JOC*Article*

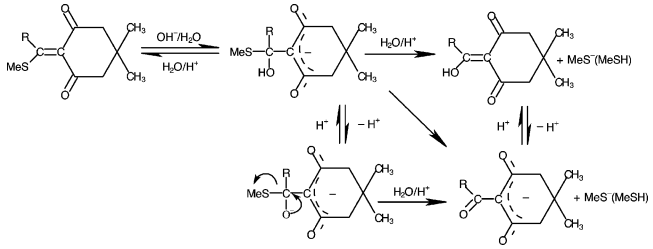
Hydrolysis of α-Alkyl-α-(methylthio)methylene Meldrum's Acids. A Kinetic and Computational Investigation of Steric Effects

Claude F. Bernasconi,*,† Shoshana D. Brown,† Mahammad Ali,†,‡ Zvi Rappoport,§ Hiroshi Yamataka,|| and Hatim Salim§

Department of Chemistry and Biochemistry of the University of California, Santa Cruz, California 95064, Department of Organic Chemistry, the Hebrew University of Jerusalem, Jerusalem 91904, Israel, and Department of Chemistry, Rikkyo University, Nishi-Ikebukuro, Toshima-ku, Tokyo 171-8501, Japan

bernasconi@chemistry.ucsc.edu

Received February 7, 2006



The rates of hydrolysis of α-*R*-α-(methylthio)methylene Meldrum's acids (**8-R** with R = H, Me, Et, *s*-Bu, and *t*-Bu) were determined in basic and acidic solution in 50% DMSO−50% water (v/v) at 20 °C. In basic solution (KOH), nucleophilic attack to form a tetrahedral intermediate (T_{OH}^-) is rate limiting for all substrates (k_1^{OH}). In acidic solution (HCl) and at intermediate pH values (acetate buffers), water attack ($k_1^{H_2O}$) is rate limiting for **8-Me**, **8-Et**, and **8-*s*-Bu**; the same is presumably the case for **8-*t*-Bu**, but rates were too slow for accurate measurements at low pH. For **8-H**, water attack is rate limiting at intermediate pH but at pH < 4.5 MeS^- departure from the tetrahedral intermediate becomes rate limiting. Our interpretation of these results is based on a reaction scheme that involves three pathways for the conversion of T_{OH}^- to products, two of which being unique to hydrolysis reactions and taking advantage of the acidic nature of the OH group in T_{OH}^-. This scheme provides an explanation why even at high [KOH] T_{OH}^- does not accumulate to detectable levels even though the equilibrium for OH^- addition to **8-R** is expected to favor T_{OH}^-, and why at low pH water attack is rate limiting for R = Me, Et, *s*-Bu, and *t*-Bu but leaving group departure becomes rate limiting with the sterically small R = H. The trend in the k_1^{OH} and $k_1^{H_2O}$ indicates increasing steric crowding at the transition state with increasing size of R, but this effect is partially offset by a sterically induced twisting of the C═C double bond in **8-R** which leads to its elongation and makes the substrate less stable and hence more reactive. Our computational results suggest that this effect becomes particularly pronounced for R = *t*-Bu and explains why k_1^{OH} for **8-*t*-Bu** is somewhat higher than for the less crowded **8-*s*-Bu.**

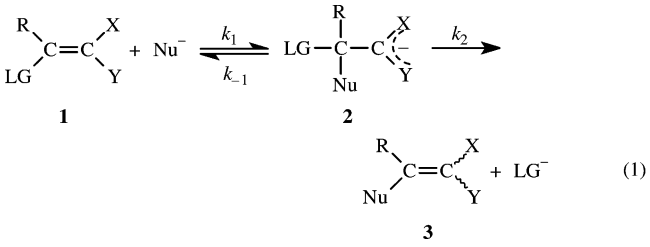
Introduction

The major features of the mechanism of nucleophilic vinylic substitutions (S_NV) on substrates activated by electron-withdrawing groups (X, Y), **1**, are quite well understood.[1] These reactions involve a minimum of two steps as exemplified by eq 1 for the case of an anionic nucleophile (Nu^-) expelling the anionic leaving group LG^- giving product **3**. A major advance in our general understanding of structure−reactivity relationships

† University of California.
‡ Present address: Department of Chemistry, Jadavpur University, Kolkata 700032, India.
§ The Hebrew University.
|| Rikkyo University.

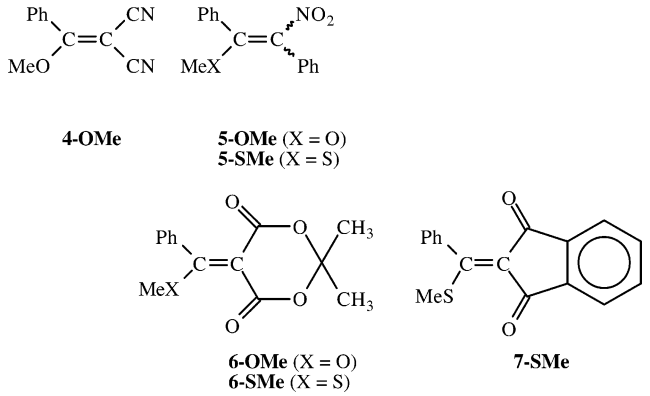
(1) For reviews, see: (a) Rappoport, Z. *Adv. Phys. Org. Chem.* **1969**, *7*, 1. (b) Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73. (c) Miller, S. I. *Tetrahedron* **1977**, *33*, 1211. (d) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7; **1992**, *25*, 474. (e) Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 309. (f) Shainyan, B. A. *Usp. Khim.* **1986**, *55*, 942.

