme}_2\text{Na}^+)\cdots{}^-\text{azulene}-\text{azulene}^-\cdots(\text{Na}^+\text{diglyme}_2)]$.[1d] Here we report on the ultrasonically activated reaction of hexaphenylbenzene in 1,2-dimethoxyethane (DME) with lithium metal powder,[3] which enforces twofold dehydrogenation and formation of two additional C–C bonds [Eq. (1)].



The crystal structure determination (Figure 1)[3] proves the formation of a partly solvent separated and partly solvent shared contact ion triple of the 9,10-diphenyltetrabenz[*a*,*c*,*h*,*j*]anthracene dianion, the threefold DME solvated Li$^+$ countercation and the singly DME solvated contact ion pair anion, which stack alternatingly along the crystallographic *x* axis (Figure 1 A).

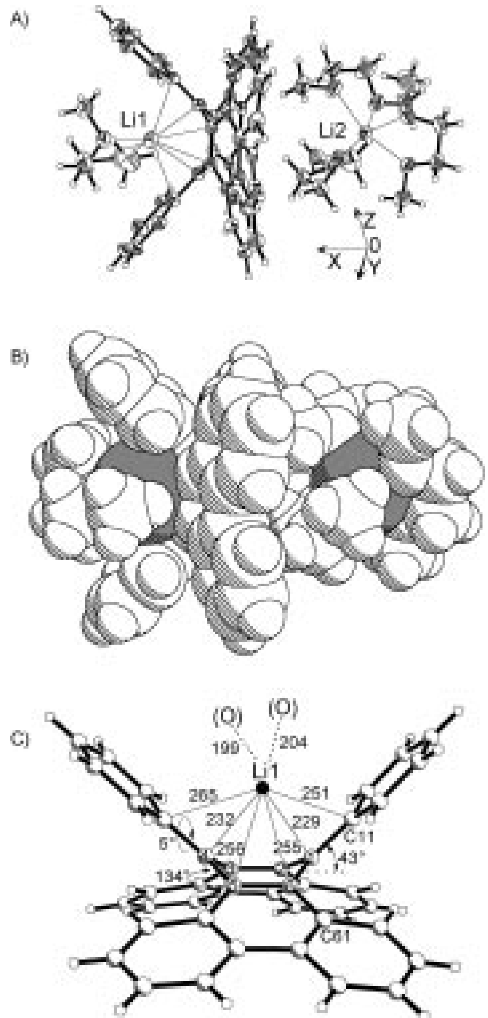


Figure 1. Crystal structure of the contact ion triple $[(\text{dme})\text{Li}^+\cdots \text{C}_{42}\text{H}_{26}{}^{2-}]^-[\text{Li}^+(\text{DME})_3]^+$ at 180 K: A) Packing (monoclinic $P2_1/n$, $Z=4$) along the *x* axis (50 % thermal ellipsoids). B) Space-filling representation (Li$^+$ grey). C) Boat conformation of the 9,10-diphenyltetrabenzanthracene dianion with Li$^+$ contact distances and bending angles. Selected bond lengths [pm] and angles [°]: C1–C6 148, C5–C6 138, C1–C11 143, C1–C61 145; C2-C1-C6 111, C1-C6-C5 117, C6-C5-C4 116, Li2-O 202 (Li1-O 216). See text for details.

The molecular skeleton of the 9,10-diphenyltetrabenz[*a*,*c*,*h*,*j*]anthracene dianion in its {(DME)Li$^+$} contact ion pair shows a drastic distortion comparable to those of the tetraphenylethene dianion,[4a] the 1,2,4,5-tetrakis(trimethylsilyl)benzene dianion,[4b] or the rubrene tetraanion[4c] in their alkali metal cation aggregates. In analogy to the π-hydrocarbon salt presented here (Figure 1 B) they are impressively solvent-wrapped and therefore kinetically stabilized. In the central planar hexacarbon ring of the precursor hexaphenylbenzene [Eq. (1); see Figure 2 A][5] the *para*-positioned centers C1 and C4 are each bent upward by 43° (!), whereas the two phenanthracene subunits at C2/C3 as well as C5/C6 are bent downward with an interplanar angle of only 143° (!) (Figure 1 C). The *para*-phenyl substituents, twisted out of the

