

Formation of *meso*-1,2-Bis(dimethylamino)-1,2-diphenylethane by Oxidative C-C Coupling Reaction

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The title compound was obtained from the reaction of *N,N*-dimethylbenzylamine with *n*-butyl lithium and sulfur in tetrahydrofuran at room temperature. Its molecular structure was investigated by means of single crystal X-ray diffraction and quantum chemical DFT methods. The formation of *meso*-1,2-bis(dimethylamino)-1,2-diphenylethane is likely to be due to an unusual α -deprotonation of *N,N*-dimethylbenzylamine, instead of the well known *ortho*-lithiation, with a subsequent oxidative C-C coupling of the anions. *Ab initio* calculations of the corresponding α - and *o*-deprotonated anions of *N,N*-dimethylbenzylamine showed the former to be more stable than the latter, due to delocalisation of the negative charge over the π -system of the phenyl ring. The choice of solvent and temperature is seen as the main reason for the unusual course of the reaction.

Key words: 1,2-Bis(dimethylamino)-1,2-Diphenylethane, C-C Coupling, Crystal Structure, *ab initio* Calculation

Introduction

C-C coupling reactions of benzaldehyde or benzamide derivatives are useful synthetic tools in order to get 1,2-diamino-1,2-diphenylethane derivatives. Seebach and co-workers reported on reductive C-C coupling reactions of benzaldehyde and its derivatives by low-valent Ti and V^{IV} reagents to give *N,N,N',N'*-tetraalkyl-1,2-diarylethylenediamines [1]. Selvakumar and Harrod developed a titanocene-catalyzed reductive amide coupling using organosilanes as reducing agents [2].

More than 40 years ago, Hauser and co-workers investigated the reaction of *N,N*-dimethylbenzylamine with organometallic compounds. They reported that *n*-BuLi exclusively deprotonates an *o*-position, while sodium alkyls deprotonate the CH₂-group, to give the α -metallated product [3,4]. On exchange of Na⁺ for Li⁺ a rearrangement with metallation of the *o*-position takes place at slightly elevated temperatures. Reich and co-workers investigated the solution structure of the *o*-lithiated *N,N*-dimethylbenzylamine and found several dimers to coexist at temperatures below –55 °C [5]. Boche *et al.* succeeded in isolating the diethylether adduct of α -lithiated

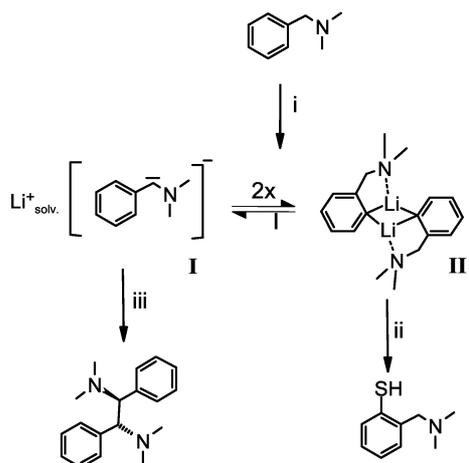
N,N-dimethylbenzylamine from the reaction of tri-*n*-butyl[α -(dimethylamino)benzyl]stannane with *n*-BuLi in hexane at 0 °C, and to investigate its molecular structure in the solid state [6].

Reaction of sulfur, selenium or tellurium with aryl lithium or Grignard reagents is a suitable method for the formation of C-E bonds (E = S, Se, Te) [7]. Several *o*-lithiated benzyl derivatives were successfully converted to the respective thiols [8], (di)selenides or (di)tellurides [9]. We report a hitherto unknown α -deprotonation of *N,N*-dimethylbenzylamine by *n*-BuLi and the oxidative dimerization of the resulting anion to give *meso*-1,2-bis(dimethylamino)-1,2-diphenylethane.

Results and Discussion

Formation of meso-1,2-bis(dimethylamino)-1,2-diphenylethane

Addition of lithiated *N,N*-dimethylbenzylamine to a suspension of sulfur in THF at –78 °C and acid workup gives 2-((*N,N*-dimethylamino)methyl)thiophenol in moderate to good yields, as was reported in the literature [8,10] and confirmed in our own syntheses (see Scheme 1). When the reaction was carried out in such



Scheme 1. Different reactions of *N,N*-dimethylbenzylamine with *n*-BuLi / S₈. Reaction conditions: i: *n*-BuLi in hexane/diethylether, 0 °C; ii: 1. S₈, THF, –78 °C, 2. HCl, 0 °C; iii: 1. S₈, THF, 20–25 °C, 2. HCl, 20–25 °C. The dimeric structure of II is according to Reich *et al.* [5].

