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Substituent Effects on ^{13}C NMR and ^{1}H NMR Chemical Shifts of CH=N in Multi-substituted Benzylideneanilines

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Fifty-three samples of multi-substituted benzylideneanilines XArCH=NArYs (abbreviated XBAYs) were synthesized and their NMR spectra were determined. An extensional study of substituent effects on the ^{1}H NMR chemical shifts ($\delta_{\rm H}$(CH=N)) and ^{13}C NMR chemical shifts ($\delta_{\rm C}$(CH=N)) of the CH=N bridging group from di-substituted to multi-substituted XBAYs was made based on a total of 182 samples of XBAYs, together with the NMR data of other 129 samples of di-substituted XBAYs quoted from literatures. The results show that the substituent specific cross-interaction effect parameter $\left(\Delta\left(\sum\sigma\right)^2\right)$ plays an important role in quantifying the $\delta_{\rm C}$(CH=N) values of XBAYs, but it is negligible for quantifying the $\delta_{\rm H}$(CH=N) values; the other substituent parameters also present different influences on the $\delta_{\rm C}$(CH=N) and $\delta_{\rm H}$(CH=N). On the whole, the contributions of X and Y to the $\delta_{\rm C}$(CH=N) of XBAYs are balanced, but the $\delta_{\rm H}$(CH=N) values of XBAYs mainly rely on the contributions of X.

Key words: Multi-substituted benzylideneanilines, Substituent effects, ^{1}H NMR chemical shifts, ^{13}C NMR chemical shifts, Substituent specific cross-interaction effect

I. INTRODUCTION

In the molecules of benzylideneanilines XArCH=NArYs (abbreviated XBAYs), CH=N is a bridge linking two aromatic rings, of which one ring carries substituent X, and another ring carries substituent Y. The changes of X and Y can affect the molecular overall electron distribution and the properties of optoelectronic materials containing the molecule of XBAY. Therefore, the effects of substituents X and Y on the performance of the CH=N bridging group play an important role. On the other hand, NMR shielding is affected by the electron density, and the field of resonance increases with the increasing electron density of the protons and carbon nucleus in molecules [1, 2]. So the NMR chemical shifts of CH=N ($\delta_{\rm H}$(CH=N) and $\delta_{\rm C}$(CH=N)) were always applied to investigate the substituent effects in past years [3–11].

Neuvonen *et al.* [12, 13] analyzed the substituent effects on the $\delta_{\rm C}$(CH=N) of 4,4′-substituted XBAYs by employing several different single and dual substituent parameter approaches, and the relatively best model equation (shown as Eq.(1)) has been obtained. In their research, they pointed out that the substituent specific cross-interaction between X and Y existed, but they didn't quantify it. Nonetheless, their work strongly promoted the research of the substituent effects on the $\delta_{\rm C}$(CH=N) of substituted XBAYs. In Eq.(1), $\sigma_{\rm F}$ is the inductive effect parameter, $\sigma_{\rm R}$ is the conjugative effect parameter, ρ are the coefficients of corresponding parameter.

$$\delta_{\rm C}({\rm CH{=}N}) = {\rm constant} + \rho_{\rm F}({\rm X})\sigma_{\rm F}({\rm X}) + \rho_{\rm F}({\rm Y})\sigma_{\rm F}({\rm Y}) + \rho_{\rm R}({\rm X})\sigma_{\rm R}({\rm X}) + \rho_{\rm R}({\rm Y})\sigma_{\rm R}({\rm Y}) \quad (1)$$

Afterwards, Cao *et al.* [14] studied the substituent effects on the $\delta_{\rm C}$(CH=N) of 4,4′-substituted XBAYs further. The substituent specific cross-interaction effect was quantified with the item $\Delta\sigma^2$ and a more effective five parameter equation (Eq.(2)) was proposed to quantify the $\delta_{\rm C}$(CH=N) of XBAYs by adding $\Delta\sigma^2$ to Eq.(1). In Eq.(2), $\Delta\sigma^2 = (\sigma({\rm X}) - \sigma({\rm Y}))^2$.

$$\delta_{\rm C}({\rm CH{=}N}) = {\rm constant} + \rho_{\rm F}({\rm X})\sigma_{\rm F}({\rm X}) + \rho_{\rm F}({\rm Y})\sigma_{\rm F}({\rm Y}) + \rho_{\rm R}({\rm X})\sigma_{\rm R}({\rm X}) + \rho_{\rm R}({\rm Y})\sigma_{\rm R}({\rm Y}) + \rho_{(\Delta\sigma^2)}\Delta\sigma^2 \quad (2)$$