10.1021/jo060254o CCC: $33.50
Published on Web 05/20/2006



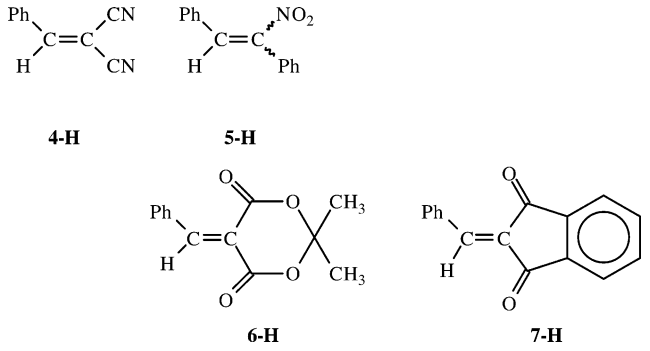
1 **2** **3** (1)

in these addition−elimination reactions has come from the study of systems where the intermediate **2** is directly observable, allowing a determination of the rate constants of each step, i.e., k_1, k_{-1}, and k_2.[2] Such systems require a combination of X,Y groups that are highly electron withdrawing, a strong nucleophile, and a poor leaving group. Examples include the reactions of thiolate and alkoxide ions with **4-OMe**,[2] **5-OMe**,[3,4] **5-SMe**,[3] **6-OMe**,[5,6] **6-SMe**,[7] **7-SMe**,[2] and others, as well as the reactions



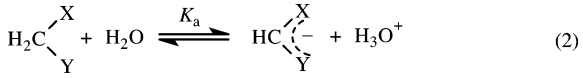
4-OMe **5-OMe** (X = O) **5-SMe** (X = S) **6-OMe** (X = O) **6-SMe** (X = S) **7-SMe**

of the same nucleophiles with the corresponding substrates lacking a leaving group (**4-H**,[2] **5-H**,[8] **6-H**,[9] **7-H**[2]).



4-H **5-H** **6-H** **7-H**

Some of the main conclusions that have emerged from these studies are as follows. (1) The equilibrium constants ($K_1 = k_1/k_{-1}$) for thiolate ion addition to **4-H**, **5-H**, **6-H**, and **7-H** and similar substrates lacking a leaving group show a linear correlation with the pK_a values of the corresponding carbon acids CH_2XY (eq 2); the slope of the correlation is -1.11 ± 0.05.[2]



(2)

Since the electronic factors that stabilize the conjugate base of CH_2XY (eq 2) are essentially the same as those that stabilize **2** (eq 1, LG = H), such a correlation is to be expected. On the other hand, the K_1 values for thiolate ion addition to a series of methoxy derivatives such as **4-OMe**, **5-OMe**, and **6-OMe** or a series of methylthio derivatives such as **5-SMe**, **6-SMe**, **7-SMe**, and others correlate poorly with the pK_a values of H_2CXY and are much lower than the K_1 values for the corresponding substrates without a methoxy or methylthio leaving group.[2] The reduction in the K_1 values and the breakdown of the correlation with the pK_a values of CH_2XY was attributed to a combination of steric and π-donor effects exerted by the leaving groups.[2] The former reduces K_1 due to increased crowding in the intermediate while the latter stabilizes the substrate, thereby decreasing its reactivity. The magnitude of the steric effect increases with the size of X, Y and is more pronounced with the more bulky methylthio derivatives while the π-donor effect is expected to increase with increasing electron withdrawing strength of X, Y and should be more important for the methoxy derivatives. These different responses to the steric and π-donor effects render a quantitative assessment of the relative contributions of these effects difficult although it was tentatively concluded that the steric effect is dominant.[2]

(2) There is very little correlation between the rate constants (k_1) and the equilibrium constants (K_1) for nucleophilic attack because the *intrinsic* rate constants[10] are strongly dependent on X, Y as well as on the nature of the leaving groups. For a given series of substrates such as **4-OMe**, **5-OMe**, and **6-OMe**, or **5-SMe**, **6-SMe**, and **7-SMe**, or **4-H**, **5-H**, **6-H**, and **7-H**, these intrinsic rate constants, k_o, correlate very well with the intrinsic rate constants for the deprotonation of CH_2XY by amine bases. Furthermore, for a given X,Y, $k_o(H) \gg k_o(OMe) \gg k_o(SMe)$. This order has been attributed to a combination of inductive, steric, and π-donor effects in the methoxy and methylthio derivatives. The π-donor resonance stabilization of the substrates is expected to lower k_o by following the common pattern of resonance effects which is to be disproportionately weak at the transition state.[11] This effect should lower k_o(OMe) more than k_o(SMe) since the methoxy group is a stronger π-donor than the thiomethyl group.[13,14] However, the fact that the observed

(2) Bernasconi, C. F.; Ketner, R. J.; Ragains, M. L.; Chen, X.; Rappoport, Z. *J. Am. Chem. Soc.* **2001**, *123*, 2155 and references cited therein.

(3) (a) Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 6861. (b) Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Rappoport, Z. *J. Am. Chem. Soc.* **1990**, *112*, 3169.

(4) (a) Bernasconi, C. F.; Schuck, D. F.; Ketner, R. J.; Weiss, M.; Rappoport, Z. *J. Am. Chem. Soc.* **1994**, *116*, 11764. (b) Bernasconi, C. F.; Schuck, D. F.; Ketner, R. J.; Eventova, I.; Rappoport, Z. *J. Am. Chem. Soc.* **1995**, *117*, 2719.

(5) Bernasconi, C. F.; Ketner, R. J.; Chen, X.; Rappoport, Z. *J. Am. Chem. Soc.* **1998**, *120*, 7461.

(6) Bernasconi, C. F.; Ketner, R. J.; Brown, S. D.; Chen, X.; Rappoport, Z. *J. Org. Chem.* **1999**, *64*, 8829.

(7) Bernasconi, C. F.; Ketner, R. J.; Chen, X.; Rappoport, Z. *Can. J. Chem.* **1999**, *77*, 58.

(8) Bernasconi, C. F.; Killion, R. B., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 7506.

(9) Bernasconi, C. F.; Ketner, R. J. *J. Org. Chem.* **1998**, *63*, 6266.

(10) For a reaction with a rate constant k_1 (barrier $\Delta G_1^{\ddagger}$) in the forward and k_{-1} ($\Delta G_{-1}^{\ddagger}$) in the reverse direction the intrinsic rate constant, k_o (intrinsic barrier $\Delta G_o^{\ddagger}$) is defined as $k_o = k_1 = k_{-1}$ ($\Delta G_o^{\ddagger} = \Delta G_1^{\ddagger} = \Delta G_{-1}^{\ddagger}$) where the equilibrium constant $K_1 = 1$ ($\Delta G_o = 0$).

