Pergamon

Tetrahedron Letters 44 (2003) 6617–6619

TETRAHEDRON
LETTERS

Bicyclo[2.1.1]hexan-2-one as a new probe for the study of π-facial selectivity in nucleophilic additions. A comment

Veejendra K. Yadav,* K. Ganesh Babu and R. Balamurugan

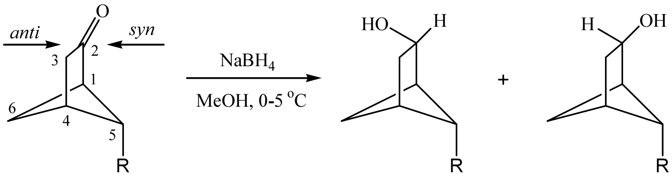
Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

Received 8 June 2003; revised 20 June 2003; accepted 3 July 2003

Abstract—The cation complexation model performs better than the hydride model and is at par with the transition state model at the HF/6-31G* and B3LYP/6-31G* levels. Electrostatic effects that rely on the residual charges on C5 and C6 of the title substrate and that are believed to contribute to the overall performance of the hydride model also perform poorly.

Mehta et al. have recently introduced 5-substituted bicyclo[2.1.1]hexan-2-ones **1** as a new probe for the experimental and computational study of electronic effects in π-facial selectivity in nucleophilic additions.[1] While the transition state model[2] failed to treat correctly the CO_2Me- and CCH-substrates, the hydride model[3] failed for the CCH-substrate at the MNDO level. The charge model[3] performed the poorest at this level as it incorrectly treated the CN-, CO_2Me- and CCH-substrates. While both the hydride model and the transition state model succeeded in predicting the experimental selectivity of all the substrates at the AM1 level; the charge model still failed for the CCH-substrate. Further, whereas the hydride model failed only for the CCH-substrate at the MNDO level, it failed for both the CO_2Me- and the CCH-substrates at the B3LYP/6-31G*, HF/6-31G* and MP2/6-31G* levels. The hydride model, therefore, is heavily dependent on the level of theory used in its application and, hence, unreliable for a confident treatment of π-selectivity. The transition state model, on the other hand, performed consistently at ab initio levels such as HF and MP and at B3LYP. However, it failed to treat correctly the $CHCH_2$-substrate.

The authors indicated that the cation complexation model[4] predicted *syn* attack for the CN-substrate and *anti* for all the others. In other words, the model incorrectly treated the CO_2Me- and CCH-substrates. This appeared surprising to us because this model has performed very well in our hands for numerous substrates that we have investigated. We therefore chose to reinvestigate the above substrates.



1a	R = CN	**2a**	75%	**3a**	25%
b	R = CO_2Me	**b**	66%	**b**	34%
c	R = CCH	**c**	60%	**c**	40%
d	R = CH_2OH	**d**	48%	**d**	52%
e	R = CH_2CH_3	**e**	47%	**e**	53%
f	R = $CH{=}CH_2$	**f**	44%	**f**	56%

To predict the π-selectivity of a substrate that contains a carbonyl function other than the carbonyl whose selectivity is to be measured, it is only logical to consider cation complexation of both as both will have similar residual charges. This amounts to considering cation complexation of both the ketone and the ester in **1b**. The natural charges on the oxygen atoms of these carbonyl functions are –0.6167 and –0.6960. The strategic dihedral angles are collected in Table 1. The dihedral angle changes predict *syn* selectivity for the CN- and CO_2Me-substrates and *anti* selectivity for the CH_2OH-, CH_2CH_3- and $CHCH_2$-substrates at both the HF/6-31G* and B3LYP/6-31G* levels.[5] The method, however, fails for the CCH-substrate for which it predicts *anti* selectivity. This performance is at par with that of the transition state model that fails for the

---

* Corresponding author. Fax: Int. code-91-512-2597436; e-mail: vijendra@iitk.ac.in

doi:10.1016/S0040-4039(03)01681-2

Table 1. The dihedral angles that estimate carbonyl pyramidalization on protonation