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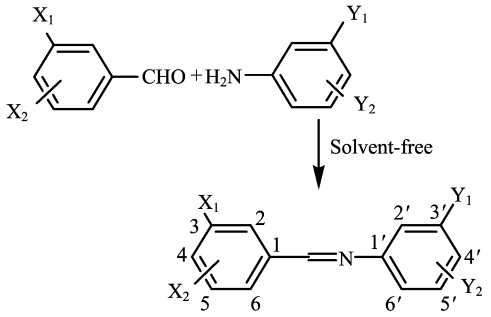
In our recent work [15], the substituent effects on the δ_C(CH=N) and δ_H(CH=N) of 4,4′/3,4′/4,3′/3,3′-substituted XBAYs have been researched based on a big set of data, and two quantitative correlation equations were obtained (shown as Eq.(3) and Eq.(4) respectively). The data indicated that the δ_H(CH=N) values and δ_C(CH=N) values of di-substituted XBAYs had no distinctive linear relationship, which was contrary to the theoretical thought that declared the δ_H(CH=N) values would increase as the δ_C(CH=N) values increase. And the results showed the substituent effects on the δ_C(CH=N) and δ_H(CH=N) of 4,4′/3,4′/4,3′/3,3′-substituted XBAYs were very different.

$$\begin{aligned}\delta_C(\text{CH=N}) &= 160.30 - 4.38\sigma_F(\text{X}) + 3.07\sigma_F(\text{Y}) - \\ &\quad 1.11\sigma_R(\text{X}) + 4.63\sigma_R(\text{Y}) - 0.61\Delta\sigma^2 \quad (3)\\ R &= 0.9938, \quad R^2{=}0.9877, \quad S{=}0.25,\\ F &= 1968.77, \quad n{=}129\end{aligned}$$

$$\begin{aligned}\delta_H(\text{CH=N}) &= 8.42 + 0.12\sigma(\text{X}) - 0.06\sigma(\text{Y}) \quad (4)\\ R &= 0.8811, \quad R^2{=}0.7764, \quad S{=}0.03,\\ F &= 218.77, \quad n{=}129\end{aligned}$$

Since the substituent effects on the δ_C(CH=N) and δ_H(CH=N) of di-substituted XBAYs have been studied, how do the substituents affect the δ_C(CH=N) and δ_H(CH=N) of multi-substituted XBAYs? Are the change regularities of δ_C(CH=N) and δ_H(CH=N) of multi-substituted XBAYs consistent with those of di-substituted XBAYs? To solve these problems, 53 samples of the multi-substituted XBAYs shown in Scheme 1 were used for analyses of the substituent effects on their δ_C(CH=N) and δ_H(CH=N) were analyzed in this work.



X_1 and/or X_2 (*m* or *p*)=NMe_2, OMe, Me, H, F, Cl, or Br;
Y_1 and/or Y_2 (*m* or *p*)=NMe_2, Me, H, F, Cl, CN, or Br.

Scheme 1 Multi-substituted XBAYs synthesized in this work.

II. DATASET

The substituted benzylideneanilines were all synthesized by the solvent-free method according to Scheme 1 [16, 17]. They were purified with anhydrous alcohol, and confirmed with ^{1}H NMR and ^{13}C NMR. The NMR spectra were recorded by Bruker AV 500 MHz in $CDCl_3$ at room temperature at an approximate concentration. The NMR chemical shifts were expressed in ppm relative to TMS (0.00 ppm) used as an internal reference.

III. RESULTS AND DISCUSSIONS

The δ_C(CH=N) values and δ_H(CH=N) values of 53 samples of multi-substituted XBAYs measured in this work were collected and listed in Table I. The substituents X and Y in the molecules of title compounds are of electron-withdrawing substituents (*e.g.*, NO_2, CN) and electron-donating substituents (*e.g.*, NMe_2, OMe). The substituent parameters of multi-substituted XBAYs were subdivided into para-parameters and meta-parameters. For multi-substituted XBAYs, in which the benzylidene rings and/or the aniline rings could be substituted by more than one meta-substituent group, the corresponding parameters of the sum of $\sigma_F(X_m)$ and $\sigma_F(Y_m)$ were used (by the symbols $\sum\sigma_F(X_m)$ and $\sum\sigma_F(Y_m)$ listed in Table I). The δ_C(CH=N) and δ_H(CH=N) values, and the correlative parameters of 53 samples of multi-substituted XBAYs were also listed in Table I. Because the conjugative effects of meta-substituents are considered to be 0, $\sigma_R(X_m)$ and $\sum\sigma_R(Y_m)$ are not listed in Table I.

Firstly, the di-substituted XBAYs and multi-substituted XBAYs were regarded as a whole, and the regression of the δ_C(CH=N) values of 182 samples of XBAYs (including 129 samples of di-substituted XBAYs from Ref.[15] and 53 samples of multi-disubstituted XBAYs synthesized in this work) was made against the corresponding substituent parameters. And the regression equation Eq.(5) was obtained.

$$\begin{aligned}\delta_C(\text{CH=N}) &= 160.29 - 4.46\sum\sigma_F(X_m) - 4.24\sigma_F(X_p) - \\ &\quad 0.98\sigma_R(X_p) + 2.66\sum\sigma_F(Y_m) + \\ &\quad 3.05\sigma_F(Y_p) + 5.13\sigma_R(Y_p) \quad (5)\\ R &= 0.9811, \quad R^2 = 0.9624, \quad S = 0.44,\\ F &= 748.32, \quad n = 182\end{aligned}$$

Eq.(5) presented good regression results based on a big set of data, but the substituent cross-interaction effect parameter was not considered in Eq.(5). So the corresponding substituent cross-interaction effect parameter $\Delta\left(\sum\sigma\right)^2$,

$$\Delta\left(\sum\sigma\right)^2 = \left(\sum\sigma(X_m) + \sigma(X_p) - \sum\sigma(Y_m) - \sigma(Y_p)\right)^2$$

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TABLE I The δ_C(CH=N) and δ_H(CH=N) values and the correlative parameters of 53 samples of multi-substituted XBAYs.