(11) The lowering of k_o is a manifestation of the principle of nonperfect synchronization (PNS),[12] which states that a product-stabilizing factor whose development at the transition state lags behind bond changes, or a reactant-stabilizing factor that is lost ahead of bond changes, lowers k_o or enhances $\Delta G_o^{\ddagger}$.

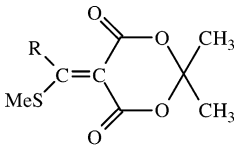
(12) (a) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301. (b) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9. (c) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119.

(13) $\sigma_R(OMe) = -0.43$, $\sigma_R(SMe) = -0.15$.[14]

(14) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

k_o(SMe) is lower than k_o(OMe) suggests that there is a reduction of k_o(SMe) relative to k_o(OMe) by a steric effect that more than offsets the π-donor effect. A reduction of k_o by a steric effect results when the development of the steric effect at the transition state is disproportionately advanced relative to bond formation;[15] the larger size of the MeS group thus should lead to a stronger reduction of k_o(SMe). A contributing factor to the enhanced k_o(OMe) over k_o(SMe) is the stronger electron-withdrawing inductive effect of the methoxy group. This is because inductive effects provide a disproportionate degree of transition state stabilization, which again is due to the lag in resonance development.

It is clear from the above discussion that steric effects are very important in S_NV reactions but there is an inherent difficulty in separating these effects from π-donor effects just based on comparison between reactions of methoxy and methylthio derivatives. It would be useful to study a reaction series where the steric factor could be modulated without, at the same time, introducing major electronic effects. The present paper reports an investigation of how steric effects affect the rates of hydrolysis of α-alkyl-α-(methylthio)methylene Meldrum's acids, **8-R**, with R = H, Me, Et, *s*-Bu, and *t*-Bu; numerous attempts to synthesize the isopropyl derivative were unsuccessful.



8-R

Electronic effects by these R-groups are expected to be small, and hence, any trend in the rates should be mainly a manifestation of steric factors. However, our kinetic data, in combination with some theoretical calculations, will show that there are other complications that make any interpretation of the results less than straightforward.

Results

Synthesis of 8-R. The substrates **8-R** (R = Me, Et, *s*-Bu, *t*-Bu) were prepared by the reaction of **8-SMe** with the respective Grignard reagents RMgBr. However, this reaction failed in trying to synthesize **8-*i*-Pr** and only yielded **8-H**.

Kinetic Studies. All rates were measured in 50% DMSO−50% water (v/v) at 20 °C. Pseudo-first-order conditions with the substrate as the minor component were used throughout. The reactions were followed spectrophotometrically by monitoring the disappearance of the substrate around 330 nm as well as by the appearance of the hydrolysis products around 260 nm. The rates were the same, within the experimental uncertainties, at both wavelengths, indicating a clean reaction without accumulating intermediates. The absence of an intermediate is also evident from the sharp isosbestic point shown in Figure 1 for a representative example.

Kinetic experiments were conducted in KOH and HCl solutions, in acetate buffers, and in some cases, in triethylamine and *N*-methylmorpholine buffers. The rates in KOH solutions and in triethylamine buffers were in the stopped-flow range

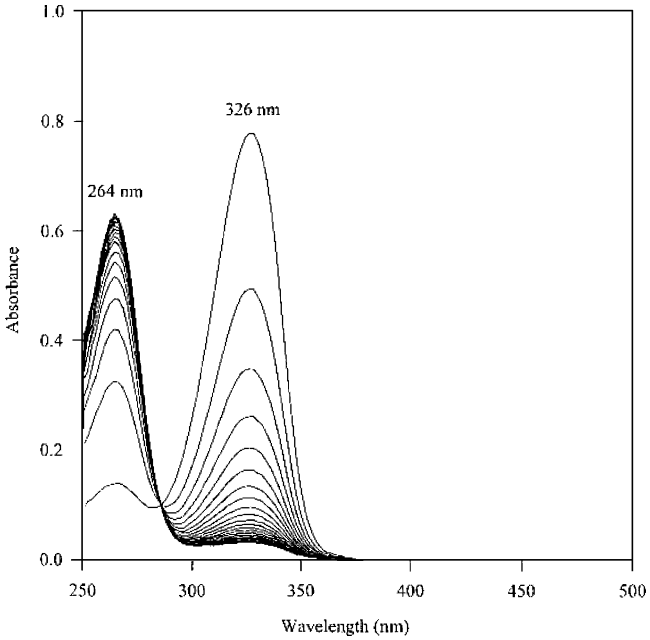
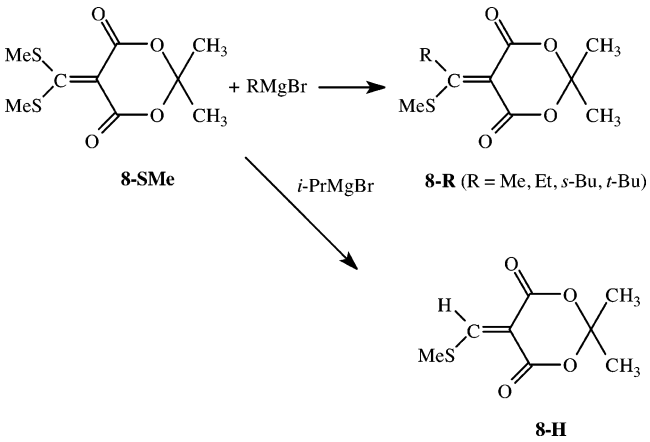


FIGURE 1. Time-resolved absorption spectra of the hydrolysis of **8-H** in a 10^{-4} M KOH solution.



while the rates in the more acidic solutions were measured by conventional spectrophotometry. The raw data are summarized in Tables S1−S14 of the Supporting Information.[16]

For all five substrates plots of k_{obsd}, the pseudo-first-order rate constants, versus [KOH] in the concentration range from 10^{-3} to 0.25 M were strictly linear, with intercepts that were indistinguishable from zero and hence followed eq 3; k_1^{OH} is assumed to refer to nucleophilic attack by OH^- (see Discussion).

$$k_{obsd} = k_1^{OH}[OH^-] \quad (3)$$

In HCl solutions ranging in concentrations from 10^{-4} to 10^{-2} M, the reactions of **8-Me**, **8-Et**, and **8-*s*-Bu** yielded pH-independent k_{obsd} values, eq 4, with $k_1^{H_2O}$ interpreted to represent nucleophilic attack by water (see Discussion). For **8-*t*-Bu**, the rates in HCl solution were too slow to yield a meaningful $k_1^{H_2O}$ value while for **8-H** there is a strong decrease in k_{obsd} with increasing [HCl]. This is shown in the pH−rate profile for this reaction (Figure 2).

