Pergamon

Tetrahedron Letters 42 (2001) 7527–7529

TETRAHEDRON LETTERS

A curious benzenoid deacylation reaction: neighbouring group participation in acylhydroxy[2.2]paracyclophanes

D. Christopher Braddock,[a,*] Iain D. MacGilp[b] and Benjamin G. Perry[a]

[a]*Department of Chemistry, Imperial College of Science Technology and Medicine, South Kensington, London SW 7 2AY, UK*
[b]*Process Chemistry, GlaxoSmithKline R&D, Temple Hill, Dartford, Kent DA1 5AH, UK*

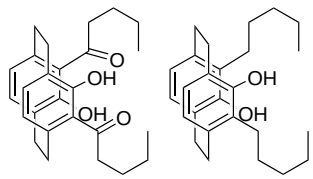
Received 20 July 2001; accepted 24 August 2001

Abstract—Attempted carbonyl reduction of acyldihydroxy[2.2]paracyclophanes with sodium borohydride led instead to competing aromatic deacylation. The effect was traced to a neighbouring group participation that can be correlated with carbonyl IR stretching frequencies. Deuterium labelling studies implicate the formal intermediacy of a solvated [2.2]paracyclophane anion via an S_E1 mechanism. © 2001 Elsevier Science Ltd. All rights reserved.

During the course of our studies we had reason to prepare diacyldihydroxy[2.2]paracyclophane **1**[†] and attempt its direct reduction to bismethylene[2.2]-paracyclophane **2**. For this reduction we were attracted by the method of Bell who has shown that the use of sodium borohydride in refluxing aqueous sodium hydroxide solution cleanly reduces *o*-hydroxyarylketone **3** to methylene compound **4** via the presumed intermediacy of an exomethylene quinone.[1] However, we were surprised to discover that treatment of analogously substituted diacyldiol **1** under these conditions resulted in the predominant formation of diol **5**[2] bearing no acyl groupings.

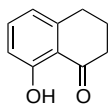
This result was intriguing since deacylation of aromatics is rare,[3] especially under basic conditions which require a strong base such as potassium *t*-butoxide,[4] and typically only substrates containing non-enolisable protons are suitable.[5] We therefore decided to investigate this system further. At the outset, we suspected a neighbouring group participation (NGP) by either (or both) of the *ortho* and *pseudo-gem* hydroxyl functionalities.

For further experiments we moved away from the aqueous system described by Bell and instead employed

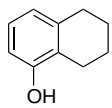


1

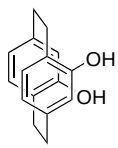
2



3



4



5

$NaBH_4$ in refluxing MeOH only.[‡] Under these conditions diacyldihydroxy[2.2]paracyclophane **1** was consumed to again provide diol **5** (isolated yield 20%) but the major component was monodeacylolefin **6** (65%

Keywords: [2.2]paracyclophane; deacylation; neighbouring group participation.

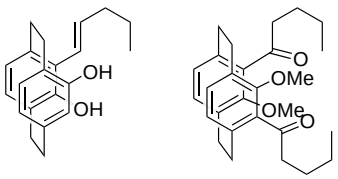
* Corresponding author. E-mail: c.braddock@ic.ac.uk

† All the [2.2]paracyclophanes described are racemic modifications and have been satisfactorily characterised.

‡ Representative procedure: To a stirred solution of **1** in MeOH (0.035 M) was added $NaBH_4$ (25 equiv.). The solution was heated to reflux for 14 h, allowed to cool to rt and treated with an excess of aqueous HCl (2.5 M). The mixture was extracted with EtOAc (2×20 mL) and the combined organic layers were washed with water (1×20 mL), saturated brine solution (1×20 mL), dried ($MgSO_4$), evaporated and chromatographed (CH_2Cl_2 through to 2% MeOH in CH_2Cl_2), to give **6** (65%) as a colourless oil and **5** (20%) as a yellow solid.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01607-0

isolated yield). This compound was clearly evident by the appearance of a doublet triplet at 6.66 ppm ($J=$ 16.3, 1.5 Hz) and a double triplet at 5.65 ppm ($J=16.3$, 6.9 Hz) in the ^{1}H NMR spectrum for the α- and β-styryl protons, respectively. Presumably, this compound is formed by deacylation of one acyl grouping followed by reduction of the other ketone to the alcohol and elimination during the acidic work-up.



6 **7**

In order to explore the notion that the hydroxyl groups were intimately involved in this deacylation reaction, a protected diol substrate was prepared. Exposure of diacyldimethoxy[2.2]paracyclophane **7** to the standard conditions resulted in no reaction and the starting material was recovered intact. This is a somewhat startling observation but simple steric factors may be responsible for the lack of reactivity. In the absence of any NGP effects, normal reactivity would result in alcohol formation. In this case it is apparent that approach of the borohydride would be from the least hindered side of the paracyclophane, leading to strong steric compression in the transition state as the substituents on one paracyclophane ring move towards those on the other.

