The Danishefsky pyranone puzzle: an explanation based on the exterior frontier orbital extension model

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ABSTRACT

The unusual facial stereoselection in the hydride reduction of the Danishefsky pyranones (2,3,5,6-tetrahydro-4-pyranones) with L-Selectride (Li-*sec*-Bu$_3$BH) has been explained based on the exterior frontier orbital extension model (the EFOE model).

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The origin of π-facial diastereoselection in nucleophilic carbonyl additions has been the subject of intense debate in recent years.[1] Attention has been focused mainly on various stabilization mechanisms in the transition state.[2,3] We have recently shown that the transition state effects in the reduction of cyclohexanone (**1**), such as the torsional strain effect and the antiperiplanar hyperconjugative stabilization effects, operate against the observed facial stereoselection.[4] To this end, we proposed the new theoretical model, called 'the exterior frontier orbital extension model, the EFOE Model',[5] based on the simple assumption that the origin of facial selection should be the π-facial difference in the reaction driving force generated in the early stages according to the Salem–Klopman equation.[6] Herein, we show using the new model that the facial diastereoselection of the hydride reduction of 2,3,5,6-tetrahydropyran-4-ones (hereafter called simply '4-pyranone', **2**) is dictated by the ground-state conformational and the electronic properties of the substrates.

Two unique features on the stereochemistry of **2** in complex metal hydride reductions have been intensively discussed to date.[1] First, simple 4-pyranones (**2**) are more reactive and give more equatorial alcohol via axial attack (ax-attack) than corresponding cyclohexanones (**1**) (Table 1).[7–9] This has been explained traditionally by the Cieplak model,[2] Anh's hyperconjugation,[3] or by the torsional strain model.[10] Second, unlike cyclohexanone or simple 4-pyranones, 2-methoxy-6-phenyl-2,3,5,6-tetrahydropyran-4-ones (the Danishefsky pyranones, **3**) undergo exclusive ax-attack upon

reduction with L-Selectride (Li-*sec*-Bu$_3$BH), a sterically demanding hydride reagent.[11] Danishefsky rationalized the unusual result in terms of the Cieplak model assuming the diminution in the electron-donating property of the C2–C3 and the C5–C6 bonds due to the oxygen(s) at C2 and C6 positions.[11] Recently, Gung has pointed out that both experimental observations could be rationalized by the ground-state conformational characteristics of these compounds: the six-membered ring of **3** is more flattened than that of cyclohexanone and the reactive conformation of **3** may be thermodynamically less stable 3-**AC** (Ph in axial position) rather than **3-EC** (Ph in equatorial position).[12]

This Letter describes the theoretical evidence that the ground-state conformational properties as well as the anisotropic extension of the frontier orbital (LUMO) over the carbonyl π-faces

Table 1
Diastereoselectivity of hydride reduction of cyclohexanones (**1**) and tetrahydropyranones (**2**) with LiAlH$_4$, NaBH$_4$, and L-Selectride

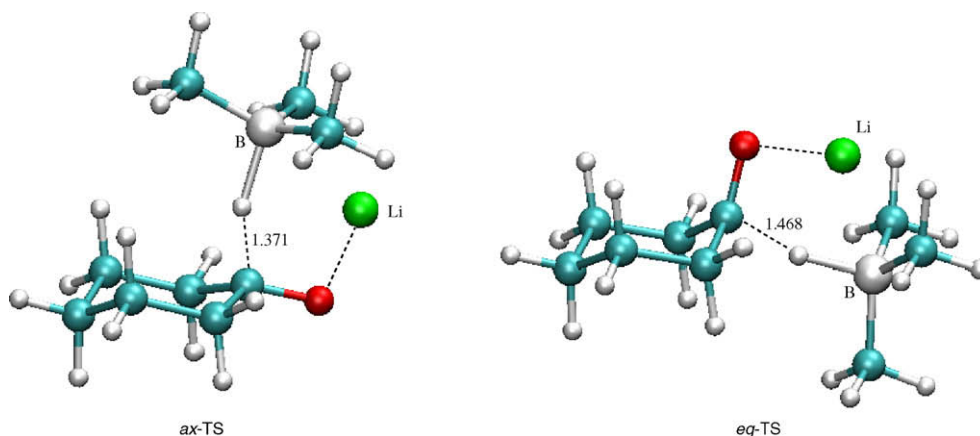| Compds.	R$_1$	R$_2$	LiAlH$_4$		NaBH$_4$		L-Selectride	
			ax	eq	ax	eq	ax	eq
1b	Me	H	75	25[a]	73	27[b]	0.7	99.3[b]
1c	H	Me	85	15[a]	77	23[b]	5.5	94.5[b]
1d	H	*t*-Bu	83	17[a]	76	24[b]	—	—
2b	Me	H	77	23[c]	—	—	3	97[c]
2c	H	Me	95	5[b]	92.5	7.5[b]	30	70[b]
2d	H	*t*-Bu	94.5	5.5[b]	89.7	10.3[b]	24	76[b]

[a] Ref. 7.
[b] Ref. 8.
[c] Ref. 9.