(15) This is a manifestation of a corollary of the PNS[11] which states that a product-*de*stabilizing factor whose development is ahead of bond formation lowers k_o or increases $\Delta G_o^{\ddagger}$.

(16) See the paragraph concerning Supporting Information at the end of this paper.

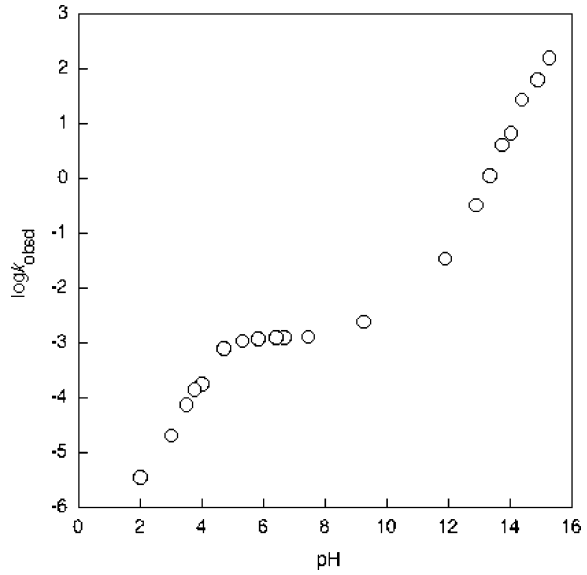


FIGURE 2. Rate−pH profile for the hydrolysis of **8-H**. Data obtained in HCl solutions (pH 2.00−4.00), acetate buffers (pH 4.72−7.49), a triethylamine buffer (pH 9.25), and KOH solutions (pH 11.89−15.28).

$$k_{obsd} = k_1^{H_2O} \quad (4)$$

For all substrates except **8-*t*-Bu** rates were also determined in acetate buffers in the pH range from 4.24 to 7.49 and for **8-*s*-Bu** also in chloroacetate buffers. For **8-Me**, **8-Et**, and **8-*s*-Bu**, the k_{obsd} values were the same as those obtained in HCl solutions; for **8-H** they were higher than in the HCl solution but pH-independent. These results indicate that general base catalysis of water addition by acetate ion is too weak to be observable at acetate ion concentrations as high as 0.1 M.

To examine whether more basic buffers would lead to detectable general base catalysis, the hydrolysis of **8-*s*-Bu** was studied in *N*-methylmorpholine (at pH 7.56) and triethylamine buffers (at pH 10.50). Figure 3 shows that there is indeed significant catalysis. The plots in Figure 3 fit eq 5; k_1^B is obtained as the slopes of the plots.

$$k_{obsd} = k_1^{H_2O} + k_1^{OH}[OH^-] + k_1^{B}[B^-] \quad (5)$$

Computational Studies. Additional insight was sought from B3LYP calculations of **8-H**, **8-Me**, **8-Et**, and **8-*t*-Bu** as well as their respective tetrahedral adducts (T_{OH}^-). Table 2 summarizes the enthalpies of the reaction of **8-R** (R = H, Me, Et, *t*-Bu) with OH^- to form the respective tetrahedral intermediate, the C═C bond lengths of the respective substrates, and some relevant angles in the reactants. Table S14 (Supporting Information) provides additional details, while Figures S1−S11 (Supporting Information) show the respective structures. The enthalpy calculations are based on the energies of the most stable conformation of each compound.

Discussion

Mechanism. The simplest mechanism for the OH^- promoted hydrolysis of **8-R** is that of eq 6. Note that the immediate product of MeS^- departure from T_{OH}^- is **9-R** but due to the high acidity of the OH group in **9-R** ($pK_a = 1.05$[5]) it is rapidly deprotonated to form **9-R**$^-$.

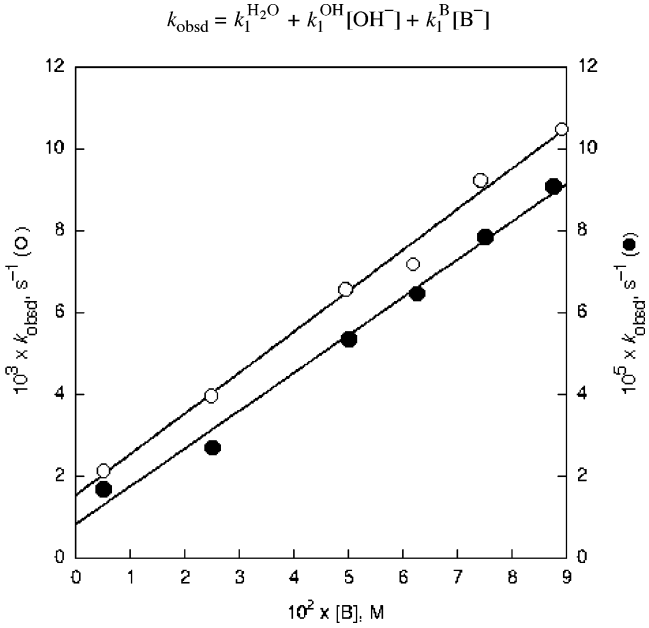
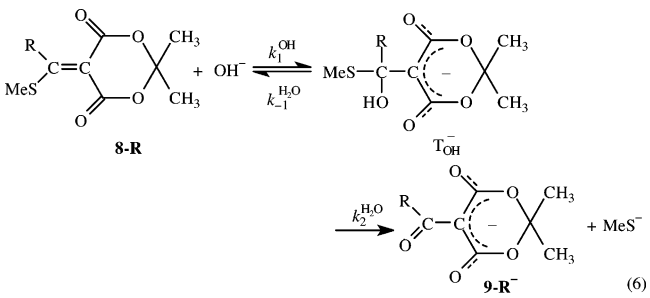
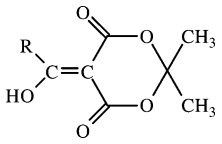


FIGURE 3. General base catalysis of the hydrolysis of **8-*s*-Bu**: ○, B = Et_3N, pH 10.50; ●, B = *N*-methylmorpholine, pH 7.56.

