Chem. Pharm. Bull. 29(10)2856—2861(1981)

Physicochemical Study on Leuco Triarylmethane Dyes; Unusual Carbon-Carbon Bond Cleavage Involving an Elimination of Dimethylaniline

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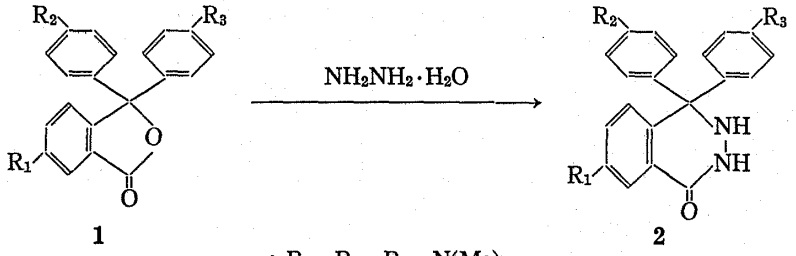
(Received April 13, 1981)

Upon heating of the leuco triarylmethane dyes (**2a**) and (**2b**) with excess phosphoryl chloride under reflux, these compounds underwent a normal chlorination followed by a de-anilination process to give (**3a**) and (**3b**), respectively.

Replacement of the *p*-dimethylamino substituent with a *p*-methoxy substituent on the 4,4-diaryl groups had a marked effect on the reaction; only the 1-chlorinated products, (**4a**) and (**4b**), were formed even upon heating under reflux for 10 hours. On heating of (**2b**) in TFA, only 1-trifluoroacetoxylation occurred. Thus, the driving force of this type of de-anilination could be ascribed to a combination of greater orbital interaction between phosphoryl chloride and the HOMO of dimethylaniline, and the aromaticity of the resulting phthalazine molecule, resulting in a special type of carbon-carbon bond cleavage.

Keywords——Leuco triarylmethane dye; carbon-carbon bond cleavage; substituent effect; 3,4-dihydro-1(2*H*)-phthalazinone; charge control; orbital control

In a previous paper, we reported that heating of crystal violet lactone (CVL) (**1a**) and its analogs with hydrazine hydrate afforded 4,4-diaryl-3,4-dihydro-1(2*H*)-phthalazinone (**2**), and that the introduction of a dimethylamino substituent in 3,3-diarylphthalides (**1**) led to an increase in the rate of formation of the dihydrophthalazinone (**2**).[1)]



1 **2**

a: $R_1=R_2=R_3=N(Me)_2$
b: $R_1=H$, $R_2=R_3=N(Me)_2$
c: $R_1=R_2=H$, $R_3=N(Me)_2$

Chart 1

Although 4,4-disubstituted-3,4-dihydro-1(2*H*)-phthalazinones seem to contain many potentially interesting features as described previously,[1)] there has been very little work done on the chemistry of such compounds. As part of our continuing work on the physicochemical properties of these compounds, we have examined the reaction of these compounds with phosphoryl chloride.

In the present paper, we describe the nature of an unusual carbon-carbon bond fission involving elimination of an aromatic molecule concomitantly with the above reactions.

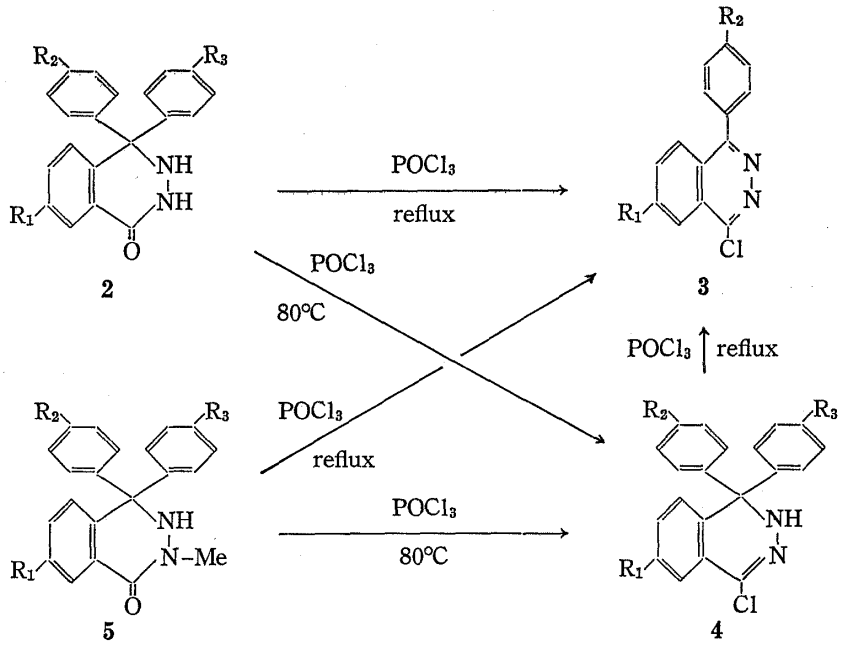
When either 4,4-bis-(*p*-dimethylaminophenyl)-7-dimethylamino-3,4-dihydro-1(2*H*)-phthalazinone (**2a**)[1)] or 4,4-bis-(*p*-dimethylaminophenyl)-3,4-dihydro-1(2*H*)-phthalazinone (**2b**)[1)] was heated with excess phosphoryl chloride under reflux, a single crystalline product was obtained in each case. These products were identified as 1-chloro-4-(*p*-dimethylaminophenyl)-7-