No.	X	Y	$\sum\sigma_F(X_m)^a$	$\sigma_F(X_p)^a$	$\sigma_R(X_p)^a$	$\sum\sigma_F(Y_m)^a$	$\sigma_F(Y_p)^a$	$\sigma_R(Y_p)^a$	$\delta_C{}^b$	$\delta_H{}^b$
1	3,4-Me	H	−0.07	0.01	−0.18	0.00	0.00	0.00	160.65	8.28
2	3,4-Me	4′-Me	−0.07	0.01	−0.18	0.00	0.01	−0.18	159.91	8.41
3	3,5-Me	H	−0.14	0.00	0.00	0.00	0.00	0.00	160.89	8.43
4	H	3′,4′-Me	0.00	0.00	0.00	−0.07	0.01	−0.18	159.41	8.48
5	H	3′,5′-Me	0.00	0.00	0.00	−0.14	0.00	0.00	159.92	8.47
6	3,4-MeO	H	0.12	0.29	−0.56	0.00	0.00	0.00	159.87	8.36
7	3,4-MeO	4′-NMe_2	0.12	0.29	−0.56	0.00	0.15	−0.98	155.82	8.42
8	3,4-MeO	4′-Me	0.12	0.29	−0.56	0.00	0.01	−0.18	159.15	8.37
9	3,4-MeO	4′-F	0.12	0.29	−0.56	0.00	0.45	−0.39	159.70	8.34
10	3,4-MeO	4′-Cl	0.12	0.29	−0.56	0.00	0.42	−0.19	160.18	8.33
11	3,4-MeO	4′-CN	0.12	0.29	−0.56	0.00	0.51	0.15	161.71	8.30
12	3,5-MeO	H	0.24	0.00	0.00	0.00	0.00	0.00	160.29	8.37
13	3,5-MeO	4′-Me	0.24	0.00	0.00	0.00	0.01	−0.18	159.51	8.38
14	3,5-MeO	4′-Cl	0.24	0.00	0.00	0.00	0.42	−0.19	160.61	8.34
15	3,5-MeO	4′-CN	0.24	0.00	0.00	0.00	0.51	0.15	162.29	8.30
16	3,4-Cl	H	0.37	0.42	−0.19	0.00	0.00	0.00	157.37	8.38
17	3,4-Cl	4′-NMe_2	0.37	0.42	−0.19	0.00	0.15	−0.98	152.20	8.43
18	3,4-Cl	4′-Me	0.37	0.42	−0.19	0.00	0.01	−0.18	156.48	8.39
19	3,4-Cl	4′-F	0.37	0.42	−0.19	0.00	0.45	−0.39	157.06	8.36
20	3,4-Cl	4′-Cl	0.37	0.42	−0.19	0.00	0.42	−0.19	157.67	8.36
21	3,4-Cl	4′-CN	0.37	0.42	−0.19	0.00	0.51	0.15	159.64	8.33
22	H	3′,4′-Cl	0.00	0.00	0.00	0.37	0.42	−0.19	161.54	8.42
23	4-NMe_2	3′,4′-Cl	0.00	0.15	−0.98	0.37	0.42	−0.19	161.21	8.26
24	4-Me	3′,4′-Cl	0.00	0.01	−0.18	0.37	0.42	−0.19	161.48	8.37
25	4-F	3′,4′-Cl	0.00	0.45	−0.39	0.37	0.42	−0.19	159.96	8.38
26	4-Cl	3′,4′-Cl	0.00	0.42	−0.19	0.37	0.42	−0.19	159.98	8.38
27	3-Cl	3′,4′-Cl	0.37	0.00	0.00	0.37	0.42	−0.19	159.85	8.37
28	3,5-Cl	H	0.74	0.00	0.00	0.00	0.00	0.00	156.98	8.33
29	3,5-Cl	4′-NMe_2	0.74	0.00	0.00	0.00	0.15	−0.98	151.60	8.40
30	3,5-Cl	4′-Me	0.74	0.00	0.00	0.00	0.01	−0.18	156.05	8.36
31	3,5-Cl	4′-Cl	0.74	0.00	0.00	0.00	0.42	−0.19	158.08	8.33
32	H	3′,5′-Cl	0.00	0.00	0.00	0.74	0.00	0.00	162.19	8.39
33	4-NMe_2	3′,5′-Cl	0.00	0.15	−0.98	0.74	0.00	0.00	161.73	8.24
34	4-F	3′,5′-Cl	0.00	0.45	−0.39	0.74	0.00	0.00	160.59	8.36
35	4-Cl	3′,5′-Cl	0.00	0.42	−0.19	0.74	0.00	0.00	160.67	8.36
36	3,4-F	4′-NMe_2	0.34	0.45	−0.39	0.00	0.15	−0.98	152.68	8.43
37	3,4-F	4′-Cl	0.34	0.45	−0.39	0.00	0.42	−0.19	157.87	8.36
38	3,5-F	H	0.68	0.00	0.00	0.00	0.00	0.00	157.39	8.39
39	3,4-Br	H	0.39	0.45	−0.22	0.00	0.00	0.00	157.35	8.36
40	3,5-Br	H	0.78	0.00	0.00	0.00	0.00	0.00	156.78	8.34
41	3-F-4-Me	H	0.34	0.01	−0.18	0.00	0.00	0.00	159.00	8.39
42	3-Br-4-Me	H	0.39	0.01	−0.18	0.00	0.00	0.00	158.52	8.37
43	H	3′-F-4′-Me	0.00	0.00	0.00	0.34	0.01	−0.18	160.45	8.45
44	H	3′-Cl-4′-Me	0.00	0.00	0.00	0.37	0.01	−0.18	160.58	8.44
45	H	3′-Br-4′-Me	0.00	0.00	0.00	0.39	0.01	−0.18	160.63	8.44
46	3,4-MeO	3′,5′-Me	0.12	0.29	−0.56	−0.14	0.00	0.00	159.44	8.35
47	3,4-Cl	3′,4′-Cl	0.37	0.42	−0.19	0.37	0.42	−0.19	158.58	8.34
48	3,4-Cl	3′-Cl-4′-Me	0.37	0.42	−0.19	0.37	0.01	−0.18	157.50	8.36

