ResearchGate

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/268685112

Boyd Group Electronegativity Influence on the Parr Global Electrophilicity of Vilsmeier Reagent-Derived Imidates: New Insights toward Improving Mitsunobu Chemistry

ARTICLE *in* HELVETICA CHIMICA ACTA · APRIL 2015

Impact Factor: 1.14 · DOI: 10.1002/hlca.201400340

READS

16

3 AUTHORS:

Jeremy M Carr

Central Alabama Community College

12 PUBLICATIONS **5** CITATIONS

SEE PROFILE

Gregory S Tschumper

University of Mississippi

88 PUBLICATIONS **2,619** CITATIONS

SEE PROFILE

Paige Lathem

Washington State University

6 PUBLICATIONS **2** CITATIONS

SEE PROFILE

Available from: Jeremy M Carr

Retrieved on: 27 January 2016

Boyd Group Electronegativity Influence on the *Parr* Global Electrophilicity of *Vilsmeier* Reagent-Derived Imidates: New Insights toward Improving *Mitsunobu* Chemistry

by **Jeremy M. Carr***[a]), **Gregory S. Tschumper**[b]), and **A. Paige Lathem**[a])

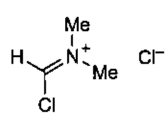
[a]) Huntingdon College, Department of Chemistry & Biochemistry, 1500 East Fairview Avenue, Montgomery, AL 36106, USA

[b]) University of Mississippi, Department of Chemistry & Biochemistry, University, MS 38677-1848, USA

Reactivities of 19 methylated imidate analogs were examined using B3LYP and M06-2X DFT methods. The resulting HOMO and LUMO energies of each optimized structure were used to calculate corresponding *Parr* global electrophilicity (ω) values. When the resulting quantities were compared against *Boyd* group electronegativity (X_G) values, a clear correlation was observed, suggesting that electron-withdrawing effects influence the reactivity of imidates. These findings represent an important first step in developing a novel method toward improving traditional *Mitsunobu* functionalization reactions.

Introduction. – The utility of (chloromethylidene)dimethyliminium chloride (**1**; *Fig. 1*), commonly known as *Vilsmeier*'s reagent (VR), has been demonstrated in the preparation of a variety of functional groups from precursor alcohols [1–6]. Although less hazardous and more atom-economical than traditional *Mitsunobu* reaction conditions [1][7], the reactivity of **1** and its corresponding intermediates has received relatively little attention [8][9]. Herein, we communicate the findings from our theoretical investigation of the reactivity of VR (**1**)-derived intermediates. We contend that the results from this study serve as a first important step toward developing a novel, relatively benign, and high-yielding alternative to traditional *Mitsunobu* conditions.

VR (**1**) is often prepared *in situ* by reacting dimethylformamide (DMF; **2**) and oxalyl chloride (**3**) [2][10][11], a process that generates both CO_2 and CO as by-products (*Scheme 1*). The introduction of an alcohol **4** to a solution of VR (**1**) results in the formation of an imidate **5**, an analog of the characteristic phosphonium intermediate featured in the *Mitsunobu* reaction (*Scheme 2*). In the presence of a nucleophile **6**, nucleophilic attack occurs at the electrophilic C-atom providing the desired product **7** while displacing **2** as the leaving group and lone by-product. Given these mechanistic details, we were intrigued to study how substituents might influence the reactivity of **5** and corresponding analogs.

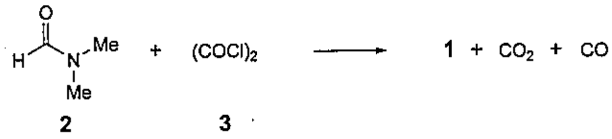


1

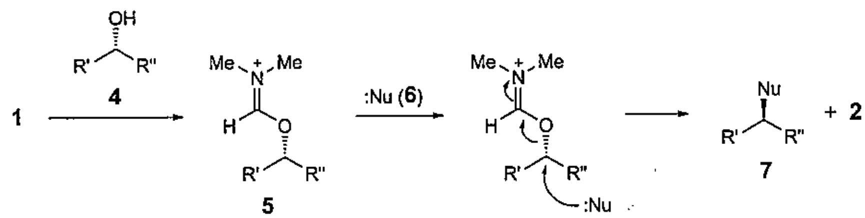
Fig. 1. *(Chloromethylidene)dimethyliminium chloride* (**1**), *commonly known as* Vilsmeier*'s reagent*

© 2015 Verlag Helvetica Chimica Acta AG, Zürich

Scheme 1. *Preparation of VR* **1** *from DMF* (**2**)



Scheme 2. *Reaction of VR* **1** *with an Alcohol* **4** *Provides Imidate Intermediate* **5**. Nucleophilic attack provides the S_N2 product and stoichiometric quantities of **2**.