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Figure 1. Transition state structures of LiMe$_3$BH reduction of cyclohexanone (**1a**) (B3LYP/6-31+G(d,p)). Bond lengths are in Å.

should be responsible for the unique facial diastereoselection observed for **2** and **3**. Geometry optimization of the axial and equatorial transition states for the reduction of **1a**, **2a**, and **2e** with LiMe$_3$BH was performed at the B3LYP/6-31+G(d,p) level,[13] and calculated energy differences between the equatorial and axial transition states ($\Delta H_{TS} = H_{eq} - H_{ax}$; H_{eq} and H_{ax} are energies of equatorial and axial transition state, respectively[14]) are −0.34, 0.18, and 1.96 kJ mol^{-1} for **1a**, **2a**, and **2e**, respectively. These energy differences indicate predominant eq-attack for **1a**, but ax-attack for **2a** and **2e**. Figures 1 and 2 show the transition state (TS) structures of **1a** and **2a**, respectively. The incipient bond distances between attacking hydride and carbonyl carbon of **2a** (1.422 Å for the axial TS (ax-TS) and 1.539 Å for the equatorial TS (eq-TS)) are longer than corresponding distances of **1a** (1.371 Å for the ax-TS and 1.468 Å for the eq-TS), which is consistent with more reactivity of pyranones than cyclohexanones. Figure 3a depicts a plot of the percent elongation of the antiperiplanar bonds (PEB)[15] against these energy differences. Two notable features are seen. First, the values of PEB for the ax-TS are negative, suggesting that the antiperiplanar bonds shorten rather than they elongate in the ax-TS, no matter whether ax or eq preference. Second, contrary to the previous proposal,[9] the antiperiplanar stabilization effects for the ax-TS decrease slightly and those for eq-TS increase as ΔH_{TS} (i.e., the axial preference of product ratio) increase (**1a**→**2a**→**2e**). The decrements in the vicinal antiperiplanar bond population due to the antiperiplanar effects (ΔBP)[16] calculated with natural bond orbital (NBO) analysis[17] show the trends consonant with these results (Fig. 3b). These theoretical findings clearly suggest that the