Table I to be continued.

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Table I continued.

No.	X	Y	$\sum\sigma_F(X_m)^a$	$\sigma_F(X_p)^a$	$\sigma_R(X_p)^a$	$\sum\sigma_F(Y_m)^a$	$\sigma_F(Y_p)^a$	$\sigma_R(Y_p)^a$	$\delta_C{}^b$	$\delta_H{}^b$
49	3,4-Cl	3′,5′-Cl	0.37	0.42	−0.19	0.74	0.00	0.00	159.33	8.33
50	3-F-4-Me	3′,4′-Cl	0.34	0.01	−0.18	0.37	0.42	−0.19	160.14	8.34
51	3-F-4-Me	3′-Cl-4′-Me	0.34	0.01	−0.18	0.37	0.01	−0.18	159.14	8.36
52	3,5-Br	3′-Cl-4′-Me	0.78	0.00	0.00	0.37	0.01	−0.18	156.87	8.31
53	3,5-Br	3′,5′-Cl	0.78	0.00	0.00	0.74	0.00	0.00	158.79	8.28

[a] The parameter values were taken from Ref.[18].
[b] δ_C and δ_H are the δ_C(CH=N) values and δ_H(CH=N) values respectively.

was added based on Eq.(5), and Eq.(6) was obtained.

$$\begin{aligned}\delta_C(\text{CH=N}) = 160.32 &- 4.25\sum\sigma_F(X_m) - 4.00\sigma_F(X_p) - \\ &1.27\sigma_R(X_p) + 2.74\sum\sigma_F(Y_m) + \\ &2.94\sigma_F(Y_p) + 4.62\sigma_R(Y_p) - \\ &0.65\Delta\left(\sum\sigma\right)^2 \qquad (6)\\ R = 0.9902,\quad R^2 = 0.9806,\quad &S = 0.32,\\ F = 1255.10,\quad n = 182\end{aligned}$$

As seen from the regression results, the regression results of Eq.(6) are better than those of Eq.(5). In Eq.(6), the correlation coefficient R is 0.9902; the standard error S is 0.32, and the F value is 1255.10. Additionally, we found that the coefficients of $\sum\sigma_F(X_m)$ and $\sum\sigma_F(Y_m)$ were close to those of $\sigma_F(X_p)$ and $\sigma_F(Y_p)$ respectively. Therefore, the parameters with the close coefficients were merged and symbolized by $\sum\sigma_F(X)$ and $\sum\sigma_F(Y)$

$$\sum\sigma_F(X) = \sum\sigma_F(X_m) + \sigma_F(X_p)$$
$$\sum\sigma_F(Y) = \sum\sigma_F(Y_m) + \sigma_F(Y_p)$$

In addition, $\sigma_R(X_m)$ and $\sigma_R(Y_m)$ are equal to 0, so

$$\sigma_R(X_p) = \sigma_R(X_m) + \sigma_R(X_p) = \sum\sigma_R(X)$$
$$\sigma_R(Y_p) = \sigma_R(Y_m) + \sigma_R(Y_p) = \sum\sigma_R(Y)$$