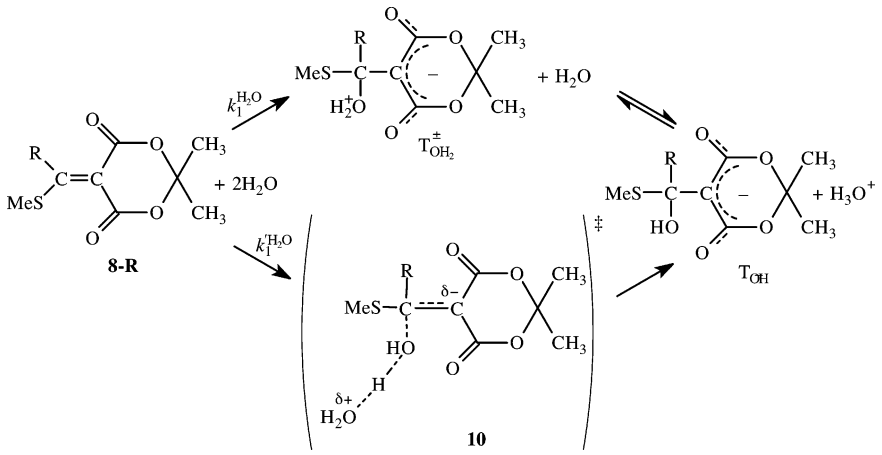




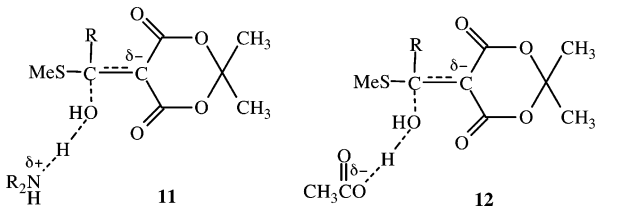
The presence of a sharp isosbestic point (Figure 1) and the fact that the rate of product formation equals the rate of substrate disappearance implies that T_{OH}^- is a nonaccumulating steady-state intermediate. Furthermore, since MeS^- is a much better leaving group than HO^-,[9] the relationship $k_2^{H_2O} \gg k_{-1}^{H_2O}$ must hold, and thus the k_1^{OH} step is rate limiting.

In acidic solution, it is reasonable to assume that $k_1^{H_2O}$ refers to rate-limiting nucleophilic attack by water. However, the results do not allow a distinction between a stepwise mechanism (upper pathway in Scheme 1) and a concerted mechanism where a second water molecule acts as base catalyst (lower pathway in Scheme 1). The observation of general base catalysis by triethylamine and *N*-methylmorpholine in the hydrolysis of **8-*s*-Bu** may be taken as suggestive evidence for the lower pathway because the amine catalysis is most plausibly interpreted in terms of a transition state (**11**) which is analogous to **10**. However,

SCHEME 1



we do not consider this as definite evidence for the lower pathway.



Another point of interest is that the catalysis by acetate ion was too weak for the determination of a meaningful rate constant. This suggests that the transition state of the acetate reaction (**12**) is destabilized and/or the transition state of the amine reactions is stabilized. Electrostatic repulsion of the negative charges in **12** could account for the former, electrostatic attraction between the opposite charges in **11** for the latter.

Why Is the Intermediate Undetectable? Without questioning the validity of the above interpretation as to what steps are rate limiting, the fact and reasons why the intermediate T_{OH}^- is not detectable need to be examined in more detail. The necessary conditions that would have to be met for T_{OH}^- to become detectable are that the equilibrium of the first step favors the intermediate (eq 7, $K_1^{OH} = k_1^{OH}/k_{-1}^{H_2O}$)

$$K_1^{OH}[OH^-] > 1 \qquad (7)$$

and that the formation of the intermediate is faster than its conversion to products (eq 8). In view of the exceptionally strong electron-withdrawing effect of the Meldrum's acid moiety in **8-R** it seems surprising that for reaction 6 these conditions are not being met at high [OH^-]. However, our findings are consistent with observations made earlier in the hydrolysis of **6-SMe**,[5,6] **6-OMe**,[5] as well as **4-OMe**,[2] **2-OMe**,[17] **5-SMe**,[17] and **7-SMe**[2] where the corresponding intermediates were not observable either. In each of these cases it could be shown that the reason for this state of affairs was not that the equilibrium constant K_1^{OH} was too small, but that the conversion of the intermediate to products was faster than expected based on reactions schemes such as eq 6.

$$k_1^{OH}[OH^-] > k_2^{H_2O} \qquad (8)$$

The faster than expected product formation has been attributed to the presence of two additional reaction pathways that are unique to the hydrolysis reaction and involve the OH group of the intermediate. It is likely that the same additional pathways apply in the hydrolysis of **8-R**; Scheme 2 shows the extended mechanism which not only includes the various pathways in basic solution but also those in neutral and acidic solution; for simplicity, pathways involving buffer species have been omitted. At high pH the pathway via T_O^{2-} is apparently faster than the $k_2^{H_2O}$ step ($(K_a^T k_3^{H_2O}/a_{H^+}) \gg k_2^{H_2O}$) because T_O^{2-} provides a strong electronic push for leaving group departure. Intramolecular acid catalysis of leaving group expulsion by the OH group in T_{OH}^- (k_2^i) may also contribute to the enhanced rate of product formation.

Steric Effects. A. Partitioning of the Intermediate. Steric effects not only affect k_1^{OH} and $k_1^{H_2O}$ but also influence the partitioning of T_{OH}^- between reactants and products. We address the latter issue first.