transition effects should not be responsible for the observed unusual facial stereoselections for **2**.
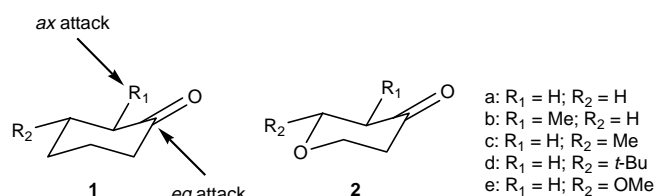
Quantitative analysis based on the EFOE model[5] for **1** and **2** was therefore performed.[18] The EFOE model defines two quantities—the π-plane-divided accessible space (PDAS) as the first term (the steric effects) and the π-plane-divided frontier orbital electron density (the EFOE density) as the third term (donor–accepter two-electron stabilizing orbital interactions) of the Salem–Klopman equation.[6] The results collected in Table 2 show some significant features. First, both the axial face (ax-face) and the equatorial face (eq-face) of parent 4-pyranone (**2a**) are sterically more relaxed (ax-PDAS = 22.0 au^3 and eq-PDAS = 47.6 au^3) than those of **1a** (ax-PDAS = 20.4 au^3 and eq-PDAS = 46.7 au^3) owing to ring-flattening of the former.[12c] This trend is also observed for other pyranones (**2b–d**) and the corresponding cyclohexanones (**1b–d**), respectively. Second, the LUMO levels for **2** are uniformly lower than those of **1**. Analogously, the EFOE densities over the ax-face of **2**
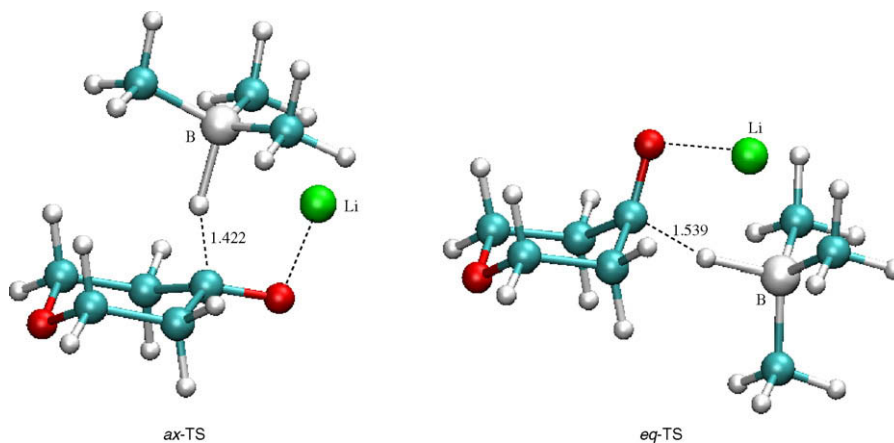
Figure 2. Transition state structures of LiMe$_3$BH reduction of 4-tetrahydropyranone (**2a**) (B3LYP/6-31+G(d,p)). Bond lengths are in Å.
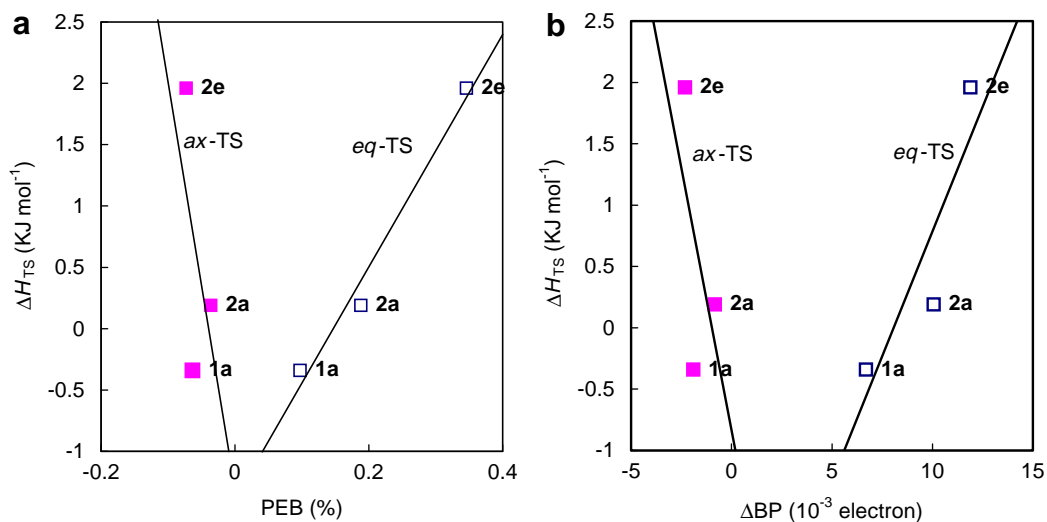
Figure 3. A plot of the antiperiplanar effects ((a) percent elongation of antiperiplanar bond (PEB)[15] and (b) NBO bond population (ΔBP)[16]) against the relative transition state energies ($\Delta H_{TS} = H_{eq} - H_{ax}$). Filled and open squares denote the ax-TS and the eq-TS, respectively.

are slightly higher (1.18%, 1.13%, 1.16%, and 1.14% for **2a**, **2b**, **2c**, and **2d**, respectively) than those of corresponding **1** (1.17%, 1.08%, 1.13%, and 1.09% for **1a**, **1b**, **1c** and **1d**, respectively). The ax-attack preferences of **2** are a little higher than that of **1**.[7,9] The trends exhibited by EFOE density, PDAS and the LUMO level are entirely consistent with ax-attack preference as well as enhanced

rate of hydride reduction of **2** compared with that of **1**. Hence, the EFOE model can give reasonable explanation based on the conformational and the frontier orbital properties of the ground state of **2**.

The results of EFOE analysis[18] of the three conformers of Danishefsky pyranones (**3**) (**3-EC**, **3-TB**, and **3-AC**; Eq. 1) along with the experimental data are collected in Table 3.[11] Preferential axial attack of the borohydride reagents (LiBH$_4$, Li-sec-Bu$_3$BH) at **3b** and **3c** is consistent not only with the relative magnitude of the EFOE densities over the two carbonyl faces of the most stable **3b-EC** and **3c-EC**, but also with the steric environment around the carbonyl carbon of these ketones, each of which possesses greater ax-PDAS value (21.7 au^3 for **3b-EC**, 16.0 au^3 for **3c-EC**) than eq-PDAS (15.3 au^3 for **3b-EC**, 15.4 au^3 for **3c-EC**). The EFOE data of the other conformers **3b-TB**, **3b-AC**, **3c-TB**, and **3c-AC** can account for the observed facial stereoselection as well. However, since they are all much less stable by more than 10 kJ mol^{-1} than **3-EC**, their contribution to the observed stereoselection may not be significant.

