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Origin of Regioselectivity in the Reactions of Nitronate and Enolate Ambident Anions

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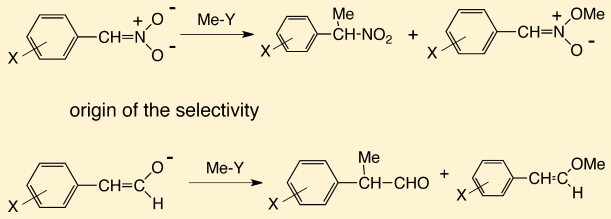
Supporting Information

ABSTRACT: The reactions of nitronates of ring-substituted phenylnitromethanes and enolates of ring-substituted 1-phenyl-2-propanones with MeOBs gave exclusively the O-methylated and C-methylated products, respectively. DFT calculations suggested that two factors, namely, intrinsic barriers and metal-cation coordination, control the C/O selectivity. The kinetic preference for O-methylation in the reactions of nitronates arises from the intrinsic barriers, which are ca. 10 kcal/mol lower for O-methylation than for C-methylation. The situation is the same for the gas-phase reaction of an enolate, in which the O-methylation is more favorable than the C-methylation. The experimentally observed C-selectivity of enolate reactions in solution is due to the metal-cation coordination, which hinders O-methylation for enolates. The effects of the enolate reactivity and the solvent on the C/O selectivity are also rationalized to arise from the two factors.



INTRODUCTION

Nitronates and enolates are useful reactive intermediates in synthetic chemistry. In alkylation reactions, these ambident anions may give two products: C-alkylated and O-alkylated ones. Understanding of the origin of the selectivity is important because C-alkylation is one of the most common ways to form a carbon−carbon bond and O-alkylation provides useful reactive intermediates, alkylnitronate, and vinyl ether. However, nitronates and enolates behave differently in many respects and the origin of this difference is not well recognized.

Alkylations of nitronates in aprotic solvents usually give the O-alkylated products.[1−4] Exceptional C-alkylation of nitronates was reported for the reactions with stable carbocations, although as in the case of protonation of nitronates,[5] fast reversible formation of low concentration of the O-alkylated intermediate was not excluded.[6] By contrast, the competition between C- and O-alkylation in enolate reactions in solution was more complex. The alkylation of enolates of simple monoketones and aldehydes normally occurred on carbon, and the alkylation on oxygen has not been observed. Enolates of acidic ketones, such as 1,3-diketones and β-ketoesters, on the other hand, gave both the C- and O-alkylated products.[7,8] Protic solvents led to the thermodynamically more favored C-alkylation products, whereas polar aprotic solvents favored alkylation at the more electronegative O atom.[9] It was also shown that the C/O selectivity depends on the metal cation and the alkylating reagent.[10,11] In the gas phase, the reaction of cyclohexanone enolate and MeBr gave only the O-methylated product, with no evidence for the C-attack.[12] The compiled experimental results thus indicated several important points: (1) Nitronates give in most cases O-alkylated products. (2) Enolates give either or both O- and C-alkylated products depending on the stability of the enolate, solvent, and the counterion. (3) A more stable and less reactive enolate leads to more O-alkylation. (4) Polar aprotic solvent favors O-alkylation.

In the present study, we have carried out the reactions of a series of ring-substituted phenylmethanenitronates and of substituted 1-phenyl-2-propanone enolates with methyl *p*-bromobenzenesulfonate (MeOBs). DFT calculations were then performed to examine the origins of the preference for C-alkylation (enolate) and O-alkylation (nitronate) and of the different behavior of enolates and nitronates. It was found that the size of intrinsic barriers of the alkylation reactions and the metal-cation complexation play essential roles in determining the C/O selectivity.

RESULTS AND DISCUSSION

Experimental Results. A series of sodium nitronates (**1**-X, X = *p*-MeO, *p*-Me, *m*-Me, H, *p*-Cl, *m*-F, *m*-Cl, *p*-CF_3, *m*-NO_2) were prepared by the reactions of ring-substituted phenylnitromethanes and NaOEt in diethyl ether. The reactions of **1**-X with MeOBs were carried out in DMF, 80% (v/v) aqueous DMF, and 90% (v/v) aqueous MeOH, and the products were analyzed. Product yields were determined by ^{1}H NMR in deuterated solvents. Table 1 lists the yields and material balances for the reactions of **1**-H in three solvent systems, and Tables S1−S3 in Supporting Information summarize the results for **1**-X. The results in Table 1 showed that in all solvent