As mentioned earlier, since MeS^- is inherently a much better leaving group than OH^-,[9,18] it is reasonable to assume that $k_2^{H_2O} \gg k_{-1}^{H_2O}$. Two additional factors favor product formation over the reverse reaction. One is the larger size of the MeS^- relative to OH^- which leads to a steric acceleration of MeS^- departure over OH^- departure for bulky R-groups; the second one is the availability of the additional pathway through T_O^{2-} and the intramolecular step, i.e., product formation is described by $k_2^{H_2O} + k_2^i + K_a^T k_3^{H_2O}/a_{H^+}$; these latter pathways also benefit from bulky R groups.

In acidic solution, the situation is less clear but because hydronium ion catalyzed pathways become important. Alkoxide and hydroxide ion departure from similar tetrahedral complexes is known to be strongly acid catalyzed even at moderately acidic pH values[6] and hence the k_{-1}^H step dominates the return of T_{OH}^- to reactants. On the other hand, acid catalysis of thiolate ion departure is quite weak,[6] i.e., $k_2^H \ll k_{-1}^H$. Thus, for the conversion of T_{OH}^- to products to be faster than its return to

(17) Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Schuck, D. F.; Rappoport, Z. *J. Am. Chem. Soc.* **1991**, *113*, 4937.

(18) For a general discussion of nucleofugalities, see: Boyd, D. B. *J. Org. Chem.* **1985**, *50*, 885.

SCHEME 2

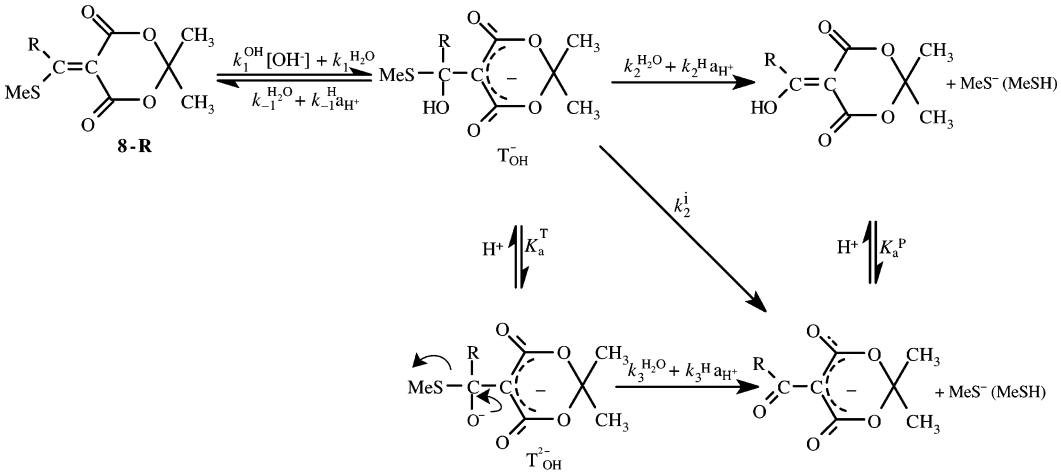


TABLE 1. Rate Constants for Nucleophilic Attack on 8-R by OH^- and Water in 50% DMSO−50% Water (v/v) at 20 °C

R	k_1^{OH} [a] (M^{-1} s^{-1})	$k_1^{H_2O}$ [a] (s^{-1})
H	667 ± 47	(1.30 ± 0.02) × 10^{-3}
Me	267 ± 6	(9.92 ± 0.07) × 10^{-6}
Et	10.9 ± 0.3	(1.02 ± 0.02) × 10^{-5}
s-Bu	3.27 ± 0.01[b]	(5.52 ± 0.03) × 10^{-6} [c]
t-Bu	8.67 ± 0.14	*d*
phenyl[e]	0.634	2.80 × 10^{-6}

[a] Average value from determinations at the wavelength of the substrate (around 330 nm) and product (around 260 nm). [b] At 334 nm. [c] k_1^{TEA} = (9.98 ± 0.45) × 10^{-2} M^{-1} s^{-1} (triethylamine catalysis); k_1^{NMM} = (9.78 ± 0.18) × 10^{-4} M^{-1} s^{-1} (*N*-methylmorpholine catalysis). [d] Too slow to measure. [e] Reference 7.

TABLE 2. Gas-Phase Reaction Enthalpies for the Reactions of 8-R with OH^-, C=C Bond Lengths of 8-R and Dihedral Angles

R	Δ*H* (kcal/mol)	$R_{C=C}$ (Å)	$D_{C-C=C-R}$[a] (deg)
H	−69.1	1.366	2.3
Me	−71.7	1.387	3.0
Et	−72.0	1.388	4.0
t-Bu	−77.0	1.405	31.3

[a] Dihedral angle defined by R−C=C−C(O) with R and C(O) in syn relationship.

reactants, so that $k_1^{H_2O}$ is rate limiting for the hydrolysis, eq 9 needs to hold.

$$k_2^{H_2O} + k_2^{i} + K_a^{T}k_3^{H} \gg k_{-1}a_{H^+} \qquad (9)$$

Our results suggest that eq 9 holds in the pH range covered by our experiments as long as there is enough steric acceleration of MeS^- departure to make it faster than the k_{-1}^{H} step. This is the case for R = Me, Et, *s*-Bu and *t*-Bu. For R = H the steric effect is too small which leads to a reversal of eq 9 to eq 10.

$$k_2^{H_2O} + k_2^{i} + K_a^{T}k_3^{H} < k_{-1}a_{H^+} \qquad (10)$$

This reversal manifests itself in the downward curvature of the rate pH-profile at pH < 5.8 shown in Figure 2, i.e., k_{obsd} is given by eq 11

$$k_{obsd} = \frac{k_1^{H_2O}(k_2^{H_2O} + k_2^{i} + K_a^{T}k_3^{H})}{k_{-1}^{H}a_{H^+} + k_2^{H_2O} + k_2^{i} + K_a^{T}k_3^{H}} \qquad (11)$$

which becomes eq 12 when $k_{-1}^{H}a_{H^+} \gg k_2^{H_2O} + k_2^{i} + K_a^{T}k_3^{H}$, with $K_1^{H_2O} = k_1^{H_2O}/k_{-1}^{H}$.

