Unusual Reactivity of [6]Paracyclophane toward Alkyllithiums

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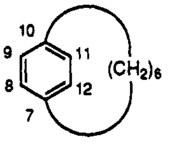
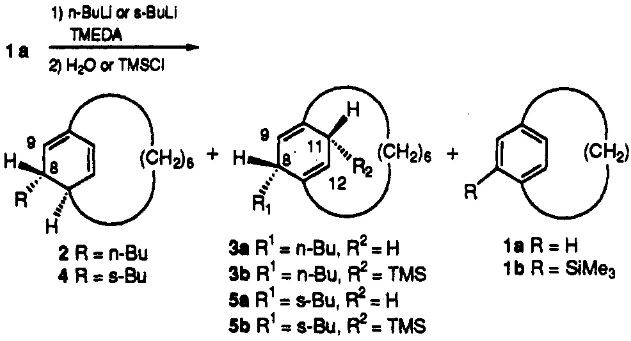
Summary: [6]Paracyclophane underwent nucleophilic addition with *n*-BuLi and *s*-BuLi and formal nucleophilic substitution with *t*-BuLi.

It has been well documented that strained [*n*]cyclophanes exhibit remarkably enhanced reactivity and sometimes undergo unusual reactions in electrophilic reactions such as addition and rearrangement.[1,2] These properties are ascribed to the strain imposed on the aromatic ring, a large amount of which is released in the initial stage of the reactions, and the high HOMO levels which lower the transition-state energy. Likewise, it may well be expected that strained cyclophanes show enhanced reactivity in nucleophilic reactions from the viewpoint of strain release and LUMO level. Indeed, Bickelhaupt reported that 8,11-dihalo-substituted [5]metacyclophanes, the smallest isolable [*n*]metacyclophane derivatives, underwent nucleophilic substitution (S_NAr) under mild conditions despite the fact that they were not activated by strongly electron-withdrawing groups.[2d,e,3] We wish to report here that [6]paracyclophane (**1a**),[1d,4] the smallest isolable representative in the [*n*]paracyclophane series, exhibits unusual reactivity toward alkyllithiums, i.e., nucleophilic addition of *n*-BuLi and *s*-BuLi and formal nucleophilic substitution with *t*-BuLi, which are, to our knowledge, without precedent in the chemistry of its aromatic counterpart, benzene.



1a

Scheme I



2 R = n-Bu
4 R = s-Bu

3a R^1 = n-Bu, R^2 = H
3b R^1 = n-Bu, R^2 = TMS
5a R^1 = s-Bu, R^2 = H
5b R^1 = s-Bu, R^2 = TMS

1a R = H
1b R = $SiMe_3$

When **1a** was treated with *n*-BuLi (5 equiv) in the presence of TMEDA (5 equiv) in hexane at rt for 1.5 h, nucleophilic addition products **2** and **3a** were obtained in 18% and 11% yields, respectively, along with unreacted **1a** (27%) after quenching with H_2O. The stereochemistry of the butyl group at C-8 of **2** and **3a** was determined on the basis of the ^1H NMR coupling constants between H-8 and H-9 (**2**, J = 9.2 Hz; **3a**, J = 7.7 Hz).[5,6] When the reaction was worked up with TMSCl, adducts **3b** (35%) and mono(trimethylsilyl)paracyclophane (**1b**)[7] (24%) were obtained. The stereochemistry of the TMS group at the new stereogenic center (C-11) of **3b** was also assigned to be anti to the bridge based on the ^1H NMR coupling constant (J = ca. 8 Hz) between H-11 and H-12.[5,6] Similarly, reaction of **1a** with *s*-BuLi under otherwise identical conditions yielded adducts **4**[9] (7%) and **5a**[9] (30%) and recovered **1a** (15%) after quenching with H_2O. Quenching with TMSCl afforded **5b**[9] (50%) and **1b** (12%) (Scheme I). These results indicated that nucleophilic