1, R =	HF/6-31G*		B3LYP/6-31G*	
	D1[a]	D2[a]	D1[a]	D2[a]
CN	139.3(136.4)	134.6(135.7)	138.0(136.1)	136.7(136.1)
CO_2Me	137.3(136.4)	136.9(135.9)	133.5(135.9)	141.5(136.3)
CO_2Me	141.7(136.4)[b]	131.7(135.9)[b]	142.8(135.9)[b]	130.8(136.3)[b]
CCH	136.8(136.1)	137.3(136.0)	132.0(135.7)	143.3(136.6)
CH_2OH	135.8(135.9)	138.0(135.9)	135.0(135.8)	139.4(136.1)
CH_2CH_3	133.8(135.4)	140.0(136.3)	131.0(135.2)	143.9(136.8)
$CHCH_2$	132.9(135.4)	141.2(136.3)	127.2(134.8)	148.5(137.1)

Values in parentheses correspond to the neutral reactant.

[a] D1 and D2 are dihedral angles O-C2-C1-C5 and O-C2-C1-C6, respectively.

[b] The ketone and the ester were both protonated.

$CHCH_2$-substrate but is superior to the hydride model that fails not only for the CCH-substrate but also for the CO_2Me-substrate at the same level of theory.

The above concept of dual cation complexation has other ramifications as well. The reaction conditions, particularly the solvent, will be expected to control the level of the selectivity of a given substrate with a given nucleophile. A non-coordinating solvent will be expected to promote effectively the multi-level cation complexation which will otherwise be compromised in a coordinating solvent. The coordinating solvents may also exert their effects by raising the effective size of the cation through solvation. These aspects are currently being explored in our group and the preliminary results are indeed encouraging. Obviously, the cation complexation of an ethereal or an alcoholic oxygen in a substrate cannot be considered if the reaction is carried out in oxygenated solvents such as THF and methanol.

Table 2. The NBO σ–$\pi^*_{C=O}$ interaction energies[7] (kcal/mol)[a] at B3LYP/6-31G* level

1, R =	$(\sigma_{C1–C5}/\sigma_{C3–H}/\sigma_{C5–H})$-$\pi^*_{C=O}$	$(\sigma_{C1–C6}/\sigma_{C3–H}/\sigma_{C6–H})$-$\pi^*_{C=O}$
CN	4.71+3.71+0.54 = 8.96	4.43+3.75+0.00 = 8.18
CO_2Me	4.93+3.70+0.63 = 9.26	4.46+3.71+0.00 = 8.17
CCH	4.99+3.72+0.58 = 9.29	4.53+3.71+0.00 = 8.24
CH_2OH	4.74+3.69+0.67 = 9.10	4.80+3.73+0.52 = 9.05
CH_2CH_3	4.88+3.69+0.68 = 9.25	4.78+3.64+0.00 = 8.42
$CHCH_2$	5.19+3.73+0.67 = 9.53	4.51+3.64+0.00 = 8.15

[a] A value of 0.00 kcal/mol indicates that the value is below the threshold level of 0.50 kcal/mol.

Table 3. The natural charges on C5/C6 of **1a**–**f** at B3LYP/6-31G* level

1, R =	Charge at C5	Charge at C6
CN	−0.36160	−0.45430
CO_2Me	−0.35079	−0.45289
CCH	−0.31560	−0.45349
CH_2OH	−0.27062	−0.45252
CH_2CH_3	−0.24412	−0.45088
$CHCH_2$	−0.27014	−0.45388

The authors have considered electron donation from only $\sigma_{C1–C5}$ and $\sigma_{C1–C6}$ to $\pi^*_{C=O}$ to assess the Cieplak selectivity[6] of **1**. Truly speaking, the through-space electron donations of all the strategic bonds to $\pi^*_{C=O}$ that support *anti* selectivity must be weighted against the combination of all those such electron donations that favor *syn* selectivity. In **1**, the electron donations from $\sigma_{C1–C5}$, one of the two $\sigma_{C3–H}$ and $\sigma_{C5–H}$ to $\pi^*_{C=O}$ will support *anti* selectivity while the electron donations from $\sigma_{C1–C6}$, one of the two $\sigma_{C3–H}$ and $\sigma_{C6–H}$ to $\pi^*_{C=O}$ will support *syn* selectivity; there is no electron donation from $\sigma_{C4–C5}$ and $\sigma_{C4–C6}$ to $\pi^*_{C=O}$. These electron donation energies are collected in Table 2. A comparison of the electron donation energies of only $\sigma_{C1–C5}$ and $\sigma_{C1–C6}$ to $\pi^*_{C=O}$ predicts *anti* selectivity for all but the CH_2OH-substrate; it predicts *syn* selectivity for the CH_2OH-substrate (cf. $\sigma_{C1–C5}$-$\pi^*_{C=O} = 4.74$ kcal/mol versus $\sigma_{C1–C6}$-$\pi^*_{C=O} = 4.80$ kcal/mol). The other interactions taken together with $\sigma_{C1–C5}$-$\pi^*_{C=O}$ and $\sigma_{C1–C6}$-$\pi^*_{C=O}$ favor *anti* selectivity throughout. The Cieplak model, therefore, incorrectly treats the CN-, CO_2Me- and CCH-substrates that also supports the authors' observations.