That is to say, $\sigma_R(X_p)$ and $\sigma_R(Y_p)$ could be replaced by $\sum\sigma_R(X)$ and $\sum\sigma_R(Y)$. And then the regression of the δ_C(CH=N) values of 182 samples of XBAYs was made against the above optimized parameters, and the relatively best regression equation (Eq.(7)) was obtained.

$$\begin{aligned}\delta_C(\text{CH=N}) = 160.33 &- 4.12\sum\sigma_F(X) - \\ &1.29\sum\sigma_R(X) + 2.85\sum\sigma_F(Y) + \\ &4.60\sum\sigma_R(Y) - 0.66\Delta\left(\sum\sigma\right)^2 \qquad (7)\\ R = 0.9899,\quad R^2 = 0.9799,\quad &S = 0.32,\\ F = 1716.71,\quad n = 182,\quad &R_{CV} = 0.9892\end{aligned}$$

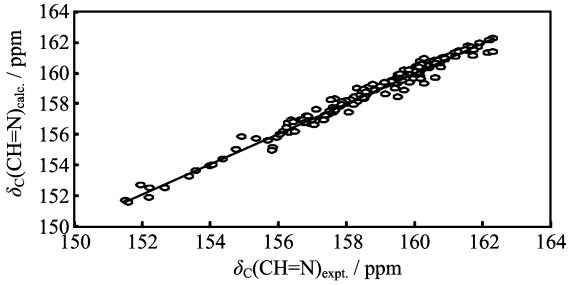

FIG. 1 Plot of the δ_C(CH=N) values predicted by Eq.(7) versus the experimental ones for 182 samples of XBAYs.

$$R^2_{CV} = 0.9786,\quad S_{CV} = 0.33$$

The correlation coefficient of Eq.(7) is a little less than that of Eq.(6), but the F value of Eq.(7) is greater than that of Eq.(6). The absolute average error of Eq.(7) between the calculated δ_C(CH=N) values and the experimental ones is 0.23 ppm. Furthemore, Eq.(7) was across verified using leave-one-out cross validation (CV), and the correlation coefficient R_{CV} was 0.9892; the standard error S_{CV} was 0.33. The cross validation results also show that Eq.(7) possessed high reliability. The predicted δ_C(CH=N) values calculated by Eq.(7) are listed in Table II (shown as $\delta_{C,calc.}$).

FIG. 1 is the plot of the predicted δ_C(CH=N) values calculated by Eq.(7) versus the experimental ones for 182 samples of XBAYs. It shows that the experimental δ_C(CH=N) values of the 182 samples of XBAYs present a good correlation with the predicted ones. That is to say, the δ_C(CH=N) values of XBAYs can be accurately quantified by Eq.(7).

The above analysis was for the substituent effects on the δ_C(CH=N) of XBAYs, and the substituent effects on their δ_H(CH=N) would be studied next. The regression of the δ_H(CH=N) values of 182 samples of XBAYs (including the 129 samples of di-substituted XBAYs from Ref.[15] and 53 samples of multi-disubstituted XBAYs synthesized in this work) was made against the substituent parameters listed in Table I. And Eq.(8) was obtained.

$$\delta_H(\text{CH=N}) = 8.44 - 0.07\sum\sigma_F(X_m) + 0.07\sigma_F(X_p) +$$

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TABLE II The δ_C(CH=N) and δ_H(CH=N) values calculated by Eq.(7) and Eq.(10).

No.	X	Y	$\delta_{C,calc.}$	$\delta_{H,calc.}$	No.	X	Y	$\delta_{C,calc.}$	$\delta_{H,calc.}$
1	3,4-Me	H	160.77	8.42	28	3,5-Cl	H	156.92	8.39
2	3,4-Me	4′-Me	160.00	8.43	29	3,5-Cl	4′-NMe_2	151.58	8.45
3	3,5-Me	H	160.89	8.45	30	3,5-Cl	4′-Me	155.94	8.40
4	H	3′,4′-Me	159.29	8.46	31	3,5-Cl	4′-Cl	157.43	8.37
5	H	3′,5′-Me	159.92	8.45	32	H	3′,5′-Cl	162.07	8.39
6	3,4-MeO	H	159.35	8.37	33	4-NMe_2	3′,5′-Cl	161.47	8.25
7	3,4-MeO	4′-NMe_2	154.98	8.42	34	4-F	3′,5′-Cl	160.78	8.36
8	3,4-MeO	4′-Me	158.56	8.38	35	4-Cl	3′,5′-Cl	160.78	8.39
9	3,4-MeO	4′-F	158.82	8.36	36	3,4-F	4′-NMe_2	152.50	8.45
10	3,4-MeO	4′-Cl	159.59	8.35	37	3,4-F	4′-Cl	157.88	8.37
11	3,4-MeO	4′-CN	161.07	8.32	38	3,5-F	H	157.22	8.39
12	3,5-MeO	H	159.30	8.43	39	3,4-Br	H	156.90	8.41
13	3,5-MeO	4′-Me	158.43	8.44	40	3,5-Br	H	156.72	8.39
14	3,5-MeO	4′-Cl	159.66	8.41	41	3-F-4-Me	H	159.10	8.39
15	3,5-MeO	4′-CN	161.36	8.38	42	3-Br-4-Me	H	158.88	8.39
16	3,4-Cl	H	157.08	8.42	43	H	3′-F-4′-Me	160.48	8.43
17	3,4-Cl	4′-NMe_2	151.90	8.47	44	H	3′-Cl-4′-Me	160.55	8.43
18	3,4-Cl	4′-Me	156.13	8.43	45	H	3′-Br-4′-Me	160.61	8.43
19	3,4-Cl	4′-F	156.61	8.41	46	3,4-MeO	3′,5′-Me	158.96	8.38
20	3,4-Cl	4′-Cl	157.55	8.40	47	3,4-Cl	3′,4′-Cl	158.69	8.38
21	3,4-Cl	4′-CN	159.46	8.37	48	3,4-Cl	3′-Cl-4′-Me	157.47	8.40
22	H	3′,4′-Cl	161.47	8.40	49	3,4-Cl	3′,5′-Cl	159.41	8.37
23	4-NMe_2	3′,4′-Cl	161.01	8.26	50	3-F-4-Me	3′,4′-Cl	160.37	8.35
24	4-Me	3′,4′-Cl	161.50	8.38	51	3-F-4-Me	3′-Cl-4′-Me	159.37	8.38
25	4-F	3′,4′-Cl	160.16	8.37	52	3,5-Br	3′-Cl-4′-Me	157.15	8.37
26	4-Cl	3′,4′-Cl	160.13	8.40	53	3,5-Br	3′,5′-Cl	159.22	8.34
27	3-Cl	3′,4′-Cl	160.14	8.38					