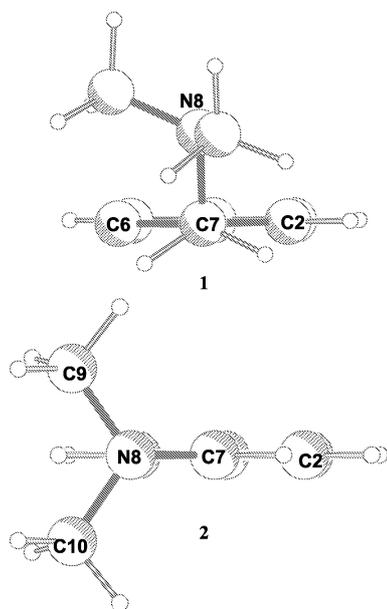


Fig. 1. MP2/6-31G(d) optimized molecular structures of *N,N*-dimethylbenzylamine anions **1**: Deprotonation in *o*-position at C6 **2**: Deprotonation in α -position at C7. View is along the bond from C7 to C1, the phenyl ring is oriented horizontally.

a way that sulfur was added to a solution of [2-((*N,N*-dimethylamino)methyl)phenyl]lithium in THF at room temperature, a brown-red and highly viscous product instead of a yellow oil was obtained. From the former, *meso*-1,2-bis(dimethylamino)-1,2-diphenylethane was

Table 1. Selected structural data of *meso*-1,2-bis(dimethylamino)-1,2-diphenylethane from a single crystal XRD experiment and B3LYP/6-31G(d) (designated as DFT) geometry optimization. Distances are given in Å, angles in degree.^a

	XRD	DFT		XRD	DFT
C(1)-C(2)	1.370(4)	1.402	C(2)-C(1)-C(6)	117.3(3)	117.8
C(1)-C(6)	1.395(5)	1.404	C(1)-C(2)-C(3)	121.7(4)	121.4
C(1)-C(7)	1.528(4)	1.531	C(4)-C(3)-C(2)	119.8(4)	120.0
C(2)-C(3)	1.386(5)	1.397	C(5)-C(4)-C(3)	119.6(4)	119.4
C(3)-C(4)	1.378(6)	1.394	C(4)-C(5)-C(6)	120.6(4)	120.4
C(4)-C(5)	1.356(6)	1.397	C(5)-C(6)-C(1)	121.0(4)	121.1
C(5)-C(6)	1.383(5)	1.394	C(2)-C(1)-C(7)	119.2(3)	119.4
C(7)-N(8)	1.485(4)	1.476	N(8)-C(7)-C(7) ^{#1}	109.8(3)	110.6
C(7)-C(7) ^{#1}	1.526(6)	1.556	C(7) ^{#1} -C(7)-C(1)	113.5(3)	113.2
N(8)-C(10)	1.434(5)	1.456	C(10)-N(8)-C(9)	110.9(3)	111.4
N(8)-C(9)	1.456(4)	1.456	C(10)-N(8)-C(7)	116.1(3)	116.7
			C(9)-N(8)-C(7)	111.7(3)	113.4
			C(2)-C(1)-C(7)-N(8)	–93.8(4)	–96.2
			C(2)-C(1)-C(7)-C(7) ^{#1}	139.1(4)	135.7
			C(1)-C(7)-N(8)-C(10)	–60.5(4)	–61.8
			C(1)-C(7)-N(8)-C(9)	68.0(4)	69.7

^a C-H bond lengths were fixed in the refinement of the XRD data: C²⁻⁶–H = 0.93, C⁷–H = 0.98, C^{9/10}–H = 0.96 Å. Symmetry transformations used to generate equivalent atoms: ^{#1} –x, –y + 1, –z.

obtained by sublimation (10^{–3} mbar, 150 °C). Hence, product selectivity depends on the reaction temperature. It must depend further on the solvent, since reaction of *n*-BuLi with *N,N*-dimethylbenzylamine at room temperature, either in pure diethylether or in a mixture of diethylether with hexane and benzene, led to the *o*-lithiated product, as was established by analyses of subsequent reaction products [3, 4].

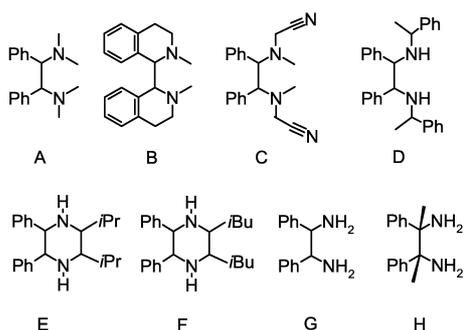
An *ab initio* investigation of the isolated anions (see Fig. 1) at the MP2/6-31G(d) level revealed **2** (negative charge at C7) to be more stable than **1** (negative charge at C6) by 72 kJ mol^{–1}. The main reason for the stabilization of **2** is the resonance of the *p*-type lone pair at C7 (α -C) with the aromatic system of the phenyl ring, as was established by a second order perturbation theory analysis of the Fock matrix in a natural bond orbital (NBO) basis [11]. Without being restricted to it, **2** adopted C_s symmetry, under which the respective orbital interaction is at its maximum.

