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ACID-PROMOTED AROMATIZATION OF PERYLENE-BASED ENDOXIDES

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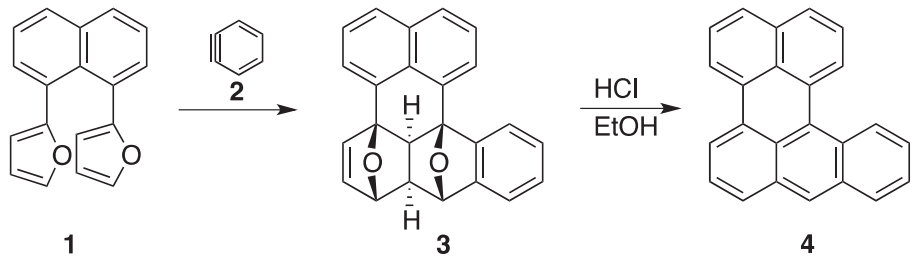
Abstract – The aromatization of perylene-based endoxides by treatment with HCl and EtOH has been studied.

We have recently reported the synthesis of benzo[*a*]perylene (**4**) as shown in Scheme 1.[1] The reaction of **1** with benzyne (**2**) triggers a tandem domino Diels-Alder sequence to afford adduct **3** in excellent yield and high stereoselectivity, which by treatment with HCl/EtOH afforded **4** in 72% yield. Following the same protocol we have prepared several analogues of **3** and the corresponding perylene-derivatives.

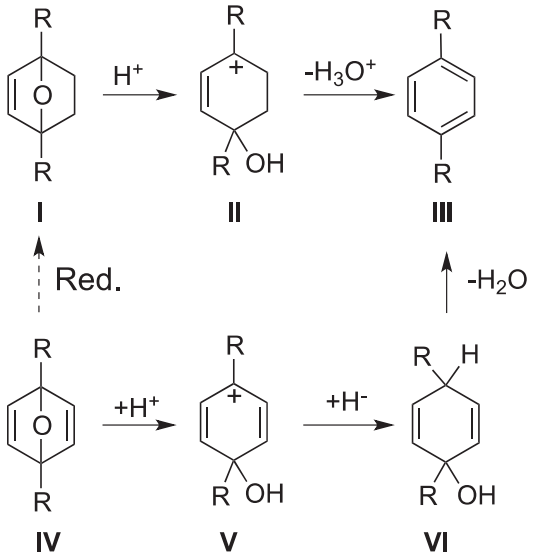


Scheme 1. Synthesis of benzo[*a*]perylene (**4**)

In that publication we focused our attention on the synthetic strategy and on the properties of perylene-derivatives, without a detailed mechanistic discussion. Only some details of the computational study of the transformation of **1** into endoxide **3** were included. However the transformation of endoxide **3** into perylene **4** is far from trivial. We will discuss here some mechanistic aspects of this reaction, but

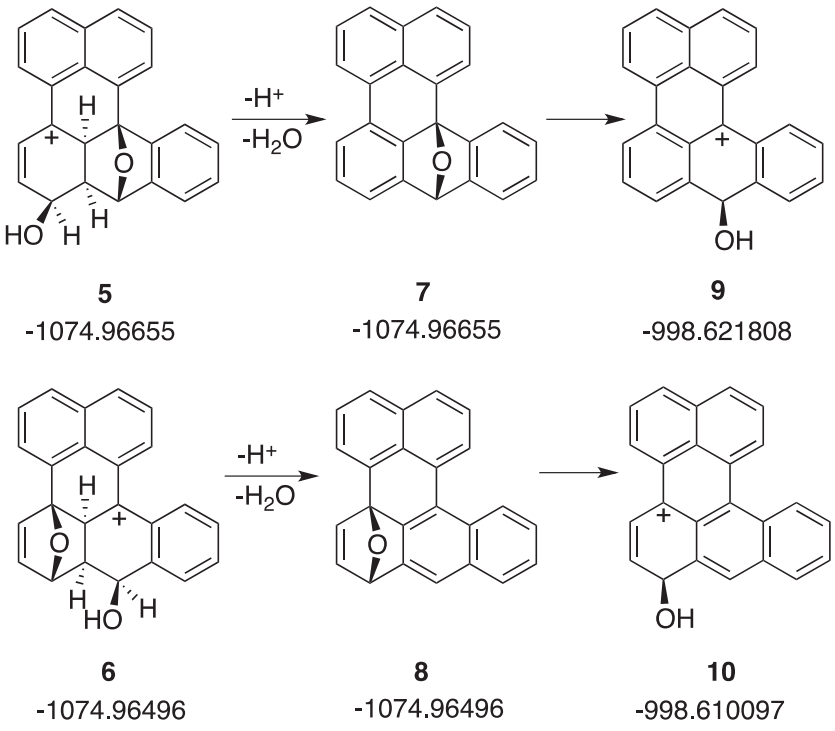
before treating the above transformation we will outline the more reasonable mechanisms for the acid-promoted aromatization of 1,4-endoxides.