To separate the effect of the positioning of the hydroxyl groups relative to the ketone functionality, monoacyl[2.2]paracyclophanes **8**–**11** were prepared. Non-protected acyl compound **8** smoothly deacylated under the reaction conditions to give diol **5** as the major component (73%) along with some alkene **6** (18%). The diprotected compound **9** was found to be unreactive, again presumably due to steric factors as per dimethoxyparacyclophane **7**. For the monoprotected systems, compound **10** underwent reduction to alkene **12** (49%), unreacted starting material was recovered (25%) but no deacylparacyclophane **13** could be detected. For orthogonally protected paracyclophane **11** a complex reaction mixture was produced but no deacyl compound **13** was detected.

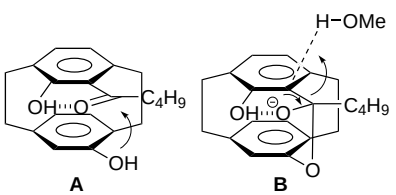
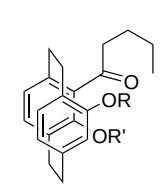
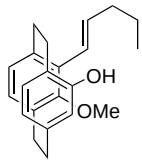


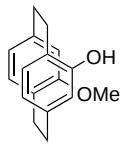
Figure 1.



8; R = R' = H
9; R = R' = Me
10; R = H, R' = Me
11; R = Me, R' = H



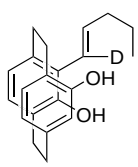
12



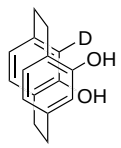
13

The results from these experiments suggest that both an *ortho* and a *pseudo-gem* hydroxyl group on the paracyclophane ring are required to be present to direct this novel deacylation reaction. This can be further validated by inspection of the carbonyl stretching frequencies in the infrared spectra of the various paracyclophane compounds **8**–**11**. For bis-methoxy paracyclophane **9**, the IR spectrum displays an unremarkable stretch at 1682 wavenumbers, characteristic of an aryl ketone. Interestingly, the effect of a free hydroxyl group *pseudo-gem* to the carbonyl in paracyclophane **10** shifts the stretching frequency to 1668 cm^{-1}. Intramolecular hydrogen bonding in orthogonally protected methoxyparacyclophane **11** leads to a stretch at 1606 cm^{-1}, and in the dihydroxyparacyclophane **8** the carbonyl stretch is observed at 1600 wavenumbers. The weakening of a carbonyl double bond by an electron rich substituent in a *pseudo-gem* position in [2.2]paracyclophane chemistry (via donation of a lone pair into the carbonyl π* orbital) has been previously noted,[6] but to date there are no examples of a hydroxyl group participating in this manner.

The mechanism of the deacylation was further probed by a series of deuterium labelling experiments. Monoacylparacyclophane **8** was exposed to the standard conditions, but using either sodium borodeuteride or MeOD in lieu of their non-deuterated reagents. When **8** was allowed to react with sodium borodeuteride in MeOH, diol **5** was isolated (50%) with no-deuterium incorporation, along with monodeuterated alkene **14** (30%; >90% D-incorporation).[§] Conversely, in the reaction of **8** with $NaBH_4$ in MeOD, which broadly gave the same product distribution, no deuterium incorporation was observed in the produced alkene **6**, and deuterium incorporation at the *ortho* position in paracyclophane **15** was observed.



14



15

[§] The resonance at 6.66 ppm as seen in non-deuterated alkene **6** was diminished by 90% relative to the other resonances in the NMR spectra, and the clean double triplet at 5.65 ppm had collapsed to a broadened multiplet.

Therefore, mechanistically it seems probable that there are two competing reaction pathways operating in the above reactions. In the first, normal borohydride reduction proceeds by attack on the ketone resulting in alkenes after elimination. In the second, we postulate that the *ortho*-hydroxyl group activates the carbonyl group via hydrogen bonding, which undergoes transannular-type attack by the *pseudo*-*gem* hydroxyl group (Fig. 1; **A**). The tetrahedral intermediate can collapse by formal loss of a paracyclophane anion where the incipient build-up of negative charge is probably solvated by MeOH (or MeOD) leading to H^+ (or D^+) transfer (Fig. 1; **2B**). The ester so produced from the transannular acyl transfer is evidently cleaved rapidly.¶ Overall, this second pathway may best be described as an S_E1-type mechanism.[7]

Finally the clean conversion of acylparacyclophane **1** into the methylene compound **2** was achieved by the application of Clemmensen reduction conditions. Bismethylene compound **2** was isolated in 70% yield after application of standard conditions (Zn/Hg, HCl, EtOH/PhMe, reflux, 20 h)[8] and no deacyl[2.2]paracyclophanes were observed.

¶ In a control experiment the dipentanoylester of diol **5** was exposed to the standard conditions at rt. Within 5 min all the ester had been cleaved to diol **5**.

Acknowledgements

We thank GlaxoSmithKline plc for a CASE award (to B.G.P.) and the EPSRC.

References

1. Bell, K. H. *Aust. J. Chem.* **1969**, *22*, 601–605.
2. Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3527–3533.
3. Cram, D. J. *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965; p. 138.
4. March, J.; Plankl, W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 460–464.
5. Gassman, P. G.; Lumb, J. T.; Zalar, F. V. *J. Am. Chem. Soc.* **1967**, *89*, 946–952.
6. Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3534–3543.
7. March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley, 1992; p. 569.
8. Cram, D. J.; Dalton, C. K.; Knox, G. R. *J. Am. Chem. Soc.* **1963**, *85*, 1088–1093.