dimethylaminophthalazine (**3a**) and 1-chloro-4-(*p*-dimethylaminophenyl)-phthalazine (**3b**), respectively, on the basis of elemental analysis and spectral properties. The structure of **3a** was confirmed by demonstrating the identity of **3a** and an authentic sample prepared by treatment of 2-(*p*-dimethylaminobenzoyl)-5-dimethylaminobenzoic acid[2] with hydrazine hydrate followed by phosphoryl chloride.

This reaction appears to involve two different types of process, a normal chlorination at an amido function and an unexpected de-anilination. Amongst the hundreds of known carbon-carbon bond cleavage reactions, a cleavage of this type is rather unusual and interesting, since one of the two carbons is eliminated from an aromatic ring with apparent ease; such an elimination usually occurs with the generation of a small molecule such as carbon monoxide or with migratory rearrangement of an aromatic ring (1,2-phenyl shift). Consequently, we decided to explore the nature of this cleavage.

Firstly, in order to determine which process is faster, chlorination or de-anilination, we carried out the same reaction of **2a** and **2b** at lower temperature (at 80°C) under otherwise identical conditions. We again obtained a single product in each case; 1-chloro-4,4-bis-(*p*-dimethylaminophenyl)-7-dimethylamino-3,4-dihydrophthalazine (**4a**) and 1-chloro-4,4-(*p*-dimethylaminophenyl)-3,4-dihydrophthalazine (**4b**), respectively. The structures of these products were supported by spectroscopic data. Heating of **4a** and **4b** with phosphoryl chloride under reflux was found to give **3a** and **3b** in good yields, respectively.

Furthermore, with the aim of suppressing chlorination and assessing the influence of structural change, 2-methyl-4,4-*bis*-(*p*-dimethylaminophenyl)-7-dimethylamino-3,4-dihydro-1(2*H*)-phthalazinone (**5**)[1] was treated similarly, but the result was identical with that for **2a**. Thus, the following reaction sequences were established, as shown in Chart 2.



a: $R_1=R_2=R_3=N(Me)_2$
b: $R_1=H$, $R_2=R_3=N(Me)_2$

Chart 2

With a view to examining the substituent effect on these carbon-carbon bond cleavages, 4-(*p*-dimethylaminophenyl)-4-phenyl-3,4-dihydro-1(2*H*)-phthalazinone (**2a**)[1] and 4,4-bis-(*p*-methoxyphenyl)-3,4-dihydro-1(2*H*)-phthalazinone (**2d**)[3] were also treated with phosphoryl chloride. In the case of **2c**, similar results were observed; the formation of 1-chloro-4-phenyl-

phthalazine (**3c**)[4] on heating under reflux, and the formation of 1-chloro-4-(*p*-dimethylaminophenyl)-4-phenyl-3,4-dihydrophthalazine (**4c**) on heating at 80°C. It should be noted, however, that the only product formed was **3c** and we found no evidence for the formation of **3b**. In the case of **2d**, similar carbon-carbon bond cleavage did not occur even upon heating under reflux for 10 hours, and the product obtained was 1-chloro-4,4-bis-(*p*-methoxyphenyl)-3,4-dihydrophthalazine (**4d**).