Parr's global electrophilicity index (ω) [12] is a convenient metric for quantifying the relative reactivities of molecular analogs [13–17]. *Elango et al.* defined ω as the measure of a molecule's stabilization energy when it acquires additional electronic charge from the environment [18]. As seen in *Eqn. 1*, ω for a given molecule is related to the species' global chemical potential (μ) and chemical hardness (η). Thus, good electrophiles generally possesses large μ and small η values [16].

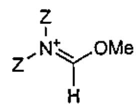
$$\omega \equiv \frac{\mu^2}{2\eta} \tag{1}$$

By applying *Koopmans*' theorem to *Parr*'s global electrophilicity, the computed highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies for a given molecule can be used to obtain values for μ and η (*Eqns. 2* and *3*). Although it is not without its limitations, this approximation has been successfully used to identify electronic relationships in families of closely related molecules [19] and even commonly utilized functional groups [20].

$$\mu \approx \frac{(E_{\mathrm{LUMO}} + E_{\mathrm{HOMO}})}{2} \tag{2}$$

$$\eta \approx E_{\mathrm{LUMO}} - E_{\mathrm{HOMO}} \tag{3}$$

Our investigations aimed to examine how local substituent effects might influence the global reactivity (*i.e.*, ω) of methylated imidate analogs **8** – VR (**1**)-derived intermediates. To do so, we examined 19 structurally related compounds with varying substituents Z (*Fig. 2*) at the iminium N-atom. Each substituent was C-atom-based and identified by the corresponding *Boyd* group electronegativity value (X_G) [21], which, as compiled in *Table 1*, served as the independent variable for this study. Substituents



8

Fig. 2. *The parent methylated imidate structure examined in this study.* The symbol Z represents various substituents that were compared in this study. Note that each analog is formally cationic.

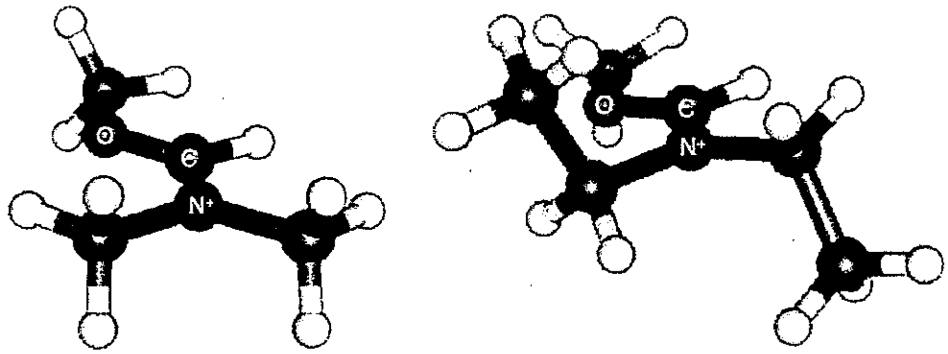
Table 1. *Computed HOMO and LUMO Values, and Corresponding Chemical Potential* (μ), *Chemical Hardness* (η), *and* Parr *Global Electrophilicity* (ω) *Values for Each Imidate Analog Using M06-2X/6-31G(d,p).* All computed and calculated are reported in Hartrees [E_h]. *Boyd* group electronegativity values (X_G) are reported in terms of their location on the *Pauling* electronegativity scale. Note that all structures are formally cationic.