$$k_{obsd} = \frac{K_1^{H_2O}}{a_{H^+}}(k_2^{H_2O} + k_2^{i} + K_a^{T}k_3^{H}) \qquad (12)$$

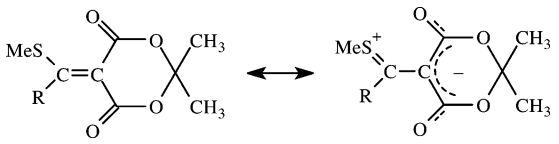
B. Steric Effects on k_1^{OH} and $k_1^{H_2O}$. The rate constants for OH^-- and water-promoted hydrolysis of **8-R** are summarized in Table 1. Previously reported results for **8-Ph** are also included. The reactivity order of the k_1^{OH} values is H > Me ≫ Et > *s*-Bu < *t*-Bu > Ph, while for $k_1^{H_2O}$ it is H ≫ Me ≈ Et > *s*-Bu > *t*-Bu < Ph. The fact that the reactivity orders for the two reactions are different suggests operation of opposing factors that may affect the reactants and/or the transition states to different degrees depending on the size of the R group. One obvious factor is steric crowding at the transition state which explains the general trend toward lower k_1^{OH} and $k_1^{H_2O}$ values as the size of R increases. As a general proposition, one might expect this factor to be more important for the transition state of the water reaction because, according to the Hammond−Leffler postulate,[19,20] C−O bond formation should be more advanced than in the thermodynamically more favorable reaction of hydroxide ion. Because of the complications from other factors our data cannot confirm this general proposition in an unambiguous way. We therefore sought some insights into these factors by performing B3LYP calculations on **8-H**, **8-Me**, **8-Et**, and **8-*t*-Bu** as well as the respective tetrahedral adducts (T_{OH}^-). Table 2 summarizes the enthalpies of the reaction of **8-R** (R = H, Me, Et, *t*-Bu) with OH^- to form the respective tetrahedral intermediates, the C=C bond lengths of the respective substrates, and relevant dihedral angles.

The enthalpies indicate that the reaction becomes more rather than less favorable as the size of R increases; the effect is particularly pronounced for R = *t*-Bu with ΔH being 5 kcal/mol more negative than for R = Et. This means that the effect of steric crowding seen in the trend of the rate constants is overshadowed by another factor. For **8-*t*-Bu** this factor appears to be a sterically induced twisting of the C=C double bond which elongates the C=C bond and makes the substrate less stable and hence more reactive. The relatively long C=C bond and the large dihedral angle are consistent with this notion. For

(19) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.
(20) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*. Wiley: New York, 1963; p 156.

8-Me and **8-Et** the C═C bond is essentially coplanar with the carbonyl groups (see dihedral angles) yet the C═C bonds are still somewhat elongated relative to that in **8-H**. Probably this is because here the planar structure requires the C−C and C−R bonds to be in an eclipsed orientation which elongates the C═C bond and makes the compounds less stable. Evidence for the eclipsed interaction, i.e., the repulsion between R and the syn carbonyl carbon, is seen in the C═C−C(O) angles which are 117.9°, 122.2° and 122.0° for R = H, Me and Et, respectively.

An additional factor that may or may not be important is the influence of the R substituent on the π-donor effect of the MeS group. π-donation leads to stabilization of the substrate and an elongation of the C═C bond. If steric hindrance were to diminish the π-donor effect by twisting the C═S bond, this could reduce the elongation of the C═C bond and enhance the reactivity of the substrate. As noted above, the observed trend in the C═C bond lengths is in the opposite direction and hence, if this factor plays a role at all, the effect on C═C bond length is more than offset by the bond lengthening factor discussed above.



Why are the kinetic results different from the gas-phase calculations? As a general proposition, it is unlikely that the relative contributions of the opposing factors would be exactly the same in solution and in the gas phase. More specifically, the solution phase results relate to the difference between transition state and reactant state energies while the gas phase calculations relate to the energy differences between the intermediate and the reactants. It is likely that the transition state is more sensitive to steric crowding than the intermediate because, at the transition state, the electrophilic carbon retains considerable sp^2-character and planarity, while in the intermediate it is sp^3 hybridized allowing more space for the surrounding groups. Regarding the very low rates for **8-Ph**, apart from steric crowding at the transition state, π-donation by the phenyl group may contribute to the low reactivity of this compound.

Conclusions. The main motivation for the present study was to examine steric effects on an S_NV reaction without the potential influence of additional factors such as π-donor and other electronic effects. The hydrolysis of **8-R** with R = H and a variety of alkyl groups seemed a good choice to probe the effect of transition state crowding on the rate of nucleophilic attack. Our kinetic results confirm that crowding at the transition state is an important effect but also show that for very large R groups destabilization of the substrate reverses the decreasing trend in the rate constants. Our theoretical calculations indicate that this destabilization results mainly from a sterically induced twisting and elongation of the C═C double bond.

Our kinetic results also reveal that no intermediate accumulates to detectable levels, not even at very high pH where addition of OH^- to **8-R** is expected to be thermodynamically favorable. This is because conversion of T^-_{OH} to products is faster than its formation. Furthermore, it was found that in acidic solution the partitioning of T^-_{OH} between return to reactants and conversion to products depends on the size of R: for R = H product formation is slower than return to reactants while for all the other R groups the opposite holds.

Experimental Section

Materials. Compounds **8-R** (R = alkyl) were prepared by substituting one SCH_3 group of 5-[1,1-bis(methylthio)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione, **8-SMe**, by an alkyl group. **8-SMe** was prepared according to Hunter and McNab[21] from Meldrum's acid and carbon disulfide, followed by methylation of the dithiolate anion formed with methyl iodide. Crystallization from 1:3 THF/petroleum ether gave yellow needles, mp 119−120 °C (lit.[21] mp 116−118 °C), ^{1}H NMR ($CDCl_3$) δ: 1.70 (6H, s) and 2.61 (6H, s).