Thus, the tautomer anion **2** appears to be favored if the deprotonated *N,N*-dimethylbenzylamine is separated from the Li⁺ ion, such that no stabilization of the *o*-lithiated form by means of intramolecular N⋯Li interaction can occur. THF is known to strongly coordinate to Li⁺ and is thus feasible to produce a separation of that cation from the deprotonated *N,N*-dimethylbenzylamine. This suggestion is supported

Table 2. Selected bond distances (in Å) at the α -C atom of some 1,2-diamino-1,2-diphenylethane derivatives from single crystal XRD experiments^a.

	$r(C^\alpha-C^i)^b$	$r(C^\alpha-C^{\alpha'})$	$r(C^\alpha-N)$	Reference
<i>meso</i> -A	1.528	1.526	1.485	this work
<i>rac</i> -B	1.516	1.564	1.482	[12]
<i>rac</i> -C	1.530	1.503	1.483	[13]
<i>rac</i> -D	1.523	1.545	1.471	[14]
(2 <i>R</i> ,3 <i>R</i> ,5 <i>S</i> ,6 <i>S</i>)-E	1.517	1.540	1.469	[15]
(2 <i>R</i> ,3 <i>R</i> ,5 <i>S</i> ,6 <i>S</i>)-F	1.506	1.543	1.461	[15]
(1 <i>R</i> ,2 <i>R</i>)-G	1.520	1.551	1.460	[16]
<i>meso</i> -H	1.522	1.637	1.471	[17]

^a For molecular structures of compounds A – H see Scheme 2; ^b Cⁱ designates the ipso C atom of the phenyl ring.



Scheme 2. Molecular structures of compounds given in Table 2.

by results of Reich *et al.*, who reported that spin-spin coupling of ⁶Li to ¹³C and ¹⁵N in a solution of 2-[(dimethylamino)methyl]phenyllithium in THF disappears at temperatures above –55 °C [5]. Since dissociation and charge separation are likely to increase the entropy of the system, it can be rationalized why formation of **2** is favored at higher temperatures in this solvent. The oxidative C-C coupling, leading to the formation of 1,2-bis(dimethylamino)-1,2-diphenylethane, is due to the action of sulfur on the anions. Preference for any mechanism of the coupling reaction would be too speculative at the present stage.

Structural investigations

The single crystal X-ray structure shows *meso*-1,2-bis(dimethylamino)-1,2-diphenylethane to exhibit inversion symmetry in the solid state. The six C atoms of the phenyl ring are coplanar, intra-ring-C-C-C angles summing to 720°. The heavy atom torsion angles of the C₆H₅CH unit are within 1.0° from 0 or 180°. The C(1)-C(7)-N(8) plane is nearly orthogonal to the plane of the phenyl ring. On the basis of a second order perturbation calculation in an NBO ba-

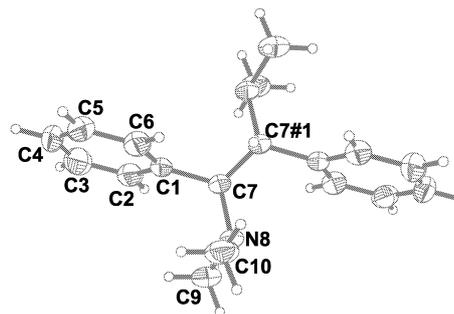


Fig. 2. ORTEP diagram of *meso*-1,2-bis(dimethylamino)-1,2-diphenylethane. Displacement ellipsoids are at the 50% probability level.

sis [11], the preference for that conformation can be attributed to a $\pi - \sigma^*$ interaction between the aromatic system and the C-N bond. The sum of the bond angles at N(8) is 338.7°. Table 2 compares bond distances at the α -C atom to those of some other 1,2-diamino-1,2-diphenylethane derivatives. For $r(C^\alpha-C^i)$ no significant differences occur between reference **A** and the other compounds. $r(C^\alpha-C^{\alpha'})$ is shorter in **A** than in the other compounds, which is likely to be a consequence of reduced repulsion of the substituents at the two C $^\alpha$ atoms (cf. the very long C $^\alpha$ -C $^{\alpha'}$ bond in **H**).