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plane of the central ring in neutral hexaphenylbenzene by dihedral angles between 62 and 69°,[5] are almost coplanarized and allow additional $Li^+-\pi$ interactions to their *ipso* centers with distances of 251 and 256 pm (Figure 1 C). The distortions of the molecular dianion skeleton by the Li^+ countercation, which is fixed slightly unsymmetrically in the "boat bay" with $Li^+\cdots C$ distances from 265 down to 229 pm (!) and $Li^+\cdots O$ distances between 204 and 199 pm (!) (Figure 1 C), are tremendous: In the central six-membered ring, for instance, the bond lengths of the parallel C–C edges of 139 pm differ from those of 148 pm in the "boat tips" by 9 pm (!), and the inner ring angles at the two phenyl-substituted *ipso* centers decrease from 117° to 111° (!). Accordingly, the DFT/NBO partial charges calculated for the "boat tip" amount to -0.30 (!) (Figure 2 D).

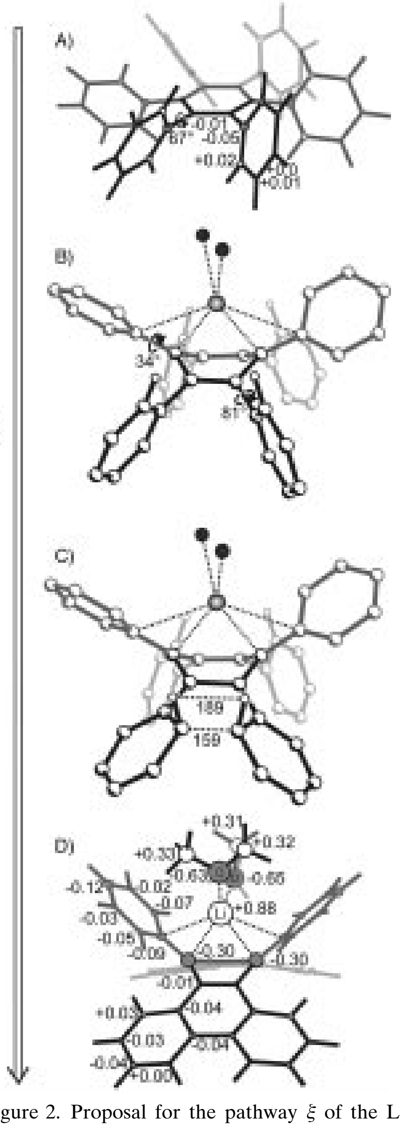
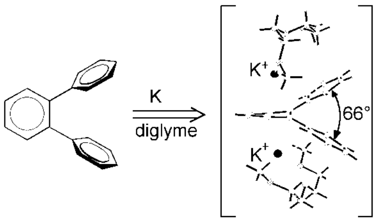


Figure 2. Proposal for the pathway ξ of the Li^+-initiated twofold dehydrogenation and C–C bond formation of hexaphenylbenzene to the Li^+ contact ion pair of the 9,10-diphenyltetrabenz[*a*,*c*,*h*,*j*]anthracene dianion, based on extensive DFT and MNDO calculations:[7] A) Side view of the hexaphenylbenzene structure.[5] B) MNDO energy hypersurface structure for the dianion perturbation by the Li^+ contact. C) MNDO-simulated transition state of the disrotatory twist dynamics of two *ortho* phenyl groups in the H–H and C–C bond formation. D) DFT structure for the solvent-wrapped contact ion pair anion $[C_{42}H_{26}{}^{2-}Li^+(dme)]^-$ with natural bond orbital (NBO) charge distribution[7] (see (A)).