$$\begin{aligned}&0.16\sigma_R(X_p)-0.08\sum\sigma_F(Y_m)-\\&0.06\sigma_F(Y_p)-0.07\sigma_R(Y_p)\qquad(8)\\&R=0.8642,\quad R^2=0.7468,\quad S=0.04,\\&F=86.01,\quad n=182\end{aligned}$$

In Eq.(8), the substituent cross-interaction effect parameter was not considered. Therefore the corresponding substituent cross-interaction effect parameter

$$\Delta\left(\sum\sigma\right)^2=\left(\sum\sigma(X_m)+\sigma(X_p)-\sum\sigma(Y_m)-\sigma(Y_p)\right)^2$$

was tentatively added based on Eq.(8), and Eq.(9) was obtained.

$$\begin{aligned}\delta_H(CH{=}N)=8.44&-0.08\sum\sigma_F(X_m)+0.07\sigma_F(X_p)+\\&0.16\sigma_R(X_p)-0.08\sum\sigma_F(Y_m)-\\&0.06\sigma_F(Y_p)-0.06\sigma_R(Y_p)-\\&0.01\Delta\left(\sum\sigma\right)^2\qquad(9)\\R=0.8653,&\quad R^2=0.7488,\quad S=0.04,\\F=74.10,&\quad n=182\end{aligned}$$

Comparing Eq.(8) with Eq.(9), the regression results of Eq.(9) are not better than those of Eq.(8). In other words, the adding of $\Delta\left(\sum\sigma\right)^2$ didn't improve the regression of the δ_H(CH=N) of XBAYs. As seen from the coefficients of the parameters in Eq.(8), the coefficients of $\sum\sigma_F(Y_m)$, $\sigma_F(Y_p)$, and $\sigma_R(Y_p)$ are close. Moreover, the conjugative effect of Y_m $\left(\sum\sigma_R(Y_m)\right)$ is equal to 0, so

$$\begin{aligned}\sum\sigma_F(Y_m)&=\sum\sigma_F(Y_m)+\sum\sigma_R(Y_m)\\&=\sum\sigma(Y_m)\\\sigma_F(Y_p)+\sigma_R(Y_p)&=\sigma(Y_p)\end{aligned}$$

$$\sum\sigma(Y_m)+\sigma(Y_p)=\sum\sigma(Y)$$

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That is to say, $\sum\sigma_{\rm F}({\rm Y}_m)$, $\sigma_{\rm F}({\rm Y}_p)$, and $\sigma_{\rm R}({\rm Y}_p)$ could be merged as $\sum\sigma({\rm Y})$. The regression of the $\delta_{\rm H}$(CH=N) values of XBAYs was made again, and the regression equation was obtained (shown as Eq.(10)).

$$\delta_{\rm H}({\rm CH{=}N}) = 8.44 - 0.08\sum\sigma_{\rm F}({\rm X}_m) + 0.07\sigma_{\rm F}({\rm X}_p) + 0.16\sigma_{\rm R}({\rm X}_p) - 0.07\sum\sigma({\rm Y}) \quad (10)$$

$$R = 0.8633, \quad R^2 = 0.7453, \quad S = 0.04,$$
$$F = 129.49, \quad n = 182, \quad R_{\rm CV} = 0.8531,$$
$$R^2_{\rm CV} = 0.7277, \quad S_{\rm CV} = 0.04$$

The correlation coefficient and standard error of the optimized equation (Eq.(10)) are almost the same with those of Eq.(9), and the F value of Eq.(10) is up to 129.49 from 86.01. The absolute average error of Eq.(10) between the calculated $\delta_{\rm H}$(CH=N) values and the experimental ones is 0.03 ppm. Eq.(10) was across verified using leave-one-out cross validation (CV) as well; and the obtained correlation coefficient $R_{\rm CV}$ was 0.8531; the standard error $S_{\rm CV}$ was 0.04. The results show that Eq.(10) is reliable. The predicted $\delta_{\rm H}$(CH=N) values calculated by Eq.(10) were listed in Table II (shown as $\delta_{\rm H,calc.}$).

