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Syntheses and applications of disubstituted [2.2]paracyclophanes

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1. Introduction

[2.2]Paracyclophane[1] (Pc) was prepared and isolated by Brown and Farthing in 1949. Cram was the first to systematically investigate its chemical behaviour, helping to grasp the peculiar reactivity it exhibits.[2] Its unique structure, with two aromatic rings held tightly parallel, was exploited by chemists, particularly because chiral molecular architectures are obtained after a single substitution of the Pc scaffold. This resulted in the synthesis of numerous Pc derivatives[3] in enantiopure form[4] some of which were intended to be used in asymmetric catalysis.[5] The uncommon features of Pc make it an interesting platform to gather information about π–π interactions. It can also constitute a brick for construction in polymer and material science.[6] This review focuses on inter-deck disubstituted Pc derivatives, as this subclass of compounds presents the full set of molecular and geometrical properties a Pc structure can hold. Hence, the unique opportunity for precisely placing functional groups in space is fully seized with these derivatives. Importantly, depending of the regioisomer considered, two appending moieties can be held parallel, proximate, but staggered, V-shaped or anti thus allowing for fine-tuning of their geometrical arrangement, each being favourable for a given application. The placement of two substituents onto Pc gives rise to seven regioisomers, all chiral; the main challenge is then the

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selective preparation of the sole isomer targeted. This contribution is thus divided into four parts, one for each isomer of inter-deck substitution, with a strong emphasis on the preparative methodologies implemented to access the considered regioisomer. In this way, a chemist interested in, for example, a *pseudo-para* Pc derivative can easily select a known compound that can constitute the starting material for his own target. Each part then details the different derivatives that were reported in their enantiopure forms. Finally, applications are covered, stressing the specific properties brought by each isomer.

2. Generality

In Fig. 1 is represented [2.2]paracyclophane **1** (Pc),[1b] which displays an abnormally small phenyl–phenyl ring distance. Hence, *para* positions are separated by only 2.78 Å, ring centres being 3.09 Å apart, when normally stacked aromatics usually show a distance of 3.40 Å. In order to prevent a totally eclipsed conformation between the facing benzylic positions, aromatic rings are constantly rotating relative to one another, inducing a twist with a mean value of 6°.

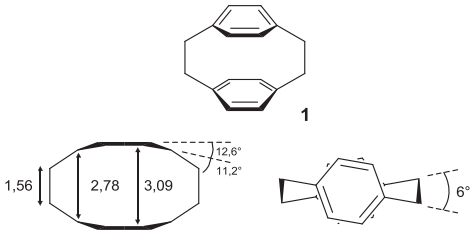


Fig. 1. Structural features of [2.2]paracyclophane.

Altogether, inherent strain within Pc derivatives results in a relative conformational 'stiffness' and, thus, well-defined and predicable shapes. The presence of one substituent breaks the initial D_{2h} symmetry of [2.2]paracyclophane[7] and, as a consequence brings chirality. Assignment of the absolute configuration and numbering rely on a specific nomenclature (Fig. 2).

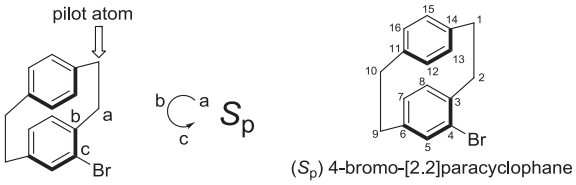


Fig. 2. Absolute configuration determination and numbering of Pc derivatives.

One has first to determine the 'pilot' atom as the nearest atom out of the chiral plane. The latter is the plane bearing the atom with the highest priority according to the Cahn–Ingold–Prelog (CIP) rules among the two aromatics; in this example, the chiral plane is the bottom one. Subsequentially, the pilot atom is chosen as the first one encountered when leaving this chiral plane and, which is the closest to the atom with the highest CIP priority; here, the methylene carbon atom of the top plane, and on the right side, closer to the bromosubstituent. The pilot atom is then the 'point-of-view' to determine the absolute configuration of the compound. From this location, one's eye considers the next atom belonging to the chiral plane (atom noted *a*), and follows the path from there to the atom with the highest CIP priority; atoms consequently noted *b* and *c*. The descriptor is then assigned according to the direction of circulation *a*–*b*–*c* viewed from the pilot atom; here counterclockwise from the bottom benzylic position to the bromine atom, leading to an (S_p) configuration. Complete numbering then follows the same circulation (see structure in Fig. 2).

If one now considers disubstituted Pc derivatives, particular descriptors are employed to designate the relation between these two positions. For substituents on the same phenyl ring, *ortho*, *meta* and *para* prefixes are still valid, while inter-ring disubstitution gives rise to *pseudo-gem*, *pseudo-meta*, *pseudo-para* and *pseudo-ortho* prefixes (Fig. 3).

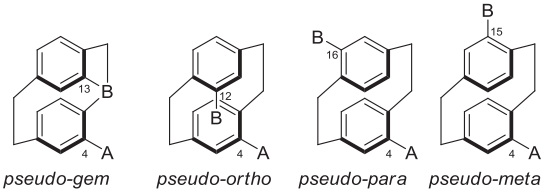
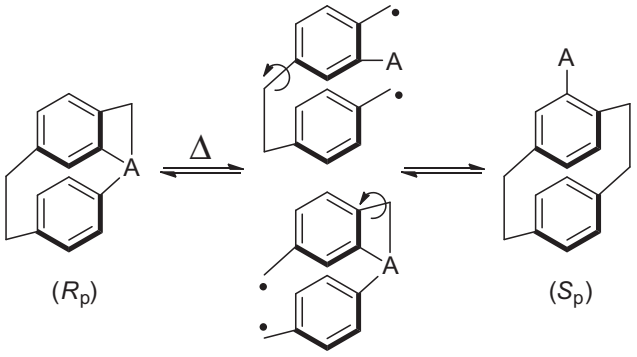


Fig. 3. Four regioisomers of disubstituted Pc derivatives.

Before entering into the chemical details for each regioisomer, a remark should be made about the configurational stability of Pc derivatives. Chiral [2.2]paracyclophanes can indeed racemize at temperature above 200 °C by a process that was proven to involve benzylic-bond homolytic scission, rotation and recombination of the diradical,[8] as shown in Scheme 1.



Scheme 1. Thermal isomerization of monosubstituted Pc.

As the most easily accessible regioisomer, we will first survey the synthesis of *pseudo-gem* compounds; followed by the related *pseudo-meta* derivatives. Very important *pseudo-para* derivatives will follow and we will close with the most used *pseudo-ortho* isomers.

3. *Pseudo-gem* isomers

Among the four possible disubstitution patterns, *pseudo-gem* is the most represented in terms of the number of compounds prepared. This originates from a specific stereoelectronic effect that favours the *pseudo-gem* diastereomer in electrophilic aromatic substitution reactions with monosubstituted Pcs bearing a Lewis-basic group. Although this isomer is the most sterically unfavoured because of repulsion between the two proximate substituents, in this particular case, it is the kinetically preferred one. This is explained by an intramolecular deprotonation process by the existing basic group ideally placed to capture the *pseudo-gem* proton within the Wheland intermediate **3**, as depicted in Scheme 2 with the bromination of ester **2** into **4**.