

## CNDO/II treatment of proton abstraction step in aromatic lithiation reaction

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**Abstract.** All valence MO calculation employing CNDO/II treatment for hydrogen abstraction step in aromatic ortho lithiation reaction is done. The predicted proton abstraction is supported by experimental observation. The lithiation of N-methyl- $\beta$ -naphthamide occurs at the 1 position and not at the 3 position.

**Keywords.** CNDO/II calculation; charge on *o*-hydrogen.

### 1. Introduction

Hetero atom directed ortho lithiation with *n*-BuLi plays an important role in synthetic organic chemistry (Narasimhan and Mali 1987). The generally accepted mechanism of aromatic lithiation reaction requires a group having a lone pair of electrons (Roberts and Curtin 1946) with which the *n*-BuLi reagent can complex; in the transition state the butyl anion can abstract a sterically close *o*-hydrogen. All valence MO calculation is likely to provide a better understanding of the proton abstraction step. Therefore, CNDO/II treatment (Pople and Segal 1966) is carried out for a few compounds for which the products of lithiation are well recognised.

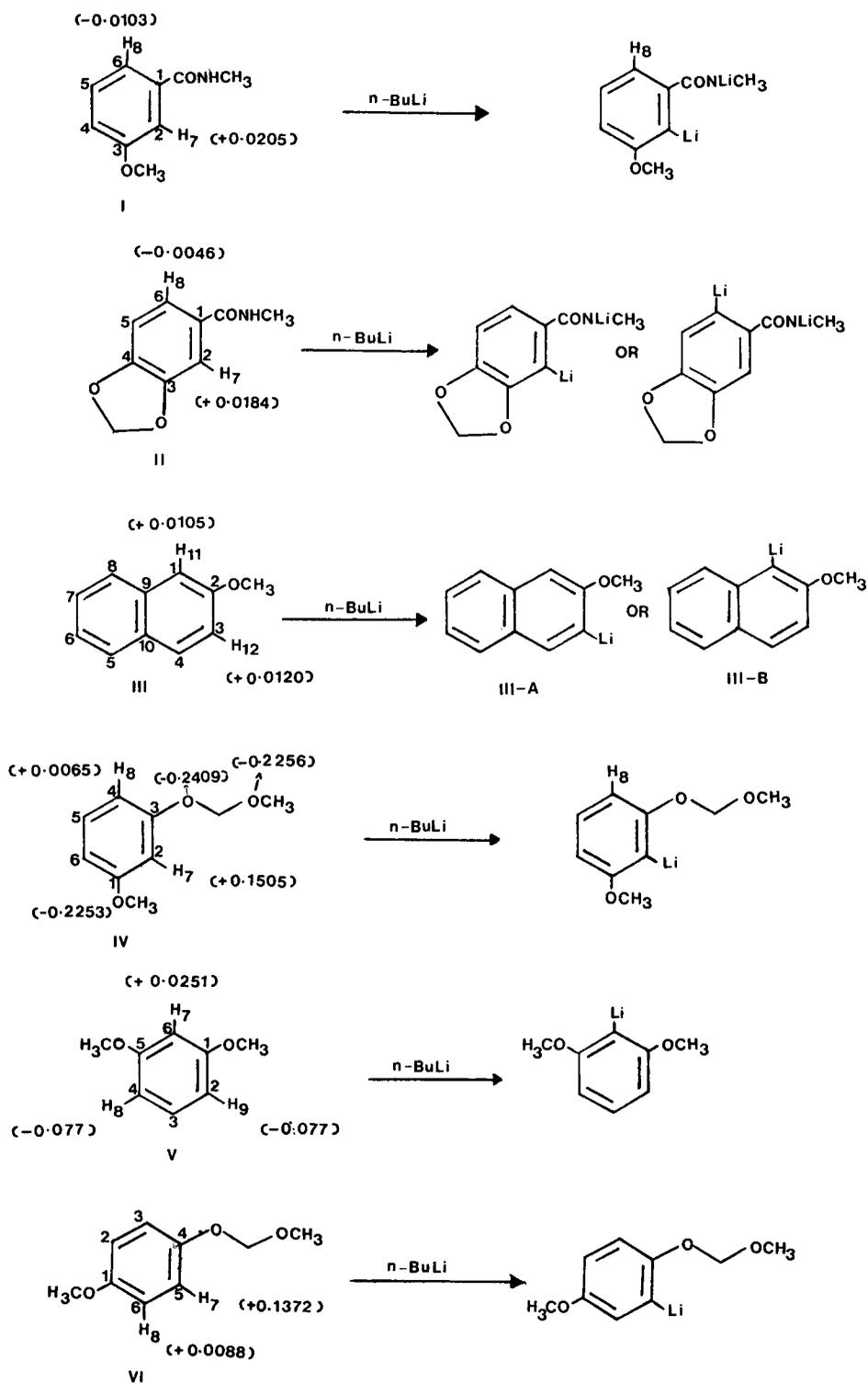
### 2. Results and discussion

The ortho lithio intermediates of a number of compounds, for which CNDO/II calculations have been performed are shown in scheme 1.