8-Me was prepared according to Hunter and McNab[21] by reacting **8-SMe** with MeMgBr and crystallization of the product from EtOH. Mp: 118−120 °C (lit.[21] mp 116−117.5 °C). ^{1}H NMR ($CDCl_3$) δ: 1.71 (6H, Me) and 2.51 (3H, Me), 2.88 (3H, SMe).

8-*s*-Bu. To a stirred solution of **8-SMe** (1.00 g, 4 mmol) in dry THF (15 mL) were added isobutyl-MgBr (2.1 mL, 4.20 mmol) dropwise during 10 min, and the reaction mixture was stirred for an additional 2 h under nitrogen. Aqueous 5% HCl solution was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layer was washed with water (3 × 25 mL), dried ($MgSO_4$), and evaporated. The crude remainder was chromatographed on silica gel column using EtOAc−petroleum ether (40−60 °C) eluant. Two main fractions were observed. The minor fraction: **8-H** (5%) and **8-*s*-Bu** mp 96−98 °C (0.48 g, 47%). ^{1}H NMR ($CDCl_3$) δ: 1.05 (6H, d), 1.69 (6H, s), 1.97 (1H, hept), 2.50 (3H, s), 3.10 (2H, d). Anal. C, 55.78; H, 6.89; S, 12.33. Calcd for $C_{12}H_{18}O_4S$: C, 55.81; H, 6.97; S, 12.40.

8-*t*-Bu. To a stirred solution of **8-SMe** (1.00 g, 4 mmol) in dry THF (15 mL) at −10 °C was added a *t*-BuLi solution in diethyl ether (2.1 mL, 4.2 mmol) dropwise during 10 min, and stirring under nitrogen was continued for 1 h. Aqueous HCl solution (5%, 13 mL) was added to the reaction mixture, the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layer was washed with water (3 × 25 mL), dried ($MgSO_4$), and evaporated in vacuo. The crude residue was crystallized from ethanol, giving 0.63 g (61%) of pure **8-*t*-Bu**. Mp: 137−139 °C. ^{1}H NMR ($CDCl_3$) δ: 1.40 (s, 9H), 2.17 (s, 3H), 2.41 (6H). MS (*m*/*z*): 201 (M − Bu), 57 (Bu). Anal. C, 55.70; H, 7.04; S, 12.33. Calcd for $C_{12}H_{18}O_4S$: C, 55.81; H, 6.97; S, 12.40.

8-Et, mp 73−75 °C, was prepared in 68% yield, similarly to the preparation of **8-*t*-Bu**, using EtMgMBr instead of *t*-BuMgBr. ^{1}H NMR ($CDCl_3$) δ: 1.27 (3H, t), 1.69 (6H, s), 2.50 (3H, s), 3.26 (2H, q). Anal. Calcd for $C_{10}H_{14}O_4S$: C, 52.40; H, 6.27. Found: C, 52.17; H, 6.09.

8-H. When the procedure described for the preparation of **8-*t*-Bu** was used but with isopropyl-MgBr instead of *t*-BuMgBr and the crude product was recrystallized from ethanol, pure **8-H** (0.59 g, 73%) mp: 134−135 °C (lit.[21] mp 116−117.5 °C) was obtained. ^{1}H NMR ($CDCl_3$) δ: 1.72 (6H, s), 2.65 (3H, s), 8.97 (1H, s). Anal: C, 47.67; H, 4.63. Calcd for $C_8H_{10}O_4S$: C, 47.52; H, 4.95.

The same procedure gave **8-H** when the reaction was conducted at −40 or −72 °C and when *i*-PrLi was used instead of *i*-PrMgBr.

Attempts To Obtain 8-*i*-Pr. (a) The reactions of *i*-PrMgBr and *i*-PrLi with **8-SMe** described above gave **8-H**. Changing the solvent to ether or dry toluene or adding **8-SMe** to the *i*-PrMgBr solution still gave **8-H**.

(b) A solution of *i*-PrMgBr in THF (2M, 1.2 mL, 2.4 mmol) was added dropwise at −70 °C to a stirred suspension of CuCN (0.49 g, 2.4 mmol) in THF (12 mL). The temperature increased to −20 °C within 30 min. The stirring continued for 10 min and the dark brown solution was recooled to −70 °C. A solution of **8-SMe** (0.496 g, 20 mmol) in dry THF (12 mL) was added dropwise to the reaction mixture. After additional stirring for 30 min at −70 °C the mixture was warmed to −25 °C, stirred for 1 h, and warmed

(21) Hunter, G. A.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1209.

to room temperature within 30 min. The solvent was evaporated and the residue was extracted with diethyl ether and dried. The solvent was evaporated. Chromatography of the mixture showed the presence of **8-H** and **8-SMe** together with decomposition products.

(c) Reaction of isopropyl-MgBr with CS_2 followed by ethylation gave *i*-PrSEt. Reaction of the latter with Meldrum's acid in the presence of EtONa gave no reaction.

Experimental Methodology. Preparation of solutions, pH measurements, recording of spectra, kinetic measurements, and data analysis were performed using the general methods described previously.[4a]

Computational Methodology. Density functional theory (B3LYP/6-31G**)[22] calculations were carried out for **8-H**, **8-Me**, **8-Et**, and **8-*t*-Bu** and their respective tetrahedral adducts (T_{OH}^-) with the Gaussian 98 suite of programs.[23] All optimized structures including higher energy conformers were verified by means of their Hessian matrices to be local minima. Thermochemical quantities such as entropy, enthalpy, and free energy were calculated from harmonic frequencies. Optimized structures and energies are listed in Figures S1−S11 and Table S14 of the Supporting Information.[16]

(22) (a) Becke, A. E. *Phys. Rev.* **1988**, *A38*, 3098. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *B37*, 785.

Acknowledgment. This research was supported by Grant Nos. CHE-0098553 and CHE-0446622 from the National Science Foundation (C.F.B.) and a grant from the U.S.−Israel Binational Science Foundation (Z.R.).

Supporting Information Available: Tables S1−S13 (kinetic data) and S14 (computational results) and Figures S1−S11 (structures). This material is available free of charge via the Internet at http://pubs.acs.org.

JO060254O

(23) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1998.