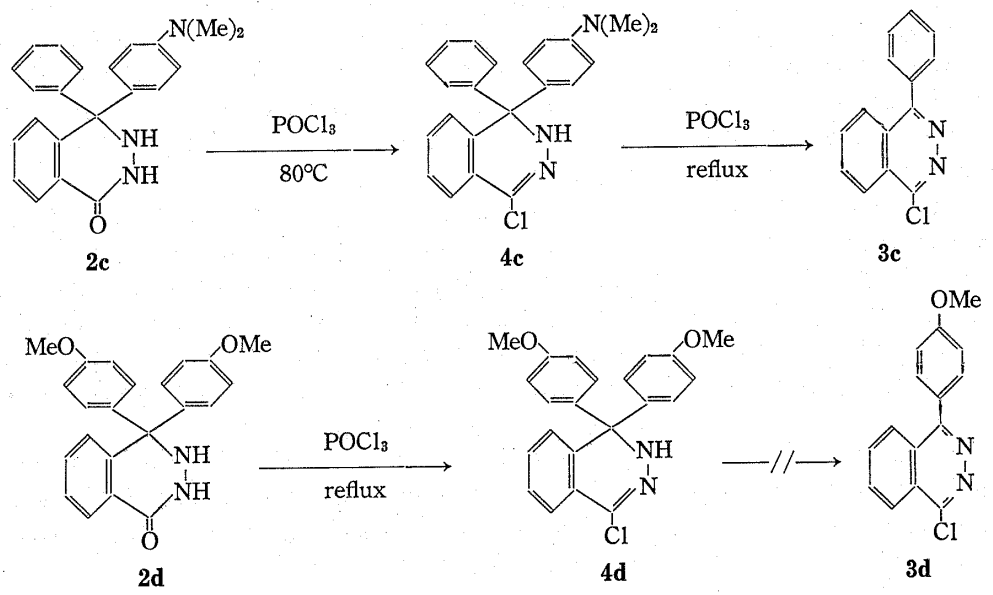


Chart 3

It follows from the above results that the dimethylamino substituent on the 4,4-diaryl groups contributes to this cleavage to a large extent, as does the aromaticity of the resulting phthalazine.

The exact function of phosphoryl chloride in this cleavage is not yet known: however, it probably complexes with the *para*-carbon atom of the dimethylaniline moiety.[5] Some evidence in support of this view was obtained by the following reactions. Heating of either **4b** or **2b** under reflux in trifluoroacetic acid (TFA) for 3 hours did not result in similar carbon-carbon bond cleavage but trifluoroacetoxylation at C-1 did occur to give 1-trifluoroacetoxy-4,4-bis-(*p*-dimethylaminophenyl)-3,4-dihydrophthalazine (**6**)[6] in good yield. Further, treatment of **4b** with either conc. hydrochloric acid or conc. sulfuric acid gave the same set of products as was obtained from **2b** (*i.e. ca.* 1: 2 mixture of malachite green lactone (MGL) **1b** and **8**[1]).

Furthermore, it is known that dimethylaniline is a good additive for chlorination by phosphoryl chloride (it aids the ionization), and the dimethylaniline moiety of **2** or **4** is essentially electronically independent of the rest of the molecule. Therefore, if phosphoryl chloride participates directly in this carbon-carbon bond cleavage, **4b** should undergo similar cleavage in the presence of dimethylaniline. In fact, treatment of **4d** under the above conditions did not give any new product, but unreacted starting **4d** was obtained in 85% yield. Consequently, phosphoryl chloride must have some other function in this cleavage.

These results, as shown in Chart 4, indicate that employing a strong hard acid would have changed the initial reaction to N-protonation at various positions (*i.e.* charge control; polarity "hardmess" of HSAB concept[7]) to form a multication, leading to a different course of reaction. Thus, carbon-carbon bond cleavage of this type could be produced only by a combination of a relatively non-polar Lewis acid such as phosphoryl chloride,[8] which is of high polarizability due to the P atom, and the HOMO of dimethylaniline which is very high in energy and has the largest coefficient at the para-position, and, in addition, the aromaticity of the