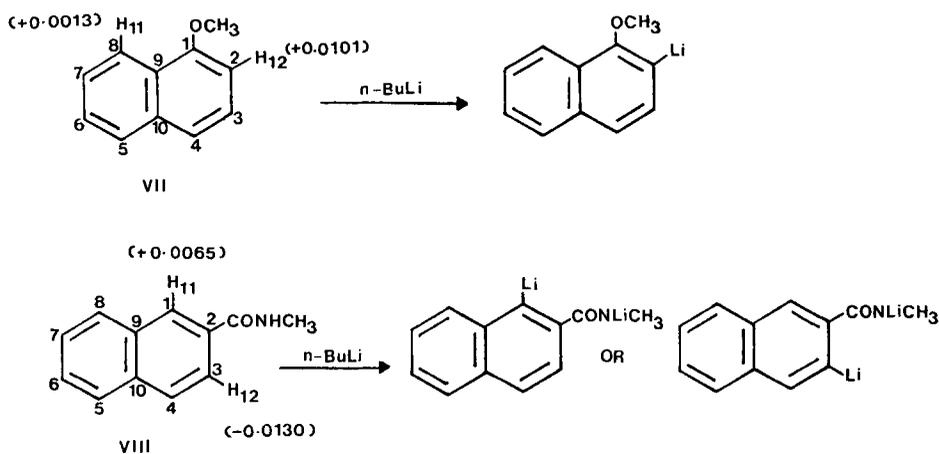
The semiempirical parameters required for the CNDO/II method were taken as such from literature (Pople and Segal 1966). The bond length and bond angles were obtained from appropriate references (Ferguson 1966; Butler and Berlin 1972). The calculations were made employing an HCL-PC-AT-386 computer.

The working hypothesis is based on the premise that after the Li atom of *n*-butyl lithium has complexed with a hetero atom having a lone pair of electrons, the butyl anion attacks the ortho hydrogen having a greater positive charge. This interaction weakens the concerned C–H bond leading to the abstraction of the proton by the butyl anion. For each compound investigated, the charge on the hydrogen atom likely to be abstracted is shown in scheme 1.

During the lithiation of compound I, the Li of the *n*-BuLi prefers to bind with the CONHCH<sub>3</sub> moiety. Of the two *o*-hydrogens H<sub>7</sub> and H<sub>8</sub> in I, the former is positively



Scheme 1. (Continued).



Scheme 1.

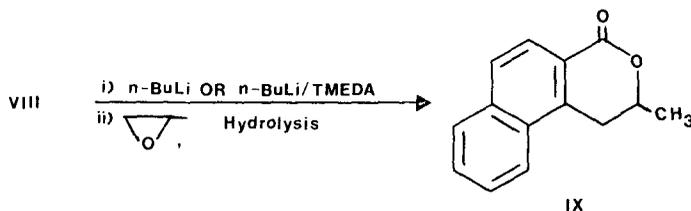
charged while  $H_8$  is negatively charged. Therefore, the butyl anion is expected to abstract the  $H_7$  atom. It would be difficult for the butyl anion to attack the  $H_8$  atom and the possibility of its being abstracted is also remote. This is borne out by the experimental observation (Narasimhan and Bhide 1971). Again, in the case of compound II the charges on the two *o*-hydrogens  $H_7$  and  $H_8$  shown in scheme 1, clearly favour exclusive abstraction of the  $H_7$  atom during lithiation and this has been experimentally observed (Bhide and Shah 1980). In the light of the discussions so far, the lithiation of compound (III) is predicted to provide preferentially compound (III-A) along with compound (III-B). This has been found to be so experimentally (Narasimhan and Mali 1975). The preceding examples give ample support to the working hypothesis. Based on this the lithiation of compounds (IV) and (V) can also be explained. During the formation of the transition state (of compound IV), the lithium atom of butyllithium might prefer to attack the oxygen of  $-OCH_2-$  in the  $-OCH_2-OCH_3$  moiety, then the  $H_7$  and  $H_8$  atoms have chances of being abstracted. Since in compound (IV), the  $H_7$  atom is several times more positive than the  $H_8$  atom, it is preferentially abstracted as observed experimentally (Mallan and Bebb 1969). The abstraction of the highly positively charged  $H_7$  atom in the lithiation of compound (V) now can easily be accounted for. Just as in the compounds discussed so far, the comparison of charges on appropriate atoms does suggest the preferential abstraction of  $H_7$  atom in compound (VI) during lithiation (Narasimhan *et al* 1979). Similarly, the preferential abstraction of the  $H_{12}$  atom during the lithiation of compound (VII) is easily understood (Barnes and Nehmsmann 1939; Graybill and Shirely 1966).