Finally, the hydride model is said to take into account electrostatic and orbital effects. The electrostatic effects will consider the charges on C5 and C6 and favor the approach of a nucleophile from the side that bears less negative charge. These charges in **1a**–**f** are collected in Table 3. It is immediately obvious that C5 is always less negatively charged than C6 and, thus, the approach of a nucleophile *syn* to C5 must be observed throughout. This is against the experimental findings of the authors. The electrostatic effects too, therefore, perform poorly.

In summary, the cation complexation model for the π-selection of **1a**–**f** performs as well as the transition state model. Whereas the transition state model treats correctly all but the $CHCH_2$-substrate at the HF/6-31G* and B3LYP/6-31G* levels, the cation complexation model treats correctly all but the CCH-substrate. In comparison, the hydride model fails for the CO_2Me- and CCH-substrates. The hydride model is deemed to have components of both the electrostatic and orbital effects. The electrostatic effect alone, however, fails miserably as it predicts uniformly *anti* selectivity for all the substrates. The failure of the cation complexation model for the CCH-substrate is not understood at present. It is heartening to note that the cation complexation model was successfully applied to selected 3-substituted tricyclo[2.1.0.0^{2,5}]pentan-3-ones; another probe that Mehta et al. have introduced recently for the investigation of π-selectivity.[8]

Acknowledgements

The authors thank the Department of Science & Technology, Government of India, for support of the research.

References

1. Mehta, G.; Singh, S. R.; Gagliardini, V.; Priyakumar, U. D.; Sastry, G. N. *Tetrahedron Lett*. **2001**, *42*, 8527.
2. Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc*. **1992**, *114*, 10638.
3. Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *J. Org. Chem*. **1993**, *58*, 1734.
4. (a) Jeyaraj, D. A.; Yadav, A.; Yadav, V. K. *Tetrahedron Lett*. **1997**, *38*, 4483; (b) Jeyaraj, D. A.; Yadav, V. K. *Tetrahedron Lett*. **1997**, *38*, 6095; (c) Yadav, V. K.; Jeyaraj, D. A. *J. Org. Chem*. **1998**, *63*, 3474; (d) Yadav, V. K.; Senthil, G.; Jeyaraj, D. A. *Tetrahedron* **1999**, *55*, 14211; (e) Yadav, V. K.; Jeyaraj, D. A.; Balamurugan, R. *Tetrahedron* **2000**, *56*, 7581; (f) Yadav, V. K.; Balamurugan, R. *J. Chem. Soc*., *Perkin Trans. 2* **2001**, 1; (g) Yadav, V. K. *J. Org. Chem*. **2001**, *66*, 2501; (h) Yadav, V. K.; Sriramurthy, V. *Tetrahedron* **2001**, *57*, 3987; (i) Yadav, V. K.; Balamurugan, R. *J. Org. Chem*. **2002**, *67*, 587.
5. All the geometry optimizations and calculations of NBO charges were performed using the program Gaussian 94, Revisiob C.2. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Jones, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A., Gaussian, Inc., Pittsburgh, PA, 1995.
6. (a) Cieplak, A. S. *J. Am. Chem. Soc*. **1981**, *103*, 4540; (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc*. **1989**, *111*, 8447.
7. The through-space interactions were calculated from second-order perturbation theory analysis of the Fock matrix in NBO basis using program NBO 3.1. Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *QCPE Bull*. **1990**, *10*, 58; Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev*. **1988**, *88*, 8899.
8. Mehta, G.; Singh, S. R.; Priyakumar, U. D.; Sastry, G. N. *Tetrahedron Lett*. **2003**, *44*, 3101.