Acid-promoted aromatization of cyclohexene-1,4-endoxides such as **I** is usually an easy process.[2-9] It involves protonation to **II** and a formal elimination of a proton and water to afford the aromatic compound **III**. The situation for cyclohexadiene-1,4-endoxides **IV** is more complex. After the opening of the endoxide to the carbenium ion **V**, there is no hydrogen available to accomplish the elimination. A formal reduction of **V** to **VI** must occur to allow dehydration to **III** (Scheme 2). One-pot procedures with combinations of an acid and a reducing agent, such as HOAc/Zn,[10,11] HOAc/Fe,[11] TFA/$NaBH_4$,[12] $TiCl_4$/$LiAlH_4$,[13-15] and $TiCl_4$/Zn,[16] or reagents such as $Fe_2(CO)_9$[17,18] or TMSI[19] have been used to perform this transformation. Alternatively, cyclohexadiene-1,4-endoxides **IV** have been transformed into arenes **III** in a two-operation process, involving a first reduction step to give **I**, followed by protonation and elimination of water.[20-22]



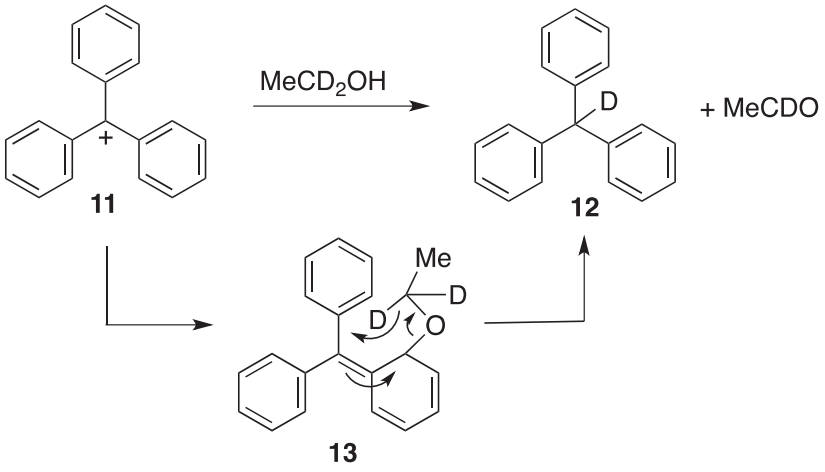
Scheme 2. Typical mechanisms for the acid-promoted aromatization of endoxides

According to the above considerations acid-promoted opening of **3** could afford carbenium ions **5** and **6**, which could lose water to afford endoxides **7** and **8**, respectively. From these, a second protonation/opening sequence would afford carbenium ions **9** and **10**, respectively (Scheme 3). DFT calculations at the B3LYP/6-31G(d) level show that the formation of **9** is thermodynamically favoured by 0.011711 Hartrees (7.3 kcal/mol). In any case, transformation of these compounds into benzo[*a*]perylene (**4**) requires a formal reduction and the elimination of water.



Scheme 3. Plausible intermediates in the opening of endoxide **3** (energies in Hartrees)

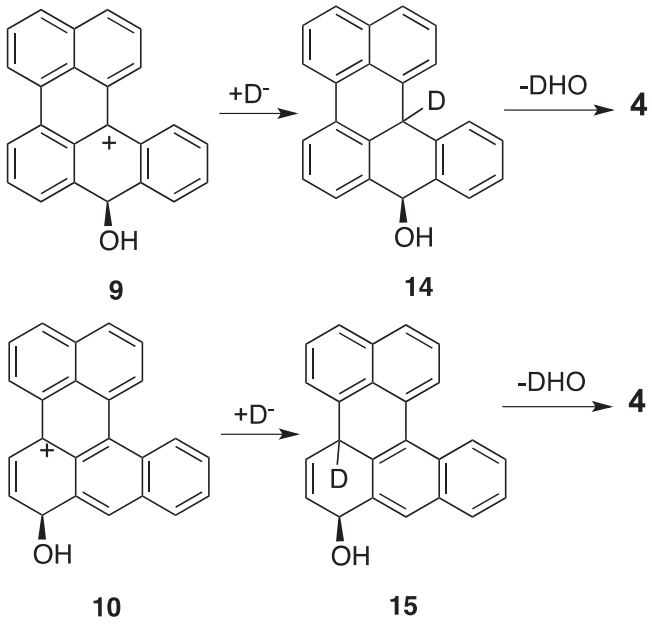
In our case, having used only HCl and EtOH as reagents for the transformation of **3** into **4**, we thought that EtOH should be the actual reducing agent. In fact, though it is not usually considered as a reducing agent, EtOH acts in this way against strong oxidants and also in biological transformations, such as the reduction of NAD^+ in liver, catalyzed by alcohol dehydrogenase.[23] Closer to our transformation, the reduction of triphenylmethyl cation (**11**) by hydride transfer from ethanol has been reported in the literature (Scheme 4).[24-26]