The simple correlation discussed so far provides a remarkably good account of the proton abstraction mechanism. In a few cases, however, the difference in charges between two *o*-hydrogens has been found to be small. This may be traced to the fact that none of the geometries of the molecules investigated here were optimized.

Equipped with above observations, it can be predicted from the results of CNDO/II calculations for compound (VIII) that the  $H_{11}$  atom is exclusively abstracted during lithiation with butyl lithium. Thus lithiation of N-methyl- $\beta$ -naphthamide (VIII) followed by condensation with propylene oxide should furnish 3-methyl-3,4-dihydro-5,6-benzisocoumarin and not 3-methyl-3,4-dihydro-6,7-benzisocoumarin as

reported earlier (Bhide and Gupta 1977). This necessitated the reinvestigation of above reaction.

Thus when N-methyl- $\beta$ -naphthamide (VIII) was lithiated with (i) *n*-BuLi or (ii) *n*-BuLi-TMEDA and the resulting red ortho-lithio derivative condensed with propylene oxide, it gave a product which was identified as (IX) (scheme 2). The structure of (IX) was fully borne out by analytical and spectral evidence.



**Scheme 2.**

The structure of IX was further confirmed as it was identical in all respects (m.p.; mixed m.p. and superposable IR) with 3-methyl-3,4-dihydro-5,6-benzisocoumarin independently synthesised by an acid-catalyzed method (Bhide *et al* 1989).

Thus the theoretical prediction regarding the proton abstraction step has helped in modifying our earlier observation.

### 3. Experimental

#### 3.1 Lithiation of N-methyl- $\beta$ -naphthamide (VIII) and its condensation with propylene oxide

To a well-stirred solution of N-methyl- $\beta$ -naphthamide (VIII) (Bhide and Gupta 1977), (4.0 g, 21.0 mmol) in dry THF (40 ml) was added, at room temperature, *n*-BuLi (54.0 mmol) in dry ether under  $N_2$  atmosphere over a period of 10 minutes. The metalation mixture upon condensation with propylene oxide (8.0 ml) in dry ether at  $0^\circ\text{C}$  and alkaline hydrolysis work up as before (Narasimhan and Bhide 1971) gave (IX).

#### 3.2 3-Methyl-3,4-dihydro-5,6-benzisocoumarin (IX)

Melting point  $124^\circ\text{C}$ , white needles from ethyl acetate-hexane; 800 mg (yield 37%) (found: C, 79.4; H, 5.5%  $C_{14}H_{12}O_2$  requires C, 79.2; H 5.7%) IR (KBr):  $1710\text{ cm}^{-1}$  ( $\delta$ -lactone; UV: 244, 285 nm ( $\log \epsilon$  4.17); PMR ( $CDCl_3$ ):  $1.6\delta$  (3H, *d*,  $J = 6.0\text{ Hz}$ ,  $-\text{CH}_2-\overset{|}{\text{C}}\text{H}-\overset{|}{\text{C}}\text{H}_3$ ),  $3.3\delta$  (2H, 8 lines, the AB part of an ABX system  $J_{AB} = 16\text{ Hz}$ ,  $J_{AX} = 4\text{ Hz}$   $J_{BX} = 11\text{ Hz}$ ),  $4.7\delta$  (1 H, complex pattern of the X part of an ABX system,  $-\text{CH}_2-\overset{|}{\text{C}}\text{H}-\overset{|}{\text{C}}\text{H}_3$ ),  $7.9\delta$  (6 H, multiplet, aromatic protons).

#### 3.3 Lithiation of N-methyl- $\beta$ -naphthamide (VIII) in the presence of TMEDA and its condensation with propylene oxide

To a well-stirred solution of N-methyl- $\beta$ -naphthamide (VIII), (4.0 g, 21.0 mmol), and TMEDA (8.0 ml, 54.0 mmol) in dry THF (40 ml) was added, at room temperature,

*n*-BuLi (54.0 mmol) in dry ether under N<sub>2</sub> atmosphere over a period of 10 minutes. The metalation mixture upon condensation with propylene oxide (8.0 ml) in dry ether at 0°C followed by alkaline hydrolysis work up as above gave (IX) (900 mg, 37.7%). It was identical in all respects (m.p., mixed m.p. and superposable IR) with 3-methyl-3,4-dihydro-5,6-benzoisocoumarin (IX) obtained in the earlier case.

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