The behavior of **3a** cannot be readily understood. In agreement with Gung's conclusions drawn from MM2 force field calculations,[12c] our ab initio calculation at the B3LYP/6-31+G(d,p) level has shown that the stability order of the three conformers in the gas phase is **EC > TB > AC**. Gung postulated **3a-AC** conformer as the most reactive one in solution.[12b] The data of the EFOE analysis (Table 3) for all the three conformers are completely consistent with the observed facial stereoselection with sterically demanding

Table 2
The EFOE analysis of the LUMO ($\pi^*_{C=O}$) of cyclohexanones and substituted 2,3,5,6-tetrahydropyran-4-ones (**2**)[a]

Compds.	R$_1$	R$_2$	EFOE density (%)		PDAS (au^3)		LiAlH$_4$
			ax	eq	ax	eq	ax:eq
1a	H	H	1.17	0.32	20.4	46.7	88.5:11.5[b,c]
1b	Me	H	1.08	0.38	15.4	48.5	75:25[b]
1c	H	Me	1.13	0.34	19.4	47.5	85:15[b]
1d	H	t-Bu	1.09	0.36	18.2	47.6	83:17[b]
2a	H	H	1.18	0.33	22.0	47.6	–
2b	Me	H	1.13	0.38	16.5	50.3	77:23[d]
2c	H	Me	1.16	0.34	21.1	48.2	95:5[e]
2d	H	t-Bu	1.14	0.35	20.4	47.6	94.5:5.5[e]
2e	H	OMe	1.23	0.31	25.9	44.0	96:4[f]

  [a] B3LYP/6-31G(d)//B3LYP/6-31+G(d,p). LUMO corresponds to $\pi^*_{C=O}$.
  [b] Ref. 7.
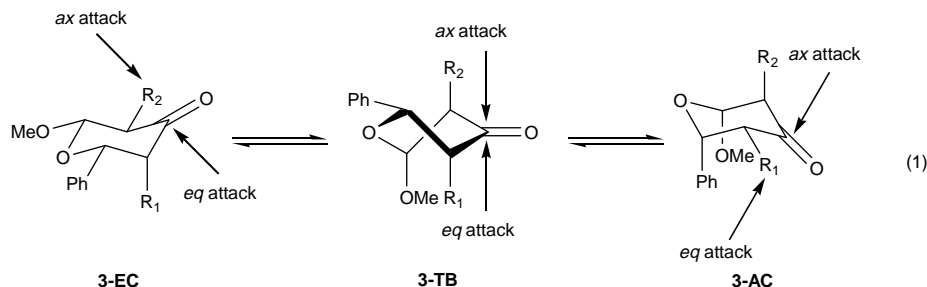 [c] Data of 4-tert-Bu-cyclohexanone.
  [d] Ref. 9.
  [e] Ref. 8.
  [f] NaBH$_4$. Data of 2-methoxy-6-pheynl-2,3,5,6,-tetrahydro-4-pyranone. Ref. 11.

3-EC   3-TB   3-AC   (1)

a: R$_1$ = H; R$_2$ = H
b: R$_1$ = H; R$_2$ = Me
c: R$_1$ = Me; R$_2$ = Me

Table 3
The EFOE analysis[a] of the LUMO ($\pi_{C=O}^*$) of the Danishefsky pyranones (**3**)

Compds.	EFOE density (%)		PDAS (au³)		Rel. E (kJ mol⁻¹)[b]		L-Selectride (NaBH₄) ax:eq[d]
	ax	eq	ax	eq	Gas phase	In THF[c]	
3a-EC	1.03	0.32	24.3	45.2	0.0	0.0	80:20
3a-AC	0.21	0.49	41.1	5.8	17.5	18.5	(96:4)
3a-TB	0.43	0.38	35.1	23.8	9.0	7.8	
3b-EC	0.96	0.34	21.7	15.3	0.0	0.0	100:0
3b-AC	0.24	0.27	39.7	3.5	14.8	15.2	(100:0)
3b-TB	0.41	0.55	36.6	10.9	11.8	10.1	
3c-EC	0.93	0.38	16.0	15.4	0.0	0.0	93:7
3c-AC	0.26	0.25	15.5	3.5	20.9	19.6	(97:3)
3c-TB	0.61	0.51	14.9	13.2	20.5	19.0	

[a] B3LYP/6-31G(d)//B3LYP/6-31+G(d,p). LUMO corresponds to $\pi_{C=O}^*$.
[b] Relative total electronic energy (ZPE corrected) with respect to the EC conformer.
[c] Calculated by CPCM method.
[d] Ref. 11.