Scheme 4. Alternative mechanisms for hydride transfer to the triphenylmethyl cation

The study of these reactions using HCl/CH_3CD_2OH had shown that the incorporation of deuterium occurs exclusively at the central atom to give **12**. Two alternative mechanisms have been considered: a direct nucleophilic attack of hydride to the carbocation **11**[24,25] and the addition of ethanol to an ortho-position to give **13**, followed by an intramolecular hydride transfer to **12** (Scheme 4).[26]

Extrapolation of this mechanisms to carbenium ions **9** and **10**, led us to predict that the incorporation of deuterium should lead to intermediates **14** and **5**, respectively, which after the elimination of DHO should afford non-deuterated benzo[*a*]pyrene **4** (Scheme 5). In fact, when we treated endoxide **3** with HCl and CH_3CD_2OH we isolated non-deuterated **4**, as proved by NMR analysis.



Scheme 5. Addition and elimination of deuterium

The transformation of endoxide **3** into benzo[*a*]perylene (**4**) has also been achieved using HCl/MeOH or HCl/*n*-BuOH, but in lower yield.

Finally, we tried the aromatization of compound **16** obtained by a similar tandem cycloaddition. However, when we treated **16** with HCl/EtOH as above a new compound was obtained having a CO band at 1653 cm^{-1} in its IR spectrum and two singlets at 7.26 (1H) and 6.13 (1H) ppm in its ^{1}H-NMR spectrum. This led us to proposed structure **17** for that compound, which was confirmed by X-ray diffraction studies, as shown in Figure 1.

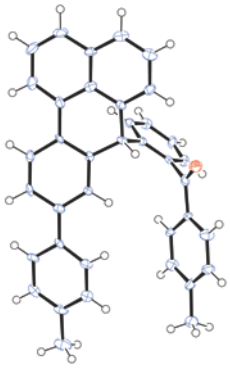
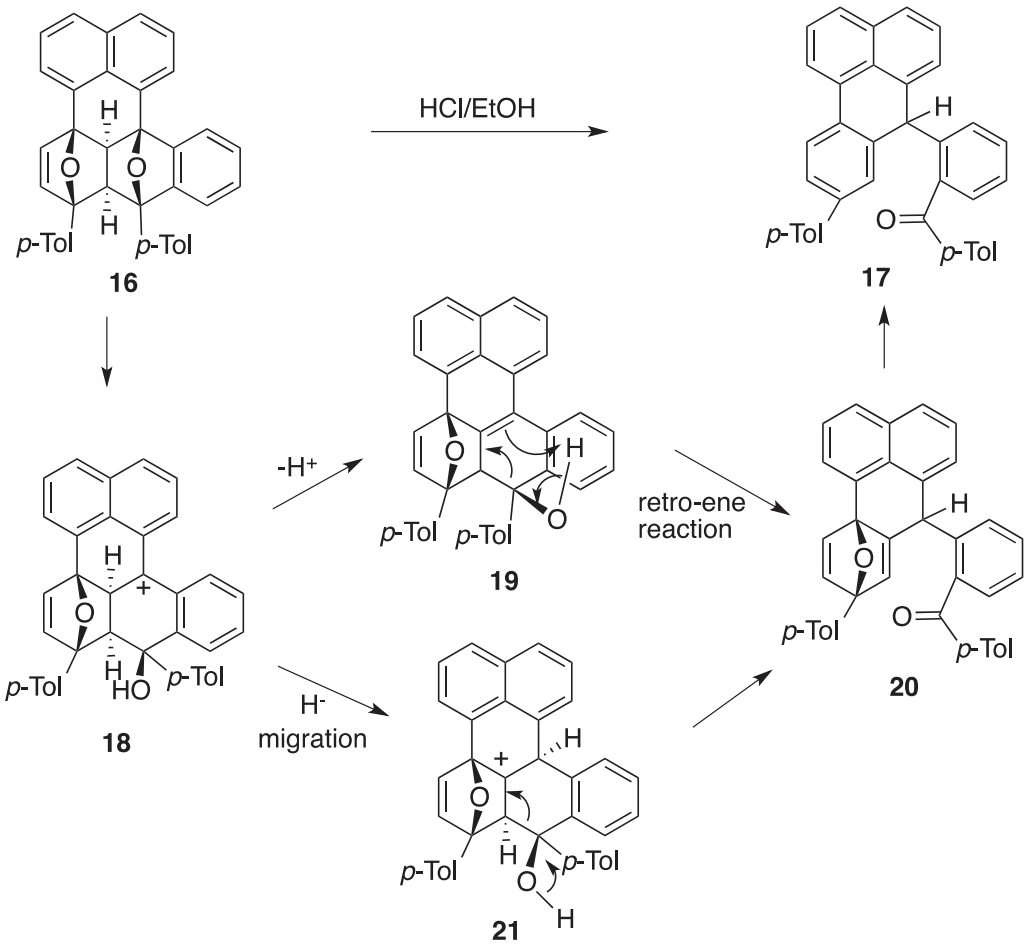