What would be a reasonable reaction mechanism for the surprising[6] dehydrogenation and C–C bond formation of hexaphenylbenzene to the Li^+ contact ion pair of the 9,10-diphenyltetrabenz[*a*,*c*,*h*,*j*]anthracen dianion? Extensive density functional theory (DFT) and semiempirical MNDO calculations[7] starting from the structural data[3, 5] suggest the following proposal for the microscopic reaction pathway ξ (Figure 2): Essential partial aspects would be the skeletal distortion of hexaphenylbenzene (Figure 2 A) due to the two-electron reduction to the dianion as well as its Li^+ contact ion pair formation (Figure 2 B) and the disrotatory rotation dynamics enforced by spatial overcrowding. The latter should turn the two *ortho* phenyl substituents into each other and close the distance between two hydrogen atoms ($H\cdots H$, Figure 2 C) until H_2 split-off and C–C bond formation occur simultaneously. The structure of the resulting Li^+ complex of the tetrabenzanthracene dianion (Figure 1) can be satisfactorily reproduced by quantum-chemical optimization of the final reaction step (Figure 2 D).

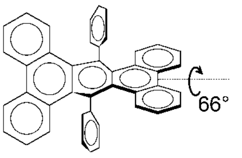
The reduction pathway for the twofold ring closure of hexaphenylbenzene to the lithium salt of the 9,10-diphenyltetrabenzanthracene dianion (Figure 2) proposed from the quantum-chemical calculations based on the crystal structure data[3, 5] can be supported by additional experimental observations. For instance, after reduction of 1,2-diphenylbenzene, a hexaphenylbenzene subunit, in aprotic diglyme at a potassium metal mirror a contact ion triple crystallizes in which two diglyme-solvated K^+ ions coordinate in a half-sandwich arrangement from above and below to the central six-membered ring [Eq. (2)].[8] The structure determination[8]

 (2)

demonstrates again considerable perturbations of the molecular skeleton, of which especially the interplanar angle of 66° between the two phenyl substituent planes is emphasized.

For the single-sided Li^+ perturbation of the hexaphenylbenzene dianion, an MNDO energy hypersurface[7] predicts a minimum for a boat conformation of the central ring, and the bent *para* phenyl substituents should exhibit dihedral angles of $\omega = 34°$, lowered relative to hexaphenylbenzene by $Li^+\cdots C$ contacts. In contrast, the dihedral angles of the *ortho* phenyl rings should be enlarged to $\omega = 81°$ due to van der Waals repulsion (Figure 2 B). The spatial overcrowding in the Li^+-coordinated hydrocarbon dianion, which is bent on both sides, can be further supported by a comparison with the known structure of neutral 9,10-diphenyltetrabenz[*a*,*c*,*h*,*j*]anthracene, the central anthracene skeleton of which is twisted around its long axis by 66° (Scheme 1).[9]

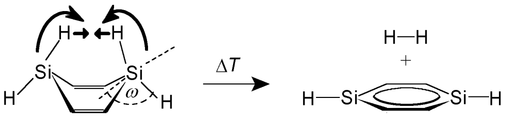
A continued search on the quantum-chemical energy hypersurface calculated for the contact ion pair anion by variation of the dihedral angle $\omega = 81°$ of the *ortho* phenyl substituents, as expected, leads to an unequivocal transition



Scheme 1.

state[7] (Figure 2C) in which the H centers of adjacent phenyl rings should close in to a distance of 189 pm and the corresponding C$\cdots$C centers to 159 pm. The enthalpy gain on H_2 split-off (H_2 dissociation energy 436 kJ mol^{-1}!) and C–C bond formation should amount to $289+23=312$ kJ mol^{-1}.[7]

The proposed reaction pathway (Figure 2) is further supported by the dynamically induced thermal H_2 split-offs from hydrocarbons and their hetero derivatives, which have been repeatedly studied both experimentally and theoretically: According to hypersurface calculations, the thermal gas-phase dehydrogenation of 1-silahexa-1,4-dienes, which yields silabenzene derivatives, is favored only by π delocalization, should proceed by the dominant boat conformation dynamics [Eq. (3)].[10, 11] The total enthalpy of formation for



(3)

the title complex [(9,10-diphenyltetrabenz[*a*,*c*,*h*,*j*]anthracene)$^{2-}$Li$^+$(dme)]$^-$ is calculated to be 264 kJ mol^{-1}, an energy increase which can be supplied under the ultrasonic conditions of its formation [Eq. (1)].