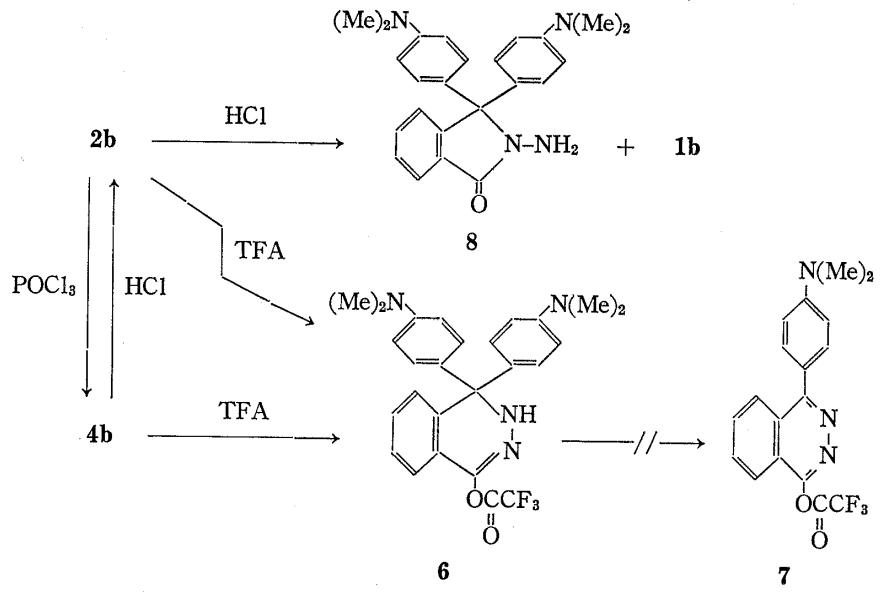


Chart 4

resulting molecules, **3**, based on the fact that **2** did not undergo similar cleavage. Hence, the interaction of **4b** with phosphoryl chloride should be much greater than of **4d** in terms of FMO theory,[9] in accordance with the experimental results (*i.e.* orbital control; polarizability, "softness" of HSAB concept[7]).

Experimental

^{1}H Nuclear magnetic resonance (NMR) spectra were obtained on a Hitachi R-20 spectrometer (60 MHz), in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard. All chemical shifts are in parts per million (δ) from TMS. Infrared (IR) spectra were taken as KBr discs using a JASCO IRA-T spectrophotometer and were calibrated against polystyrene. Ultraviolet (UV) spectra were measured in 95% ethanol using a Hitachi 323 spectrophotometer. Mass spectra were obtained at 70 eV with a JEOL JMS-D300 spectrometer. Elemental analyses were carried out by the Microanalytical Laboratory, Gifu College of Pharmacy. All melting points are uncorrected.

1-Chloro-4-(*p*-dimethylaminophenyl)-7-dimethylaminophthalazine (3a)——a) A solution of **2a** (1.29 g, 3 mmol) in phosphoryl chloride (20 ml) was heated under reflux for 6 hours. The reaction mixture was concentrated almost to dryness under reduced pressure. Cold water was added to the residue. The aqueous solution was neutralized with dilute ammonia solution and then extracted with chloroform. The chloroform layer was washed once with water and dried over anhydrous sodium sulfate. The residue obtained by removing the chloroform under reduced pressure was chromatographed over silica gel (Wako-gel C-300) with chloroform as an eluent to give **3a** (0.67 g, 68.5%), which was further purified by recrystallization from ethanol to give brown needles, mp 196°C. UV λ_{max} nm (ε): 265 (14500), MS *m/e*: 326 (base, peak M^+), NMR δ: 3.04 (6H, s, N-methyl), 3.17 (6H, s, N-methyl), 6.72—8.03 (7H, m, aromatic). *Anal.* Calcd for $C_{18}H_{19}ClN_4$: C, 66.15; H, 5.86; N, 17.14. Found: C, 66.25; H, 5.74; N, 17.01.

b) Treatment of **5a** (0.89 g 2 mmol) as described above gave **3a** (0.50 g, 76.7%) as pale yellow needles.

c) **3a** (0.15 g, 68.7%) was also obtained by treating **4a** (0.30 g, 0.67 mmol) in the manner described above. The compounds obtained in b) and c) were identical with **3a** obtained from **2a**.