Z	Compound	HOMO [E_h]	LUMO [E_h]	Chemical potential [E_h]	Chemical hardness [E_h]	Global electrophilicity [E_h]	X_G
Me	**8a**	–0.52817	–0.16718	–0.34768	0.36099	0.16743	2.55
Et	**8b**	–0.51386	–0.15988	–0.33687	0.35398	0.16029	2.55
^{i}Pr	**8c**	–0.50294	–0.15432	–0.32863	0.34862	0.15489	2.55
^{t}Bu	**8d**	–0.49635	–0.14468	–0.32052	0.35167	0.14606	2.55
Me_3CCH_2	**8e**	–0.48129	–0.15211	–0.31670	0.32918	0.15235	2.55
$CH_2{=}CCH_2$	**8f**	–0.46014	–0.15690	–0.30852	0.30324	0.15695	2.55
$CH{\equiv}CCH_2$	**8g**	–0.46314	–0.16667	–0.31491	0.29647	0.16724	2.58
Ph	**8h**	–0.42122	–0.16464	–0.29293	0.25658	0.16721	2.58
$CH_2{=}CH$	**8i**	–0.46890	–0.18476	–0.32683	0.28414	0.18797	2.58
FCH_2	**8j**	–0.56326	–0.19269	–0.37798	0.37057	0.19276	2.60
$ClCH_2$	**8k**	–0.51841	–0.19779	–0.35810	0.32062	0.19998	2.61
NO_2CH_2	**8l**	–0.52918	–0.21389	–0.37154	0.31529	0.21891	2.62
F_2CH	**8m**	–0.58357	–0.20911	–0.39634	0.37446	0.20975	2.65
$CH{\equiv}C$	**8n**	–0.47946	–0.21402	–0.34674	0.26544	0.22647	2.66
Cl_2CH	**8o**	–0.51953	–0.20776	–0.36365	0.31177	0.21208	2.66
ClFCH	**8p**	–0.53520	–0.20935	–0.37228	0.32585	0.21266	2.66
Cl_3C	**8q**	–0.51044	–0.20616	–0.35830	0.30428	0.21096	2.70
ClF_2C	**8r**	–0.55111	–0.21579	–0.38345	0.33532	0.21924	2.71
F_3C	**8s**	–0.59923	–0.22118	–0.41021	0.37805	0.22255	2.71

that could participate in other stabilizing effects (*e.g.*, resonance) were generally not considered in this initial investigation. HOMO and LUMO energies of each molecule were computed using popular DFT methods, values of which were used to calculate the corresponding *Boyd* global electropilicity (ω) values.

We initially expected that *Parr* global electrophilicity values should relate to electronegativity, since ω is proportional to the global electronegativity of the molecule ($-\mu$). Fortunately, the influence of local substituent effects on global reactivities remains apparently void in the literature. The results from these studies would ultimately allow us to identify key intermediates that might be utilized in developing novel alternatives to traditional *Mitsunobu* methods.

Results and Discussion. – *Fig. 3* shows the optimized structures of **8a** and **8b**, respectively. Note that the N-, O-, and three C-atoms associated with the imidate ester moiety are essentially coplanar, even though they were not constrained to be so. This



8a **8b**

Fig. 3. *Optimized structures for dimethyl- and diethyl-substituted imidates,* **8a** *and* **8b**, *respectively.* Note that both structures are formally cationic.

structural feature is shared by all of the minima identified in this work and is entirely consistent with the expectation that resonance plays a role in the stabilization of these cationic species [9].

Table 1 compiles the computed HOMO and LUMO energies for each DFT-optimized structure, *via* the M06-2X/6-31G(d,p) method, calculated values for μ, η, ω, and the corresponding *Boyd* group electronegativity value (X_G) for each substituent [21]. Generally, the aliphatic-substituted imidates exhibited the lowest reactivities. By comparison, the halomethyl-substituted imidates exhibited relatively high global electrophilicity values. As expected, calculated ω values appeared to increase with an increase in electronegative atoms. Specifically, in comparing ω values for **8a**, **8j**, **8m**, and **8s**, calculated reactivity increased with increasing number of F-atoms. Similar trends are observed for the chloromethyl-substituted structures.

As seen in *Table 2*, all DFT-calculated ω quantities correlated with *Boyd* group electronegativity values (X_G), indicating a linear trend. Although this relationship was apparent for every level of theory employed, the strongest correlation was obtained with the M06-2X/6-31G HOMO and LUMO energies ($r = 0.908$); B3LYP/6-31G(d,p), and B3LYP/6-311G(2df,2pd) had slightly lower correlations. When the *Parr* global electrophilicities, obtained from computed M06-2X/6-31G(d,p) HOMO and LUMO energies, were plotted *vs.* X_G values, a clear linear trend was observed (*Fig. 4*). While not the aim of this communication, variations in the data points relative to the trend line suggest that additional substituent effects might be influencing the reactivity of these molecules. These minor variations remain the focus of future studies.

Conclusions. – Our results confirm that group electronegativity – a local quantity – correlates with the global reactivity of imidates. Given these findings, we hypothesize that 'electronegative' groups pull electron density from the already deficient iminum N-atom, which, in turn, augments the electrophilic nature of the imidate intermediate. Given that VR (**1**)-mediated functionalization reactions are typically limited by modest yields, our results suggest that substituent effects may possibly enhance the reactivity of

Table 2. *Comparison of* Parr *Electrophilicity Values* [E_h] *and Their Correlation with* Boyd *Values* (X_G) *for Three Computational Methods*. Note that all structures are formally cationic.

