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Vilsmeier Reaction on Carbazole: Theoretical and Experimental Aspects†

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The pathway of the Vilsmeier reaction on carbazole has been studied by AM1 semiempirical MO calculations, which includes the characterization of the various transition structures; an experimental study of the actual reaction shows the formation of diformyl derivative along with a monoformyl derivative.

Among various bioactive heterocycles carbazole is an important nucleus. Reports on the biological activities of the 3-substituted and 3,6-disubstituted carbazoles are quite common in literature.[1] One method of inserting a functionality at the 3-position of carbazole is the Vilsmeier reaction, used by Buu-Hoi and Hoán to synthesize 3-formyl-9-methylcarbazole.[2] In their process they used *N*-phenyl-*N*-methyformanilide and phosphorus oxychloride to formylate 9-methylcarbazole at the 3-position in an *o*-dichlorobenzene medium.

As it is not always possible to elucidate every aspect of the mechanism of an organic reaction experimentally, theoretical methods are necessary to understand it and to develop new approaches of synthesis. In this paper we have studied the mechanism of the formylation of 9-methylcarbazole using a semiempirical quantum mechanical method. We also report our experimental findings in obtaining 3,6-diformyl-9-methylcarbazole along with 3-formyl-9-methylcarbazole while conducting a Vilsmeier reaction on 9-methylcarbazole.

Computational methods

Semiempirical MO calculations were performed using a AM1[3] Hamiltonian. Full geometry optimization was carried out using the MOPAC 7 program[4] and each species was characterized as corresponding to either a minimum or a saddle point on the energy hypersurface by means of vibrational analysis: a transition state possesses a single imaginary vibrational frequency, whereas a minimum energy structure has none. Intrinsic reaction coordinate (IRC) calculations were performed to determine the reactant and product for each saddle point.

Results and discussion

Fig. 1 outlines the mechanism that we have studied. The AM1 calculated heat of formation (H.O.F) for each stationary structure, obtained after appropriate optimisation, is given in Table 1. Formylation on the aromatic nucleus is initiated by the electrophilic attack of the intermediate (**A**) (generated by the reaction of the formamide derivative with phosphorus oxychloride) on the electron-rich centre of the aromatic nucleus. To avoid the complexity of calculation we have replaced *N*-methyl-*N*-phenylformanilide with *N,N*-dimethylformamide (DMF) in our model building program. Moreover, many experimental studies in literature have been found to use DMF in the Vilsmeier reaction.[5] As the 3-position of the *N*-methylcarbazole nucleus is highly electron-rich and less sterically hindered, the electrophilic attack takes place here. Depending on the direction of this attack, a number of configurations and conformations may exist in a transition state, of which the most sterically favourable conformations ±ap along 3C–3′C in the 3*R*, 3′*S* configuration and −sc along the same bond in the 3*S*, 3′*S* configuration result in two diastereomeric transition states (TS-1 in Fig. 1 represents only one diastereomer). In an achiral environment, enantiomers of these two diastereomers possess identical characteristic parameters (*e.g.* bond length, bond angle, *etc.*). It is clear from the H.O.F of TS-I (Table 1) that formation of both these diastereomeric transition states are equally favourable. Reactant **1** and product **2** corresponding to TS-I, were obtained after IRC calculation and appropriate optimization.

In the next step the formation of intermediate **4** (Fig. 1) is possible by the elimination of hydrogen and the phosphoryl group from 3 and 3′ carbon atoms respectively, and **4**, on subsequent hydrolysis, yields the desired formyl derivative. Scrutinizing the intermediate **2** (or TS-I) it appears that this process may go through a concerted *syn* elimination step by forming a six-membered cyclic transition state. With this view, models have been built where the double-bonded oxygen attached to the phosphorus may serve as a proton abstractor (TS–II in Fig. 1). Out of the three possible

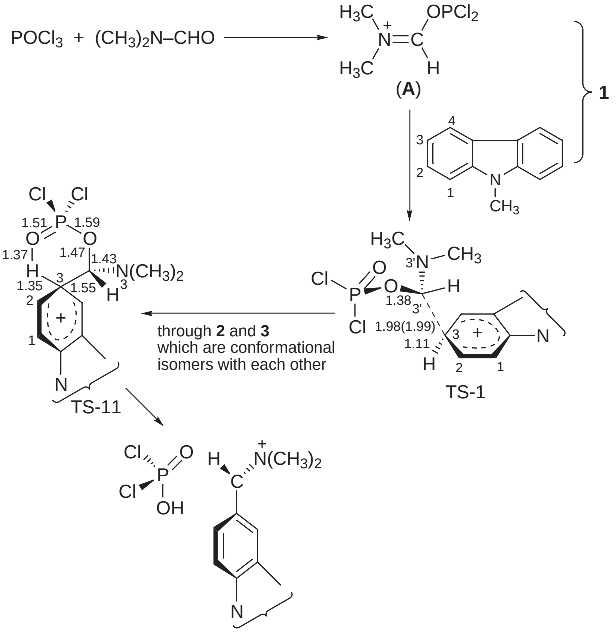

Fig. 1 Outline of the mechanism of formylation in Vilsmeier reaction. The fractional number in TS-I and TS-II (in 3*R*, 3′*S* configuration) indicates some relevant bond lengths. A change in any bond length, detected in another diastereomeric transition state (3*S*, 3′*S*), has been indicated in parentheses. Conformations of the species **2** and **3** are identical with TS-I and TS-II, respectively (details are not shown here).