The preparation, crystallization,and structure determination of the unexpected[6] alkali metal complex [(9,10-diphenyltetrabenz[*a*,*c*,*h*,*j*]anthracene)$^{2-}$Li$^+$(dme)][Li$^+$(dme)$_3$] is reported here together with a proposal for the reaction mechanism, supported by both experiment and quantum-chemical calculations. Accordingly, a Li$^+$-initiated skeletal deformation of hexaphenylbenzene produces in a first step a sterically overcrowded molecular dianion, the dynamics of which leads to a twofold H_2 split-off and C–C bond formation. It is hoped that further investigations of reductions with lithium metal powder under ultrasonic activation and, especially, C–C connections in suitable unsaturated hydrocarbons will be stimulated.

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[3] Preparation and growth of single crystals of [(9,10-diphenyltetrabenz[*a*,*c*,*h*,*j*]anthracenyl)$^{2-}$Li$^+$(dme)][Li$^+$(dme)$_3$]: lithium powder (10 mg, 1.44 mmol; particle size 50–200 μm) is filled in a Schlenck trap (flame-dried at 10^{-3} mbar) under an atmosphere of argon covered with a solution of hexaphenylbenzene (150 mg, 0.28 mmol)) in waterfree DME (10 mL). The Schlenck trap is subjected to ultrasonic irradiation for apporoximately 20 min, until the solution turns deep green. The reaction mixture is then filtered under argon through a G5 frit into another flame-dried Schlenck trap and covered after 12 h with waterfree *n*-hexane (15 mL). After 3 d black blocks with a violet luster have crystallized at the bottom of the trap. Crystal structure determination: Dark blocks, $C_{58}H_{66}O_8Li_2$ ($M_r = 905.0$ g mol^{-1}), $a = 1248.1(2)$, $b = 1804.5(2)$, $c = 2187.9(3)$ pm, $\beta = 97.85(1)^\circ$, $V = 4881(1) \times 10^6$ pm^3 ($T = 180$ K), $\rho_{\text{ber.}} = 1.231$ g cm^{-3}, monoclinic, space group $P2_1/n$, $Z = 4$, Siemens P4 four-cycle diffractometer, $\text{Mo}_{K\alpha}$ radiation, $\mu = 0.08$ mm^{-1}; of 10241 measured reflections between $3^\circ \leq 2\Theta \leq 50^\circ$, 5677 were independent and used in the refinement ($R_{\text{int}} = 0.0387$). Structure solution with direct methods and the difference Fourier technique (SHELXS-86), refinement against F^2 (SHELXL-93), 622 parameters, $w = 1/[\sigma^2(F_o^2) + (0.0437\,P)^2 + 2.67\,P]$, R for 5677 $F_o > 4\sigma(F_o) = 0.0479$, $wR2$ for all 10241 data $= 0.1261$, GOF $= 1.071$, residual electron density $0.26/-0.20$ e Å^{-3}. All C, O, and Li$^+$ positions were anisotropically refined, the hydrogen atoms placed in geometrically ideal positions and refined using individual isotropic displacement parameters ($[U_{\text{iso}} = 1.2 \times U_{\text{eq}}(\text{C–H/CH}_2)]$; $[U_{\text{iso}} = 1.5 \times U_{\text{eq}}(\text{CH}_3)]$ within the riding model. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-115814. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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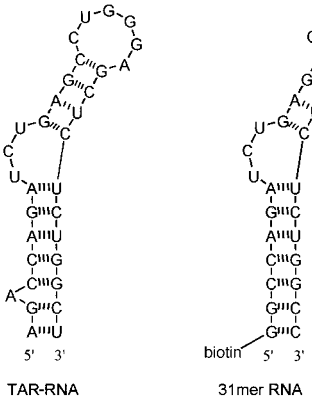
Selective Cleavage of the HIV-1 TAR-RNA with a Peptide–Cyclen Conjugate[**]

Katrin Michaelis and Markus Kalesse[*]