Z		X_G	Calculated ω values [E_h] by computational method		
			B3LYP/6-31G(d,p)	B3LYP/6-311G(2df,2pd)	M06-2X/6-31G(d,p)
Me	**8a**	2.55	0.22701	0.23196	0.16742
Et	**8b**	2.55	0.21799	0.22317	0.16029
^{i}Pr	**8c**	2.55	0.20547	0.21059	0.15489
^{t}Bu	**8d**	2.55	0.19516	0.20029	0.14606
Me_3CCH_2	**8e**	2.55	0.20955	0.21523	0.15235
$CH_2{=}CCH_2$	**8f**	2.55	0.22784	0.23267	0.15695
$CH{\equiv}CCH_2$	**8g**	2.58	0.24787	0.25240	0.16724
Ph	**8h**	2.58	0.24879	0.25450	0.16721
$CH_2{=}CH$	**8i**	2.58	0.27406	0.27836	0.18797
FCH_2	**8j**	2.6	0.26531	0.27189	0.19276
$ClCH_2$	**8k**	2.61	0.29086	0.29280	0.19998
NO_2CH_2	**8l**	2.62	0.32606	0.32726	0.21891
F_2CH	**8m**	2.65	0.28531	0.29095	0.20975
$CH{\equiv}C$	**8n**	2.66	0.34396	0.35143	0.22647
Cl_2CH	**8o**	2.66	0.30958	0.30998	0.21208
ClFCH	**8p**	2.66	0.30586	0.30845	0.21266
Cl_3C	**8q**	2.7	0.30639	0.30613	0.21096
ClF_2C	**8r**	2.71	0.30963	0.31214	0.21924
F_3C	**8s**	2.71	0.29987	0.30491	0.22254
Correlation with X_G			0.84985	0.84548	0.90797

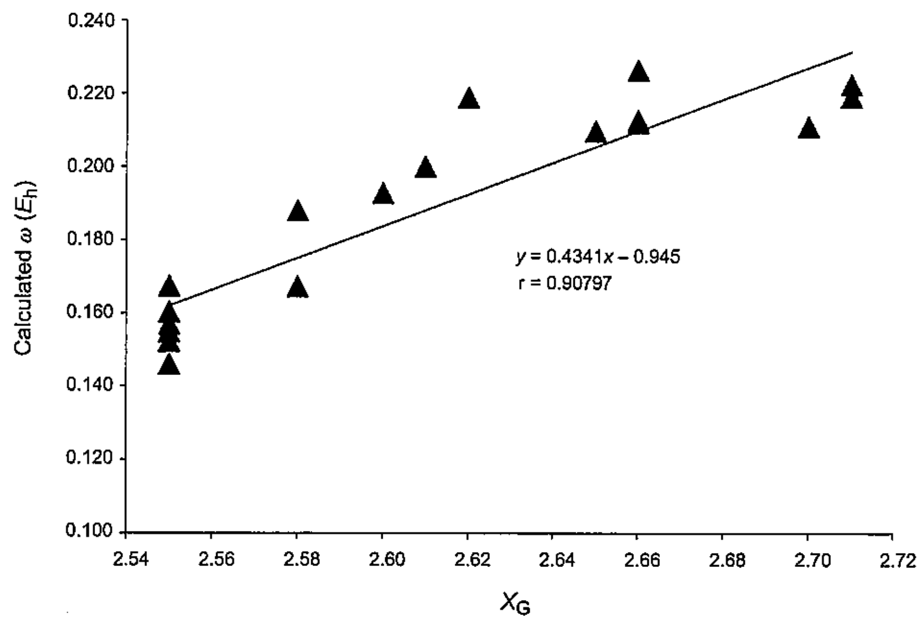


Fig. 4. *Plot of* Parr *global electrophilicity* (ω) *values for cationic, methylated imidates* **8a**–**8s**, *calculated using the M06-2X-6-31G(d,p) method,* vs. *corresponding* Boyd *group electronegativity values*

imidate intermediate, leading to improved product outcomes. Collectively, these findings represent an important first step in developing a novel alternative to traditional *Mitsunobu* methods.

This work was supported by the *National Science Foundation* under Grant No. EPS 1430364.