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Table 1 AM1 calculated heat of formation in kcal mol^{-1} for the species given in Fig. 1.

Configuration	**1**	TS-I	**2**	**3**	TS-II	**4**
$3R,3'S$	97.0	104.6	94.8	98.2	110.7	60.7
$3S,3'S$	97.0	104.6	94.5	98.4	110.9	60.7

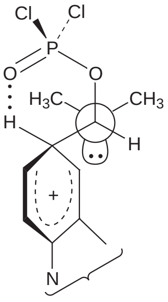

Fig. 2 Antiperiplanar arrangement of the leaving groups and lone pair of nitrogen in ± ap conformation (along the 3′C → 3′N bond) of TS-II

staggered conformations along the 3′C–3′N bond in TS-II (owing to the orientation of the *N,N*-dimethyl group) only ± ap results in a true saddle point (Fig. 2), which is capable of forming the product by a concerted *syn* elimination process (as indicated by the mode of vibration corresponding to the negative force constant in the transition structure). It is interesting to note that in this conformation the periplanarity of the lone pair of the adjacent atom (3′N) is maintained along with the periplanar orientation of the two leaving groups (phosphoryl and hydrogen). The other two conformations, +sc and −sc of TS-II are not able to form the product by a concerted process due to the lack of periplanarity of the lone pair, though the conformation in −sc suffers less steric strain. Owing to the presence of two chiral carbon, 3C and 3′C, in this transition state, the ± ap conformation may exist in two diastereomeric forms. H.O.F (Table 1) reveals that both these diastereomers are equally favourable. Reactant **3** and product **4** corresponding to TS-II were obtained by running IRC calculation.

From Table 1 it is evident that the H.O.F. of the second step (12.5 kcal mol^{-1}) is much higher than that of the first step (7.6 kcal mol^{-1}). This suggests that the elimination step is the rate-determining step. As this step involves the transfer of a proton (Fig. 1), a primary kinetic isotope effect is expected for this reaction.

The observation of the assistance of the lone pair of an adjacent atom in the elimination step may help a chemist to develop a synthetic route where an elimination process may be assisted by the antiperiplanar arrangement of the electron pair of an adjacent group that is not directly involved in the elimination step. This may help to reduce the activation energy required for the elimination step.

Our experimental observations reveal that the Vilsmeier reaction on 9-methylcarbazole results in 3-formyl-9-methylcarbazole as well as 3,6-diformyl-9-methylcarbazole. It is quite expected that the mechanism of formation of the diformyl derivative is similar to that for the monoformyl derivative. As the diformyl derivative is formed along with monoformyl derivative it is logical that another nucleophilic attack at the 6-position of intermediate **4** occurs before hydrolysis of the group at 3-position takes place.

Experimental

3,6-*Diformyl*-9-*methylcarbazole*.—A mixture of 3.6 g (0.02 mol) of 9-methylcarbazole (prepared by shaking carbazole with dimethyl sulfate and conc. potassium hydroxide solution in acetone medium)[6] 3.7 ml (0.04 mol) of phosphorus oxychloride, 4.9 ml (0.04 mol) of *N*-methylformanilide and 20 ml of *o*-dichlorobenzene was boiled under reflux for 6 h. The solution was then cooled and a viscous mass was obtained. To this mass was added a 30% sodium acetate solution and the solvent, *o*-dichlorobenzene, was removed from the mixture by steam distillation. The resulting gummy mass, after washing with water, was dissolved in glacial acetic acid. The whole solution was then poured into water and extracted with di-ethyl ether. The ether layer, on evaporation, furnished white crystals of 3,6-diformyl-9-methyl carbazole. This product was purified by crystallization from methanol (m.p. 230 °C, yield 10%). $\nu_{\max}$/cm^{-1} (KBr) 1675, 1620, 1590; $\delta_{\rm H}$ (90 MHz, CDCl$_3$) 3.77 (3 H, s, N-CH$_3$), 7.17 (2 H, d, $J = 7.5$ Hz, 1-H, 8-H), 7.74 (2 H, d, $J = 7.5$ Hz, 2-H, 7-H), 8.25 (2 H, s, 4-H, 5-H), 9.73 (2 H, s, –CHO).

3-*Formyl*-9-*methylcarbazole*.—The mother liquor, after separation of the 3,6-diformylcarbazole crystals, was evaporated to dryness and the resulting gummy mass was chromatographed over silica gel. On elution with a mixture of light petroleum (60–80 °C) and benzene (1:1) a yellow mass of 3-formyl-9-methycarbazole was obtained (m.p. 74 °C, yield 20%), and its structure was confirmed by comparison of its properties with literature data.[2]

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