Figure 1. X-Ray diffraction structure of ketone **17**

We firstly considered that the formation of **17** could involve an initial protonation of **16** followed by opening to carbenium ion **18**,[27] deprotonation to **19** and retro-ene fragmentation to **20** (Scheme 6). Aromatization of the endoxide **20** with HCl/EtOH as above would afford **17**.



Scheme 6. Mechanistic proposals for the formation of **17**

However, an alternative mechanism for the transformation of **18** into **20**, involving a hydride migration to give **21** followed by a fragmentation to give the final ketone, could not be discarded.[28] To evaluate the feasibility of these mechanisms we carried out the reaction with DCl/CD_3OD, assuming that if the first mechanism were in operation the alcohol **19** would undergo H/D exchange with the medium and the product **20** would incorporate deuterium. On the contrary, if **20** were formed by 1,2-migration of H, deuterium should not be incorporated. After doing the experiment, non-deuterated **17** was isolated, supporting the second mechanistic hypothesis.

In summary, calculations and experimental data for the aromatization of endoxide **3** with HCl/EtOH suggest a mechanism involving the formation of intermediary carbenium ions, its reduction and the elimination of water. A mechanistic proposal involving a hydride donation from the solvent has been discussed.

EXPERIMENTAL

Benzo[*a*]perylene (4).[1] Concentrated HCl solution (50 μL, 37.5% in water) was added to a solution of adduct **3** (50 mg, 0.15 mmol) in EtOH, MeOH or *n*-BuOH (3 mL), and the mixture was stirred under argon in the absence of light at 78 ºC for 5 h. Then, H_2O (1 mL) was added and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (under argon in the absence of light; SiO_2; 9:1 hexane/CH_2Cl_2), affording benzo[*a*]perylene derivatives (**4**). Yield: 72% in EtOH, 32% in MeOH, 31% in *n*-BuOH.

***p*-Tolyl(2-(9-(*p*-tolyl)-7*H*-benzo[*de*]anthracen-7-yl)phenyl)metanone** (**17**). Concentrated HCl solution (140 μL, 0.16 mmol, 37.5% in water) was added to a solution of endoxide **16** (42 mg, 0.08 mmol) in EtOH (5 mL), and the mixture was stirred under argon in the absence of light at 78 °C for 4 h. Then, H_2O (1 mL) was added and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (under argon in the absence of light; SiO_2; 9:1 hexane/CH_2Cl_2), affording ketone **17** (30 mg, 75% yield) as a green solid, mp 213-216 ºC; IR 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.9 Hz, 2H), 7.93 (*J* = 8.1 Hz, 2H), 7.77 (*J* = 8.2 Hz, 1H), 7.67 (*J* = 7.7 Hz, 1H), 7.58-7.50 (m, 2H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.45-7.42 (m, 1H), 7.41-7.29 (m, 5H), 7.262 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.15-7.10 (m, 2H), 6.99-6.96 (m, 1H), 6.13 (s, 1H), 2.50 (s, 3H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), δ 198.2 (C), 147.0 (C), 144.5 (C), 140.1 (C), 139.0 (C), 137.3 (C), 137.1 (C), 137.03 (C), 137.00 (C), 135.4 (C), 133.7 (C), 130.8 (2CH), 130.7 (CH), 130.6 (CH), 130.3 (C), 130.0 (C), 129.4 (2CH), 129.3 (2CH), 128.7 (CH), 127.8 (CH), 127.7 (CH), 127.6 (C), 127.1 (CH), 126.5 (2CH), 126.3 (CH), 126.0 (CH), 125.9 (CH), 125.2 (CH), 124.9 (CH), 123.7 (CH), 118.9 (CH), 44.9 (CH), 21.6 (CH_3), 20.9 (CH_3) ppm. LRMS (EI), m/z (%): 500 (63, M^+), 408 (100), 379 (48); HRMS (EI) calculated for

$C_{38}H_{28}O$: 500.2140, found: 500.2139; X-Ray Diffraction Studies: Deposition number CCDC-942555 for compound **17**. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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27. DFT calculations at the B3LYP/6-31G(d) level shown that **18** (-1615.71133 au) is thermodynamically more stable than the cation formed by protonation on the left endoxide (-1615.70731 au).
28. This mechanistic proposal has been suggested by a referee.