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[1] For [*n*]paracyclophanes: (a) Gassman, P. G.; Bailey, T. F.; Hoye, R. C. *J. Org. Chem.* **1980**, *45*, 2923. (b) Noble, K.-L.; Hopf, H.; Ernst, L. *Chem. Ber.* **1984**, *117*, 455. (c) Liebe, J.; Wolff, C.; Krieger, C.; Weiss, J.; Tochtermann, W. *Chem. Ber.* **1985**, *118*, 4144. (d) Tobe, Y.; Ueda, K.-I.; Kakiuchi, K.; Odaira, Y.; Kai, Y.; Kasai, N. *Tetrahedron* **1986**, *42*, 1851. (e) Tobe, Y.; Sorori, T.; Kobiro, K.; Kakiuchi, K.; Odaira, Y. *Tetrahedron Lett.* **1987**, *28*, 2861. (f) Kostermans, G. B. M.; Kwakman, P. J.; Pouwels, P. J. W.; Somsen, G.; De Wolf, W. H.; Bickelhaupt, F. *J. Phys. Org. Chem.* **1989**, *2*, 331. (g) Tobe, Y.; Takemura, A.; Jimbo, M.; Takahashi, T.; Kobiro, K.; Kakiuchi, K. *J. Am. Chem. Soc.* **1992**, *114*, 3479.

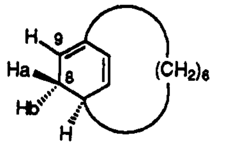
[2] For [*n*]metacyclophanes: (a) Van Straten, J. W.; De Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* **1977**, 4667. (b) Turkenburg, L. A. M.; Blok, P. M. L.; De Wolf, W. H.; Bickelhaupt, F. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 298. (c) Turkenburg, L. A. M.; De Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* **1983**, *24*, 1817. (d) Jenneskens, L. W.; Klamer, J. C.; De Wolf, W. H.; Bickelhaupt, F. *J. Chem. Soc., Chem. Commun.* **1984**, 733. (e) Jenneskens, L. W.; De Boer, H. J. R.; De Wolf, W. H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1990**, *112*, 8941. For a review: (f) Bickelhaupt, F.; De Wolf, W. H. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 459.

[3] Kraakman, P. A.; Valk, J.-M.; Niederländer, H. A. G.; Brouwer, D. B. E.; Bickelhaupt, F. M.; De Wolf, W. H.; Bickelhaupt, F.; Stam, C. H. *J. Am. Chem. Soc.* **1990**, *112*, 6638.

[4] (a) Kane, V. V.; Wolf, A. D.; Jones, M., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 2643. (b) Kammula, S. L.; Iroff, L. D.; Jones, M., Jr.; Van Straten, J. W.; De Wolf, W. H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1977**, *99*, 5815.

[5] The same numbering as that for cyclophane **1a** is used for the adducts **2–5** for convenience.

[6] We observed coupling constants of 6–8 Hz for the relevant protons of the related structures.[1g] Moreover, in order to support the assignments, we undertook MM2 calculations for the model compounds **9** and **10**. The calculated dihedral angles between H-9 and H-8a and between H-9 and H-8b of **9** and **10** are 23.5°, 95.1°, 5.8°, and 115.1°, respectively. The coupling constants between these protons estimated by using the Karplus equation are 6.9, 0.2, 8.1, and 1.2 Hz, respectively, which are in agreement with the experimental data.



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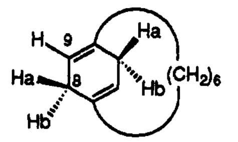

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[7] We found that metalation of **1a** with a strong base (Lochmann's base[8]) gave rise to regioselective metalation at the aromatic ring rather than the benzyl position: Tobe, Y.; Jimbo, M.; Ishii, H.; Saiki, S.; Kakiuchi, K.; Naemura, K. *Tetrahedron Lett.* **1993**, *34*, 4969.

[8] Lochmann, L.; Pospisil, J.; Lim, D. *Tetrahedron Lett.* **1966**, 257. Schlosser, M. *Pure Appl. Chem.* **1988**, *60*, 1627.

[9] *s*-BuLi adducts **4**, **5a**, and **5b** were obtained as inseparable mixtures of diastereomers (1:1) arising from the additional stereogenic center in the the *sec*-butyl group. The stereochemistry of C-8 (and that of C-11 of **5b**) was assumed to be the same as those of **2**, **3a**, and **3b**.