Experimental Part

Preliminary conformational searches for each substrate were performed with the universal force field (UFF). Two popular implementations of density-functional theory (DFT) were then used to fully optimize the lowest-energy conformations, and determine the HOMO and LUMO energies. The B3LYP [22][23] and M06-2X [24] functionals were employed for these computations, along with the 6-31G(d,p) [25][26] double-zeta and 6-311G(2df,2pd) [27][28] triple-zeta split valence basis sets. The DFT optimizations were unconstrained, and harmonic vibrational frequencies were computed to confirm that each optimized structure corresponds to a minimum on the potential-energy surface. Although exhaustive conformational searches were not performed with the DFT methods, the optimized structures identified here are representative of the low-energy conformations available to these species. All computations were performed with the *Gaussian 09* quantum-chemistry software package [29]. Default convergence criteria, numerical integration grids, *etc.*, were employed for the DFT computations.

REFERENCES

[1] P. A. Procopiou, A. C. Brodie, M. J. Deal, D. F. Hayman, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2249.
[2] H. Nagao, M. Michida, T. Mukaiyama, *Synth. Commun.* **2008**, *38*, 3208.
[3] M. Rao, M. Yang, D. Kuehner, J. Grosso, R. P. Deshpande, *Org. Process Res. Devel.* **2003**, *7*, 547.
[4] R. R. Amaresh, P. T. Perumal, *Synth. Commun.* **2000**, *30*, 2269.
[5] A. G. M. Barrett, N. Koike, P. A. Procopiou, *J. Chem. Soc., Chem. Commun.* **1995**, 1403.
[6] H. Affandi, A. V. Bayquen, R. W. Read, *Tetrahedron Lett.* **1994**, *35*, 2729.
[7] A. S. Thompson, G. R. Humphrey, A. M. DeMarco, D. J. Mathre, E. J. J. Grabowski, *J. Org. Chem.* **1993**, *58*, 5886.
[8] X. Zheng, W. A. Tao, R. G. Cooks, *J. Am. Soc. Mass Spectrom.* **2001**, *12*, 948.
[9] Y. Loidreau, S. Melissen, V. Levacher, C. Loge, J. Graton, J.-Y. Le Questel, T. Besson, *Org. Biomol. Chem.* **2012**, *10*, 4916.
[10] M. Sellstedt, *Eur. J. Org. Chem.* **2010**, 6171.
[11] A. Jarrahpour, M. Zarei, *Tetrahedron* **2009**, *65*, 2927.
[12] R. G. Parr, L. Szentpály, S. Liu, *J. Am. Chem. Soc.* **1999**, *121*, 1922.
[13] D. Nalbantova, D. Cheshmedzhieva, B. Hadjieva, S. Ilieva, B. Galabov, *J. Phys. Org. Chem.* **2011**, *24*, 1166.
[14] P. R. Campodonico, R. Contreras, *Bioorg. Med. Chem.* **2008**, *16*, 3184.
[15] S. J. Enoch, M. T. D. Cronin, T. W. Shultz, J. C. Madden, *Chem. Res. Toxicol.* **2008**, *21*, 513.
[16] P. Perez, L. R. Domingo, M. J. Aurell, R. Contreras, *Tetrahedron* **2003**, *59*, 3117.
[17] L. R. Domingo, M. Arnó, R. Contreras, P. Pérez, *J. Phys. Chem. A* **2002**, *106*, 952.
[18] M. Elango, R. Parthasarathi, G. K. Narayanan, A. M. Sabeelullah, U. Sarkar, N. S. Venkatasubramaniyan, V. Subramanian, P. K. Chattaraj, *J. Chem. Sci.* **2005**, *117*, 61.
[19] Z. B. Maksić, R. Vianello, *J. Phys. Chem. A* **2002**, *106*, 6515.
[20] L. R. Domingo, P Pérez, R. Contreras, *J. Org. Chem.* **2003**, *68*, 6060.
[21] R. J. Boyd, S. L. Boyd, *J. Am. Chem. Soc.* **1992**, *114*, 1652.
[22] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.
[23] C. Lee, W. Yang, R. G. Parr, *Phys. Rev.* **1988**, *37*, 785.
[24] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.
[25] W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys. B* **1972**, *56*, 2257.
[26] P. C. Hariharan, J. A. Pople, *Theor. Chim. Acta* **1973**, *28*, 213.

[27] R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, *J. Chem. Phys.* **1980**, *72*, 650.
[28] M. J. Frisch, J. A. Pople, J. S. Binkley, *J. Chem. Phys.* **1984**, *80*, 3265.
[29] Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, *Gaussian, Inc.*, Wallingford CT, 2009.

Received October 27, 2014