1-Chloro-4-(*p*-dimethylaminophenyl)-phthalazine (3b)——a) A solution of **2b** (0.85 g, 2.2 mmol) in phosphoryl chloride (15 ml) was heated under reflux for 6 hours. The reaction mixture was then worked up as above to give **3b** (0.44 g, 73.5%) as colorless crystals, mp 193°C. UV λ_{max} nm (ε): 268 (11700). MS *m/e*: 283 (M^+), 265 (base peak). NMR: 3.30 (6H, s, N-methyl), 6.70—8.37 (8H, m, aromatic). *Anal.* Calcd for $C_{16}H_{14}ClN_3$: C, 67.72; H, 4.97; N, 14.81. Found: C, 67.91; H, 5.11; N, 15.00.

b) Treatment of **5b** (0.40 g, 1 mmol) as described above gave **3b** (0.20 g, 73.4%) as colorless crystals.

c) **3b** (0.23 g, 78.5%) was also obtained by treating **4b** (0.40 g, 1 mmol) in the manner described above. The compounds obtained in b) and c) were identical with **3b** obtained from **2b**.

1-Chloro-4,4-bis-(*p*-dimethylaminophenyl)-7-dimethylamino-3,4-dihydrophthalazine (4a)——a) A solution of **2a** (1.05 g, 2.4 mmol) in phosphoryl chloride (16 ml) was heated at 80°C for 6 hours. The reaction mixture was then worked up as for **3a** to give **4a** (0.70 g, 65.08%), which was further purified by recrystalliza-

tion from ethanol to give pale green needles, mp 219°C. UV λ_{max} nm (ε): 267 (29800). MS *m/e*: 447 (M^+), 327 (base peak). *Anal.* Calcd for $C_{26}H_{30}ClN_5$: C, 69.70; H, 6.75; N, 15.63. Found: C, 69.91; H, 6.75; N, 15.89.

b) **4a** (0.35 g, 78.1%) was also obtained by treating **5a** (0.44 g, 1 mmol) in a similar manner. The product thus obtained was identical with **4a** obtained from **2a**.

1-Chloro-4,4-bis-(*p*-dimethylaminophenyl)-3,4-dihydrophthalazine (4b)——A solution of **2b** (1.00 g, 2.6 mmol) in phosphoryl chloride (25 ml) was heated at 80°C for 6 hours. The reaction mixture was then worked up as abave to give **4b** (0.88 g, 83.6%), which was further purified by recrystallization from ethanol to give pale green crystals, mp 212°C. UV λ_{max} nm (ε): 264 (27000), MS *m/e*: 404 (M^+), 284 (base peak). NMR δ: 2.93 (12H, s, 2×N-methyl), 6.57—7.41 (12H, m, aromatic). *Anal.* Calcd for $C_{24}H_{25}ClN_4$: C, 71.19; H, 6.22; N, 13.84. Found: C, 71.08; H, 6.27; N, 13.81.

1-Chloro-4-(*p*-dimethylaminophenyl)-4-phenyl-3,4-dihydrophthalazine (4c)——A solution of **2c** (1.03 g, 3 mmol) in phosphoryl chloride (15 ml) was heated at 80°C for 6 hours. The reaction mixture was then worked up as above to give **4c** (0.63 g, 58.0%), which was further purified by recrystallization from ethanol to give pale yellow crystals, mp 197°C. MS *m/e*: 361 (M^+), 284 (base peak). NMR δ: 2.69 (6H, s, N-methyl), 6.63—7.60 (13H, m, aromatic). *Anal.* Calcd for $C_{22}H_{20}ClN_3$: C, 73.02; H, 5.57; N, 11.61. Found: C, 72.76; H, 5.76; N, 11.42.

1-Chloro-4,4-bis-(*p*-methoxyphenyl)-3,4-dihydrophthalazine (4d)——A solution of **2d** (1.00 g, 2.8 mmol) in phosphoryl chloride (30 ml) was heated under reflux for 10 hours. The reaction mixture was then worked up as above to give **4d** (0.88 g, 83.8%) as colorless crystals (from cyclohexane), mp 114—115°C. UV λ_{max} nm: 278 (3800), 284 (3700), 322 (4700). MS *m/e*: 378 (M^+), 271 (base peak). NMR δ: 3.77 (6H, s, O-methyl), 6.65 (1H, br, NH), 6.82—7.70 (12H, m, aromatic). *Anal.* Calcd for $C_{22}H_{19}ClN_2O_2$: C, 69.75; H, 5.06; N, 7.39. Found: C, 69.70; H, 4.91; N, 7.41.