The hydrolysis of phosphodiesters by small molecules is of great interest since efficient catalysis of phosphodiester hydrolysis can significantly change the life cycle of cells or viruses. In order to assess the effect of metal ions in such hydrolyses we investigated the hydrolysis of metal complexes covalently linked to peptides. We chose the TAR-RNA of HIV-1 as the target for our hydrolysis studies (Scheme 1). The TAR-RNA of HIV-1 is recognized by the HIV-1 regulatory protein Tat (Scheme 2). It has been found that the binding of Tat to TAR-RNA up-regulates HIV-1 mRNA transcription.[1] Detailed spectroscopic methods have been used to investigate the Tat–TAR interactions in which arginine residues (52 or 53) make specific contacts to the bulge region of the TAR-RNA.[2] It is known that the binding of the Tat protein to the TAR-RNA is a crucial event in the transcription of the viral DNA, because it stabilizes the active complex between the polymerase, the DNA template, and the nascent mRNA. When the Tat protein is not bound to the TAR-RNA premature abortion of transcription takes place.[3] Even more interesting is the fact that the arginine-rich region of the Tat protein is sufficient to induce budding of the virus in vivo. The fact that peptide fragments containing the basic region of Tat show similar TAR binding as the wild-type Tat protein[4] encouraged us to investigate the hydrolysis of this particular RNA with metal complexes bound to the arginine-rich region of the Tat protein.



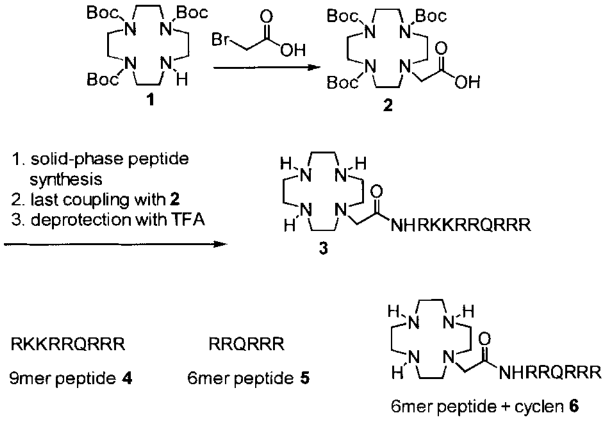
Scheme 1. The TAR-RNA of HIV-1 and the 31mer RNA used in the cleavage experiments.

M E P V D P R L E P W K H P G S Q P K T A C T N C T Y C K K C
C F H C Q V C F I T K A L T I S Y G **R K K R52 R53 Q54 R R R** P
P Q G S Q T H Q V S L S K Q P T S Q S R G D P T G P K E.

Scheme 2. The Tat protein. The arginine-rich region is written in bold letters. The arginine residues Arg52 and Arg53 are responsible for the selective binding to the bulge region.

Our initial idea was to use 1,4,7,10-tetraazacyclododecane (cyclen) as the metal-coordinating ligand and to conjugate it to the arginine-rich region of the Tat protein. This strategy would then allow the cleavage of the TAR-RNA by various metal ion complexes of cyclen to be examined. The arginine-rich nonamer should specifically bind to the targeted RNA and bring the metal complex in close proximity to phosphodiester bonds. As a result of this event RNA strand cleavage should occur.

The nonamer **3** with the attached cyclen moiety was synthesized by solid-phase synthesis using the Fmoc protocol (Scheme 3). As the last coupling step, the Boc-protected cyclen acetic acid[5] (**2**) was coupled to the N-terminus of the nonapeptide with subsequent cleavage from the resin by using standard conditions (TFA) to yield the desired peptide–cyclen conjugate. The peptides were purified by semi-preparative RP-HPLC and the molecular weight was determined by matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS).[6] For the purpose of control experiments we also synthesized the corresponding nonamer peptide without the cyclen moiety (**4**) and the hexamer peptides with and without the cyclen moiety. We synthesized both hexamers **5** and **6** to probe whether the distance of the cyclen moiety from the crucial arginine residues (Arg52 and Arg53) would have an effect on the cleavage of the RNA.



Scheme 3. Synthesis of the peptides **3**–**6** by solid-phase synthesis. Boc = *tert*-butoxycarbonyl, Fmoc = fluorene-9-ylmethoxycarbonyl, TFA = trifluoroacetic acid.

The target TAR-RNA of HIV was purchased from Genset with a slight modification at the termini. The unpaired

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