FIG. 2 is the plot of the predicted $\delta_{\rm H}$(CH=N) values calculated by Eq.(10) versus the experimental ones for 182 samples of XBAYs. Although several samples deviate from the trend line, there still exists a good correlation between the calculated $\delta_{\rm H}$(CH=N) values and the experimental ones.

Above research results proved that the $\delta_{\rm C}$(CH=N) and $\delta_{\rm H}$(CH=N) values of multi-substituted XBAYs could be quantified by Eq.(7) and Eq.(10) respectively. The biggest difference between Eq.(7) and Eq.(10) is that: the substituent cross-interaction effect parameter $\Delta\left(\sum\sigma\right)^2$ plays an important role in quantifying the $\delta_{\rm C}$(CH=N) of XBAYs, but it is negligible in the regression of $\delta_{\rm H}$(CH=N) values of XBAYs. The inductive effects and conjunctive effects of X and Y on the $\delta_{\rm C}$(CH=N) and $\delta_{\rm H}$(CH=N) of XBAY are different, or even opposite. In Eq.(7), the coefficients of $\sum\sigma_{\rm F}({\rm X})$ and $\sum\sigma_{\rm R}({\rm X})$ are negative, which demonstrates that the inductive effects and conjunctive effects of X(m/p) present a negative correlation with the $\delta_{\rm C}$(CH=N) of XBAYs. On the contrary, the coefficients of $\sum\sigma_{\rm F}({\rm Y})$ and $\sum\sigma_{\rm R}({\rm Y})$ are positive, which demonstrats that the inductive effects and conjunctive effects of Y(m/p) present a positive correlation with the $\delta_{\rm C}$(CH=N) of XBAYs. In Eq.(10), the coefficients of $\sum\sigma_{\rm F}({\rm X}_m)$ and $\sum\sigma({\rm Y})$ are negative, but the coefficients of $\sigma_{\rm F}({\rm X}_p)$ and $\sigma_{\rm R}({\rm X}_p)$ are positive; these demonstrate that the inductive effects and conjunctive effects of $\rm X_m$ and Y(m/p) present a negative correlation with the $\delta_{\rm H}$(CH=N) of XBAYs; but the inductive effects and conjunctive effects of $\rm X_p$ present a positive correlation with the $\delta_{\rm H}$(CH=N) of XBAYs. The above result shows that the change regularities of the $\delta_{\rm C}$(CH=N) and $\delta_{\rm H}$(CH=N) of multi-substituted XBAYs are almost consistent with those of di-substituted XBAYs. However the substituent effects were studied more comprehensively in this work.

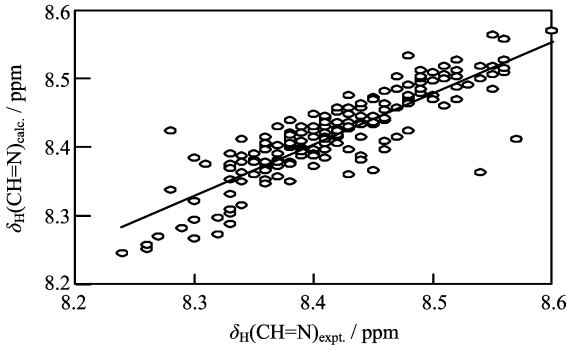

FIG. 2 Plot of the $\delta_{\rm H}$(CH=N) values predicted by Eq.(10) versus the experimental ones for 182 samples of XBAYs

In addition, the contributions of parameters to the $\delta_{\rm C}$(CH=N) and $\delta_{\rm H}$(CH=N) are different. Here the relative importance of parameters in Eq.(7) and Eq.(10) were investigated from the relative contributions (Ψ_γ) or fraction contributions ($\Psi_{\rm f}$) of the corresponding parameters to the $\delta_{\rm C}$(CH=N) and $\delta_{\rm H}$(CH=N) [19, 20].

$$\Psi_\gamma = m_i\bar{X}_i \quad (11)$$

$$\Psi_{\rm f}(i) = \frac{R^2|\Psi_\gamma(i)|}{\sum_i|\Psi_\gamma(i)|}\times 100\% \quad (12)$$

where m_i and $\bar{X}_i$ are the coefficient and the average value of the ith parameter in Eq.(7) or Eq.(10), and R is the correlation coefficient of Eq.(7) or Eq.(10). The sum is over the parameters in the equations. The contribution results for the corresponding parameters of Eq.(7) and Eq.(10) are all shown in Table III.