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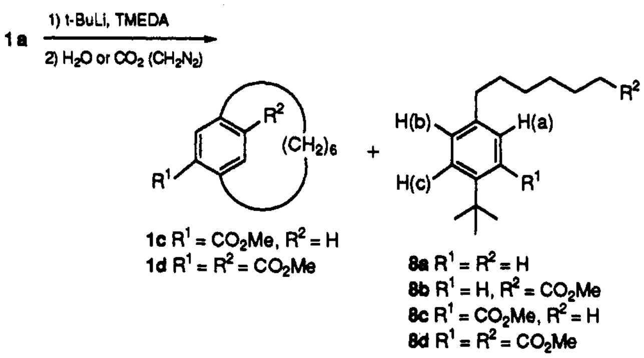
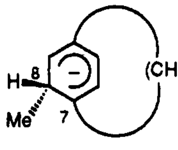
Scheme II



addition of *n*- and *sec*-butyl anions took place as the major reaction which was accompanied by metalation of the aromatic ring. The former reaction represents the first example of nucleophilic addition of a benzene derivative which does not bear an activating electron-withdrawing group.

It should be pointed out that the addition of butyllithiums took place regioselectively at the ortho position of the bridgehead carbon. In order to explain the regioselectivity, semiempirical PM3[10,11] calculations were undertaken for the carbanion intermediates **6** and **7**, which would be formed by addition of methyl anion to the ortho (C-8) or ipso (C-7) position of **1a**. As a result, **7** turned out to be more stable than **6** by 10.7 kcal/mol. This can be readily understood from the fact that more (anti-Bredt) bridgehead double bonds are involved in the resonance structures of **6** than those of **7**. Moreover, PM3 calculations of **1a**[1g] indicate that net charge distribution in the aromatic ring of **1a** is almost equal. These results suggest that the regioselectivity is not controlled by either stability of the intermediates or charge effect. The calculations show, however, that the LUMO of **1a** resembles ψ_4 of benzene and the coefficients of bridgehead carbons (C-7, -10) are larger than those of ortho carbons (C-8, -9, -11, -12), in contrast to the observed regioselectivity. On the other hand, NLUMO of **1a**, which is 0.47 eV above the LUMO, resembles ψ_5 of benzene, and the coefficients of the ortho carbons (C-8, -9, -11, -12) are much larger than those of the bridgehead carbons (C-7, -10). Consequently, we suppose that FMO interactions between the NLUMO of **1a** and the HOMO of alkyl anion plays a major role in determination of the regioselectivity.



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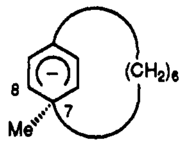

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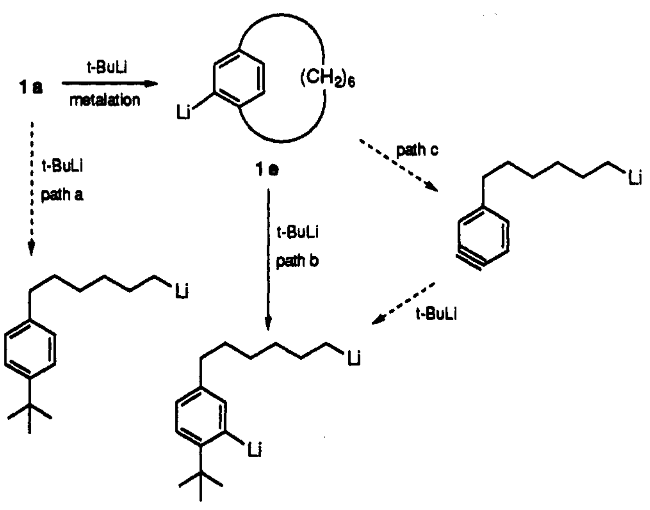
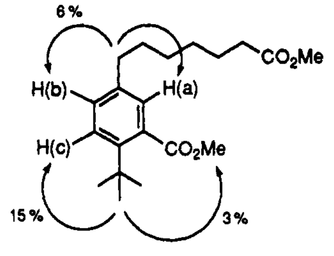
Scheme III