1-Trifluoroacetoxy-4,4-bis-(*p*-dimethylaminophenyl)-3,4-dihydrophthalazine (6)——a) A small glass tube containing **2b** (250 mg, 0.65 mmol) in TFA (3 ml) was sealed and heated on a water bath (95—100°C) for 3 hours. After cooling, the reaction mixture was poured into ice, and extracted with chloroform. The chloroform solution was washed fully with water and dried over anhydrous sodium sulfate. The residue obtained by concentration of the chloroform under reduced pressure was recrystallized from ethanol to give **6** (0.25 g, 85.2%) as colorless crystals, mp 263°C. IR cm^{-1}: $\nu_{C=O}$ 1760; ν_{NH} 3410. MS *m/e*: 482 (base peak, M^+). NMR δ: 2.91 (12H, m, aromatic), 8.32—8.72 (1H, br, NH). *Anal.* Calcd for $C_{26}H_{25}F_3N_4O_2$: C, 64.72; H, 5.22; N, 11.62. Found: C, 64.71; H, 5.22; N, 11.65.

b) Heating of **4b** (250 mg, 0.62 mmol) in TFA (3 ml) and similar work-up afforded **6** (300 mg, 96.2%) as colorless crystals. The product was identical with **6** obtained from **3b**.

Formation of 1-chloro-4-phenylphthalazine (3c)——a) A solution of **2c** (1.03 g, 3 mmol) in phosphoryl chloride (20 ml) was heated under reflux for 6 hours. The reaction mixture was concentrated almost to dryness under reduced pressure. Cold water was added to the residue. The aqueous solution was neutralized with dilute ammonia solution and extracted with chloroform. The chloroform solution was washed with water and dried over anhydrous sodium sulfate. The residue obtained by removal of the solvent under reduced pressure was recrystallized from ethanol to give **3c** (0.50 g, 69.2%) as colorless needles, mp 160°C (mp 161°C in the literature).[4] This product was identical with an authentic sample.

b) Similar treatment of **4c** (360 mg, 1 mmol) with phosphoryl chloride gave **3c** (170 mg, 70.8%), which was identical with that obtained from **2c**.

Treatment of 4b with conc. Hydrochloric Acid——Compound **4b** (204 mg, 0.5 mmol) was added to conc. hydrochloric acid (3 ml) and the solution was heated on a water bath (96—100°C) for 2 hours. After cooling, the reaction mixture was diluted with water and neutralized with 20% sodium hydroxide solution with ice cooling, then extracted with chloroform. The chloroform layer, combined with washings, was washed with water and dried over anhydrous sodium sulfate. The NMR spectrum of the residue obtained by removal of the chloroform under reduced preseure showed it to be a *ca.* 1:2 mixture of MGL (**1b**) and **8** by commparison with the NMR spectra of authentic samples.

Independent Synthesis of 3a——A solution of 2-(*p*-dimethylaminophenyl-benzoyl)-5-dimethylaminobenzoic acid (1.87 g, 6 mmol) in ethanol was heated with hydradine hydrate (3.0 g, 60 mmol) under reflux for 3 hours. On cooling, a solid precipitated; it was collected and dried. Prior to further purification, the crude product (1.1 g) was heated with phosphoryl chloride (10 ml) under reflux for 3 hours. Work-up in the manner described above gave **3a** (1.16 g, 59.5%) as pale brown needles (ethanol), mp 195—196°C. This compound was identical with that obtained from **2a**.

References and Notes

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5) Although the one-electron transfer mechanism involving the unshared electron pairs of nitrogen is not completely ruled out, the qualitative treatment of **4b** with bromine in chloroform did not give **3b**, but resulted in the formation of a large amount of polymeric products.
6) The IR spectrum of **6** exhibited a 1760 cm^{-1} carbonyl stretching band, which is characteristic of trifluoroacetate, thus eliminating the possibility of N-trifluoroacetylation.
7) G. Klopman, "Chemical Reactivity and Reaction Path," Wiley, New York, 1974.
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9) The HOMO energy difference between dimethylaniline and anisole was calculated by CNDO/2 to be -10.799(DMA) -12.335(anisole) $=1.536$ eV.