As seen from the relative contributions in Table III, in Eq.(7), the inductive effects of X $\left(\sum\sigma_{\rm F}({\rm X})\right)$, the conjunctive effects of Y $\left(\sum\sigma_{\rm R}({\rm Y})\right)$, and the substituent specific cross-interaction effect parameter $\left(\Delta\left(\sum\sigma\right)^2\right)$ decrease the $\delta_{\rm C}$(CH=N) values of XBAY, but the conjunctive effects of X $\left(\sum\sigma_{\rm R}({\rm X})\right)$ and the inductive effects of Y(m/p) $\left(\sum\sigma_{\rm F}({\rm X})\right)$increase the $\delta_{\rm C}$(CH=N) values of XBAY. In Eq.(10), the inductive effects of $\rm X_p$ $\left(\sum\sigma_{\rm F}({\rm X}_p)\right)$ increase the $\delta_{\rm H}$(CH=N) values of XBAY, but the rest parameters decrease the $\delta_{\rm H}$(CH=N) values of XBAY.

As seen from the fraction contributions in Table III, the inductive effects and the conjunctive effects of X(m/p) contribute 46.05% to the $\delta_{\rm C}$(CH=N) of XBAY,

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TABLE III The relative and fraction contributions of parameters in Eq.(7) and Eq.(10).

Parameters	$\sum\sigma_{\rm F}({\rm X}_m)$	$\sum\sigma_{\rm F}({\rm X}_p)$	$\sum\sigma_{\rm R}({\rm X})/\sigma_{\rm R}({\rm X}_p)$	$\sum\sigma_{\rm F}({\rm Y})$	$\sum\sigma_{\rm R}({\rm Y})$	$\Delta\left(\sum\sigma\right)^2$
Ψ_γ in Eq.(7)	−1.5188		0.2215	0.8035	−0.9022	−0.2567
$\Psi_{\rm f}$ in Eq.(7)	0.4019		0.0586	0.2126	0.2388	0.0679
Ψ_γ in Eq.(10)	−0.0108	0.0162	−0.0276	−0.0059		-
$\Psi_{\rm f}$ of Eq.(10)	0.1333	0.1996	0.3400	0.0724		-

of which the inductive effects of X(m/p) contribute 40.19%, yet the conjunctive effects of X(m/p) contribute only 5.86%; the inductive effects and the conjunctive effects of Y(m/p) contribute 45.14% to the $\delta_{\rm C}$(CH=N) of XBAY, of which the inductive effects of Y(m/p) contribute 21.26%, and the conjunctive effects of Y(m/p) contribute 23.88%; the substituent specific cross-interaction effect parameter $\left(\Delta\left(\sum\sigma\right)^2\right)$ contributes 6.79% to the $\delta_{\rm C}$(CH=N) of XBAY. The contributions to the $\delta_{\rm H}$(CH=N) of XBAY mainly rely on the inductive effects and the conjunctive effects of X(m/p), and their fraction contributions are up to 67.29%, of which the fraction contributions of the inductive effects and conjunctive effects of X(m/p) are balanced relative to the contributions of X to the $\delta_{\rm C}$(CH=N) of XBAY. The inductive effects of $\rm X_{\it m}$ contribute 13.33%; the inductive effects of $\rm X_{\it p}$ contribute 19.96%; the conjunctive effects of $\rm X_{\it p}$ contribute 34.00%; but the inductive effects and conjunctive effects of Y(m/p) contribute only 7.24% to the $\delta_{\rm H}$(CH=N) of XBAY.

IV. CONCLUSION

The change regularities of the $\delta_{\rm C}$(CH=N) and $\delta_{\rm H}$(CH=N) of multi-substituted XBAYs were studied in this work; Eq.(7) and Eq.(10) were proposed to quantify their change regularities respectively. The results show that their change regularities are basically consistent with those of the $\delta_{\rm C}$(CH=N) and $\delta_{\rm H}$(CH=N) of di-substituted XBAYs. The substituent specific cross-interaction effect parameter $\left(\Delta\left(\sum\sigma\right)^2\right)$ plays an important role in quantifying the $\delta_{\rm C}$(CH=N) values of XBAYs, but it is negligible for quantifying the $\delta_{\rm H}$(CH=N) values. The inductive effects and the conjunctive effects of X present negative correlations with the $\delta_{\rm C}$(CH=N) of XBAYs, but the inductive effects and the conjunctive effects of Y present positive correlations. For the $\delta_{\rm H}$(CH=N) of XBAYs, the inductive effects and conjunctive effects of $\rm X_{\it p}$ present positive correlations; the inductive effects of $\rm X_{\it m}$, the inductive effects and conjunctive effects of Y present negative correlations. On the whole, the contributions of X and Y to the $\delta_{\rm C}$(CH=N) of XBAYs are balanced, but the $\delta_{\rm H}$(CH=N) values of XBAYs mainly rely on the inductive effects and conjunctive effects of X.

Supplementary materials: The detailed data of the synthesized compounds are available in the Supporting Information.

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