8e

In constrast to *n*- and *s*-BuLi, treatment of **1a** with 5 equiv of *t*-BuLi and TMEDA in hexane for 3 h at rt gave monosubstituted cyclophane **1b** in 66% yield after quenching with TMSCl. Thus, with *t*-BuLi, nucleophilic addition did not take place; the major reaction with this base was metalation.[7] However, when a large excess of *t*-BuLi (ca. 20 equiv) was allowed to react for a longer period (20 h), a new product, 4-*tert*-butylhexylbenzene (**8a**), was produced in 41% yield along with unreacted **1a** (24%) after quenching with H_2O. Quenching the reaction with CO_2 followed by treatment with CH_2N_2 gave diester **8d** as the major product (38%) along with diester **1d**[7,12] (13%) and monoesters **1c**[1d,7] (4%), **8b** (5%), and **8c** (8%) (Scheme II). The position of the methoxycarbonyl group in the aromatic ring of **8d** was unambiguously established to be ortho to the *tert*-butyl group on the basis of the ^1H NMR coupling constants (H(a) δ 7.07 (d, J = 2.2 Hz), H(b) δ 7.14 (dd, J = 8.1, 2.2 Hz), H(c) δ 7.35 (d, J = 8.1 Hz)) and the NOE experiments. This represents, to our knowledge, the first example of formal nucleophilic substitution of an unactivated benzene derivative. The above results strongly suggested that the substitution took place on lithiated species **1e** to give dilithio compound **8e** (path b) but not directly on **1a** (path a) as shown in Scheme III. Likewise, the observed regioselectivity precluded the elimination–addition pathway through a benzyne intermediate (path c).



8d

In order to clarify the activating property of the ortho lithio group toward nucleophilic substitution, MNDO[11,13] calculations were undertaken for **1e**. As is expected from the electron-donating property of lithium, the LUMO level of **1e** is considerably higher than that of **1a** (MNDO) by 0.74 eV suggesting that **1e** itself would not be susceptible to nucleophilic attack of *tert*-butyl anion. Taking into account the well-known tendency of organolithiums to

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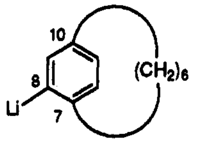
(10) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.

(11) The calculations were performed using MOPAC Version 5.00 (QCPE No. 445): Stewart, J. J. P. *QCPE Bull.* **1989**, *9*, 10. Hirano, T. *JCPE Newsl.* **1989**, *1*, 36. Ver. 5.01: Toyoda, J. *JCPE Newsl.* **1990**, *2*, 56.

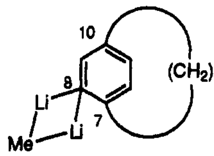
(12) Tobe, Y.; Nakayama, A.; Kakiuchi, K.; Odaira, Y.; Kai, Y.; Kasai, N. *J. Org. Chem.* **1987**, *52*, 2639.

(13) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

aggregate in nonpolar solvents,[14] we performed MNDO calculations for a postulated MeLi–1e mixed dimer 9.[15] The LUMO level of 9 turned out to be only slightly higher than that of 1a by 0.26 eV. The LUMO of 9 as well as that of 1e resemble the benzene ψ_4 orbital, suggesting that attack of *tert*-butyl anion would take place at the bridgehead carbon (C-7, -10). Since the coefficients of C-7 and C-10 are almost same, the regioselective substitution at C-7 may be attributed to the proximity of the alkyllithium which aggregates to C-8 of 1e. Further works are in progress to clarify the mechanism of the reactions.



1e



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Supplementary Material Available: Listing of spectral properties and ^{1}H and ^{13}C NMR spectra of **2**, **3a**,**b**, **4**, **5a**,**b**, and **8a**–**d** (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) For reviews: (a) Wakefield, B. J. *The Chemistry of Organilithium Compounds*; Pergamon: Oxford, 1974. (b) Wardell, J. L. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 1, p 43. (c) Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353.

(15) For a similar MNDO calculation for mixed dimer aggregate of naphthyllithium–MeLi: Neugebauer, W.; Clark, T.; Schleyer, P. v. R. *Chem. Ber.* **1983**, *116*, 3283.