The agreement between the XRD and the B3LYP/6-31G(d) structure is good for bond distances and even very good for bond angles. This is rather surprising, since the XRD experiment gives an r_α structure at 298 K in the solid state, while the DFT geometry optimization leads to an r_e structure of an isolated molecule. These results suggest that intermolecular forces in the solid state do not have a significant impact on the molecular structure. This conclusion is supported by the torsion angles given in Table 1. Torsion angles are “soft” structural parameters, *i. e.* their magnitude can be substantially changed with small energy efforts. The four torsion angles in Table 1 give the relative orientations of the dimethylamino group and the phenyl ring, *i. e.* they define the shape of the molecule. Hence, since the agreement between XRD and DFT torsions is quite high, *meso*-1,2-bis(dimethylamino)-1,2-diphenylethane is not distorted to a significant degree by packing forces in the solid state.

Experimental Section

General procedures

N,N-dimethylbenzylamine, diethylether, THF and chloroform were purified by distillation according to standard procedures.

Table 3. Crystal data for *meso*-1,2-bis(dimethylamino)-1,2-diphenylethane.

Empirical formula	C ₁₈ H ₂₄ N ₂
FW [g mol ⁻¹]	268.39
Temperature [K]	298(2)
Wavelength [Å]	1.54178
Crystal size [mm]	0.43 × 0.32 × 0.23
Crystal system	monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> [Å]	6.0537(12)
<i>b</i> [Å]	6.9486(10)
<i>c</i> [Å]	19.422(4)
β [°]	107.20(2)
<i>Z</i> , ρ_{calcd} [g cm ⁻³]	2, 1.142
μ [mm ⁻¹]	0.507
<i>F</i> (000)	292
θ -Range	4.77 ≤ θ ≤ 73.04°
Limiting indices	0 ≤ <i>h</i> ≤ 7, 0 ≤ <i>k</i> ≤ 8, -24 ≤ <i>l</i> ≤ 23
Reflections measured	1721
Unique reflections	1570
Ref. $ F > 4\sigma(F)$	1570
$R[F > 4\sigma(F)]^a$	0.0892
<i>wR</i> ₂	0.2513
goodness-of-fit on <i>F</i> ²	1.078
largest diff. peak and hole [10 ⁻³ e·nm ⁻³]	0.310 and -0.468

$$^a R = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}$$

Synthesis of *meso*-1,2-bis(dimethylamino)-1,2-diphenylethane

Under an Ar atmosphere, 100 ml of a 2.5 M solution of *n*-BuLi in hexane was slowly added to a stirred solution of *N,N*-dimethylbenzylamine (33.8 g, 0.25 mol) in 250 ml of THF. When no more gas was evolved, sulfur (8.02 g, 0.25 mol) was added in small portions. The reaction mixture was stirred for another 4 h, before 100 ml of H₂O, 25 ml of 10 M HCl and 100 ml of diethylether were added. Organic and aqueous phase were separated, and the latter extracted five times with a total of 500 ml of chloroform.

The combined organic phases were dried over Na₂SO₄, the solvents were distilled off under normal pressure to leave 36.2 g of a red-brown, highly viscous crude product. Heating this product to 150 °C under high-vacuum conditions (*p* = 10⁻³ mbar) led to the sublimation of pale yellow crystals (less than 500 mg). The product could be identified by ¹H NMR spectroscopy as *meso*-1,2-bis(dimethylamino)-1,2-diphenylethane. Crystals suitable for single crystal X-ray diffraction were taken from the sublimate. No other reaction products could be isolated or identified in the mixture.

Crystal structure determination

The diffraction experiment was performed on a TurboCAD 4 (Nonius) diffractometer. The crystal structure was solved by direct methods and difference Fourier techniques (SIR-92) [18]. Structural refinement was against *F*² (SHELXL-97) [19]. Details of the crystal structure determination and the crystal data are given in Table 3 [20].

Theoretical methods

Ab initio and density functional theory (DFT) calculations were performed with the GAUSSIAN98 software package [21]. The molecular structure of *meso*-1,2-bis(dimethylamino)-1,2-diphenylethane was fully optimized using a 6-31G(d) basis set and DFT employing a combination of local, gradient-corrected, and exact exchange functionals according to the prescription of Becke [22] and the gradient-corrected correlation functional of Lee, Yang and Parr [B3LYP/6-31G(d)] [23]. The geometries of the monoanions of *N,N*-dimethylbenzylamine, obtained by deprotonation of the α - or the *o*-position, were fully optimized with the same basis set and second order perturbation theory according to Møller and Plesset [MP2/6-31G(d)]. With the respective model chemistry, analysis of the bonding situation in an NBO basis was performed [11]. All stationary points were characterized by calculation of analytical force constants.

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