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Table 1. Product Yields and Material Balances for the Reactions of 1-H and MeOBs at 25 °C[a]

solvent	reaction time	conversion (%)	O-adduct[c] (%)	Z:E	material balance (%)
DMF	5 min	59.3	59.0	6.7:1.0	99.5
	15 min	79.6	78.2	6.4:1.0	98.2
	50 min	94.7	95.9	6.6:1.0	101.3
80% DMF-d_7/ 20% D_2O (v/v)	5 min	16.7	13.5	3.6:1.0	96.8
	15 min	32.8	29.9	3.6:1.0	97.1
	30 min	48.0	44.2	3.3:1.0	96.2
	104 min	79.9	65.3	3.3:1.0	85.4
90% CD_3OH/ 10% H_2O (v/v)[b]	15 min	4.6	2.5	1.8:1.0	97.9
	72 min	14.2	9.2	2.4:1.0	95.0
	2.5 h	30.1	18.4	2.4:1.0	88.3
	4 h	33.4	27.0	2.3:1.0	83.5
	5.5 h	46.4	34.1	2.3:1.0	87.7
	1 day	87.0	44.5	4.7:1.0	57.5

[a]Toluene was used as an internal standard. [b]CD_3OH/H_2O mixture, rather than CD_3OD/D_2O, was used as the solvent to avoid H-D exchange in $PhCH{=}NO_2^-$. [c]% O-adduct is relative to initial concentration of the starting nitronate.

systems only O-methylated products were obtained as a mixture of *E*- and *Z*-isomers, with no C-methylated product detected in ^{1}H NMR. We ascribed the major isomer to *Z*, since B3LYP/6-31+G* calculations showed that the *Z*-isomer is 18.9 kcal/mol more stable than the *E*-isomer. This is likely due to a steric effect. The nature of the solvent did not influence the C/O selectivity for the reactions of nitronates, in sharp contrast to the enolate cases where aprotic solvent tends to lead to O-alkylation.[9] The material balance was nearly perfect in DMF but decreased as the reaction proceeded in aqueous solvents. This is likely due to the decomposition of the product especially of the *E*-isomer in aqueous methanol, since it was reported that O-alkylated products of nitronates, especially the less stable *E*-isomer, were not stable and decomposed to give aldehydes.[4] We indeed detected benzaldehyde in the reaction mixture as expected for the decomposition and hydrolysis of the O-methylated product.

The rates of the reactions were determined photometrically in DMF and aqueous DMF and are listed in Table 2. It appears that the reaction in DMF is 5 times faster than that in aqueous DMF when the difference in the MeOBs concentration is taken into account, which arises from stabilizing solvent effect on the nitronate salts in the aqueous solvent. Correlation between the two sets of rate constants in Figure 1 gave a linear plot with the slope of 0.76, indicating that the substituent effect is smaller in aqueous DMF. The Hammett plot in Supplementary Figure S1 showed a good linear correlation with ρ of −0.84. The Brønsted-type plots for the reactions in DMF and aqueous DMF are shown in Figures 2 and 3. Here, since the pK_a values in DMF and in aqueous DMF were not available, plots were made by using pK_a values in DMSO[13] and in aqueous MeOH,[14] respectively. The use of the pK_a values of related solvent systems would cause no serious error since the pK_a values in

Table 2. Pseudo-first-order Rate Constants, with Associated Standard Deviations, for the Reactions of 1-X and MeOBs in DMF and in 80% (v/v) Aqueous DMF at 25.0 °C

X	k_{obs}[a] (10^{-3} s^{-1})	k_{obs}[b] (10^{-3} s^{-1})
p-MeO	2.00 ± 0.08	*c*
p-Me	1.38 ± 0.08	2.18 ± 0.13
m-Me	1.45 ± 0.01	2.20 ± 0.04
H	1.24 ± 0.05	2.03 ± 0.02
p-Cl	0.675 ± 0.023	1.22 ± 0.04
m-F	0.567 ± 0.044	1.12 ± 0.06
m-Cl	0.556 ± 0.020	*c*
p-CF_3	0.395 ± 0.014	*c*
m-NO_2	0.301 ± 0.006	*c*

[a][**1**-X] = 0.046 mmol/L, [MeOBs] = 0.46 mmol/L, in DMF. [b][**1**-X] = 0.1 mmol/L, [MeOBs] = 5.0 mmol/L, in 80% aqueous DMF. [c]Not determined.