L-Selectride. The ax-face of the **EC** form is much less sterically hindered (ax-PDAS = 24.3 au³) than cyclohexanone (**1**) or alkyl substituted pyranone **2b–d** (ax-PDAS = 20.4, 16.5, 21.1, and 20.4 au³, respectively), whereas the eq-face of the **EC** is more hindered (eq-PDAS = 45.2 au³) than those of others (eq-PDAS = 46.7, 50.3, 48.2, and 47.6 au³, respectively). There will be enough space for L-Selectride to access both sides of the carbonyl faces of the **EC** form of **3a**, while there is a significant difference in the EFOE densities between at the ax- and the eq-face (1.03% and 0.32%, respectively). Although the ax-faces of the other two conformers (**AC** and **TB**) are much less hindered (ax-PDAS = 41.1 au³ for and 35.1 au³, respectively) than that of **1**, their contribution to the observed stereoselection may not be significant since they are much less stable by 17.5 and 9.0 kJ mol⁻¹, respectively, than **EC**. As shown in Table 3, only marginal solvent effects for conformer populations were observed by CPCM method calculation.

In summary, 'the unusual' behavior of the Danishefsky pyranones (**3**) with L-Selectride can be understood basically by the significant steric relaxation at the ax-faces in the **EC** conformers owing to the electron-withdrawing property of the methoxy substituent at C2 position. Their EFOE data agree completely with the experimental stereoselectivity. It is strongly suggested that the antiperiplanar effects operate against the observed facial stereoselection.

Acknowledgments

References and notes

1. (a) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263; (b) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449.
2. Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.
3. (a) Anh, N. T.; Eisenstein, O.; Lefour, J.-M.; Tran Huu Dau, M. E. *J. Am. Chem. Soc.* **1976**, *95*, 6146; (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1976**, *1*, 61.
4. Tomoda, S.; Senju, T. *Chem. Commun.* **1999**, 423.
5. (a) Tomoda, S. *Chem. Rev.* **1999**, *99*, 1243; (b) Tomoda, S.; Senju, T. *Tetrahedron* **1997**, *53*, 9057; (c) Tomoda, S.; Senju, T. *Tetrahedron* **1999**, *55*, 3871.
6. (a) Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223; (b) Salem, L. *J. Am. Chem. Soc.* **1968**, *90*, 543; (c) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: London, 1977.
7. Rei, M.-H. *J. Org. Soc.* **1979**, *44*, 2760.
8. Catelani, G.; Monti, L.; Ugazio, M. *J. Org. Chem.* **1980**, *45*, 919.
9. Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* **1994**, *50*, 1261.
10. Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908.
11. Danishefsky, S.; Langer, M. E. *J. Am. Chem. Soc.* **1985**, *50*, 3672.
12. (a) Gung, B. W.; Zhu, Z.; Mareska, D. A. *J. Org. Chem.* **1993**, *58*, 1367; (b) Gung, B. W.; Wolf, M. A.; Mareska, D. A.; Brockway, C. A. *J. Org. Chem.* **1994**, *59*, 4895; (c) Gung, B. W.; Wolf, M. A.; Mareska, D. A.; Karipides, A. *J. Org. Chem.* **1994**, *59*, 4899.
13. M. J. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N. Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; GAUSSIAN 03 (Revision E.01); Gaussian: Wallingford, CT, 2004.
14. These energies are corrected with thermal enthalpy at −78 °C.
15. PEB = $(\Delta r/rs) \times 100$, where Δr is the difference in bond lengths between the vicinal antiperiplanar bond (C–H for ax-attack and C–C bond for eq-attack) in transition state (r_{TS}) and the corresponding bond of starting ketone (rs); $\Delta r = r_{TS} - rs$. Both structures (transition state and the starting ketone) were optimized at the same level of calculation method and basis set (B3LYP/6-31+G(d,p)).
16. $\Delta BP = BP_{TS} - BP_{GS}$, where BP_{TS} and BP_{GS} denote the NBO bond populations for the antiperiplanar bond in the transition state and in the ground state structures, respectively.
17. Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.
18. Geometry optimizations of all compounds were performed at the B3LYP/6-31+G(d,p) level with GAUSSIAN 03. The EFOE analyses were performed at B3LYP/6-31 G(d) level and 0.1 au lattice mesh.[5]