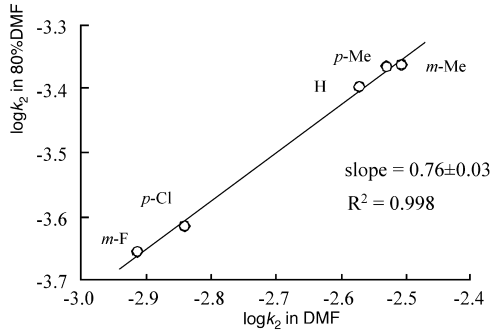

Figure 1. Logarithmic plots of second-order rate constants for the reaction of **1**-X and MeOBs in DMF against those in 80% (v/v) aqueous DMF at 25.0 °C.

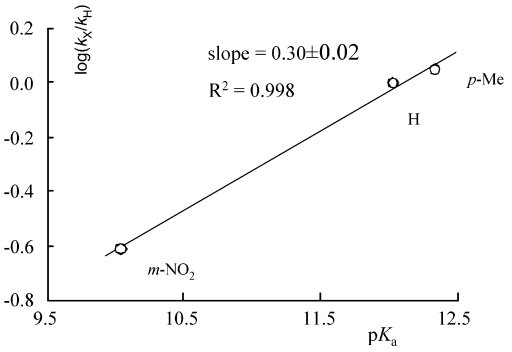

Figure 2. Brønsted-type plot for O-methylation of **1**-X and MeOBs in DMF at 25.0 °C. The pK_a values are those in DMSO.

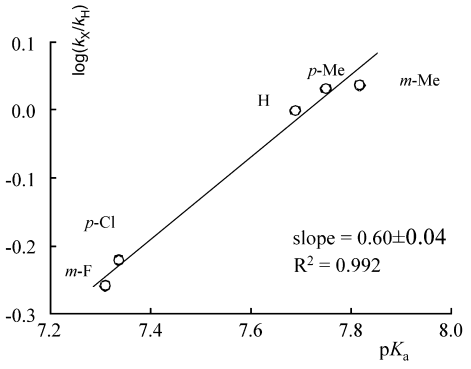

Figure 3. Brønsted-type plot for O-methylation of **1**-X and MeOBs in 80% (v/v) aqueous DMF at 25.0 °C. The pK_a values are those in 50% (v/v) aqueous MeOH.

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DMF and DMSO, at least in some compounds, were reported to vary in the same direction and correlate with the pK_a values of these species in water.[15] Although the number of points is small due to the lack of pK_a values, there appears no anomaly in the size of the slopes. Thus, no nitroalkane anomaly was detected in the methyl-transfer reaction of nitronates at the O atom. This is due to the absence of charge imbalance at the O-alkylation TS, and the result, in turn, supports the TS imbalance rationale[16] for nitroalkane anomaly, which has been observed for proton-transfer reactions of nitroalkanes.[17]

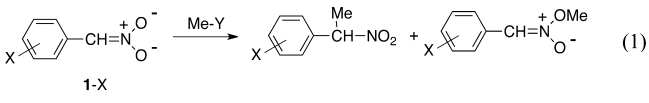
For comparison, a series of sodium enolates (**2**-X, X = *p*-MeO, *p*-Me, *m*-Me, H, *p*-Cl, *p*-CF_3) were prepared from the reactions of ring-substituted 1-phenyl-2-propanones and sodium hexamethyldisilazide (NaHMDS) in THF, and C/O selectivity was determined for the reaction with MeOBs at 25 °C. As shown in Table 3, the reaction gave the C-methylated product as the only product.

Table 3. Product Yields and Material Balances for the Reactions of 2-X and MeOBs in THF at 25 °C[a]

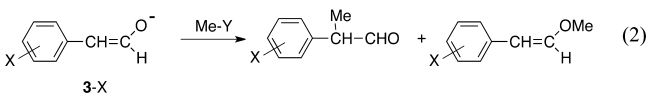
X	reaction time	conversion (%)	C-adduct (%)	material balance (%)
p-MeO	15 min	82.8	72.7	89.9
	60 min	98.9	86.2	87.3
	overnight	99.6	87.3	87.6
p-Me	14 min	90.2	69.1	88.9
	60 min	97.7	87.5	89.9
	overnight	100.0	91.6	91.6
m-Me	10 min	60.7	47.3	86.7
	60 min	91.2	81.7	80.4
	overnight	100.0	82.1	82.1
H	10 min	54.4	54.1	99.7
	60 min	92.6	93.6	103.7
	overnight	100.0	97.1	97.1
p-Cl	10 min	45.0	37.4	92.4
	60 min	90.4	78.1	87.7
	overnight	100.0	82.9	82.9
p-CF_3	10 min	22.2	16.0	93.2
	60 min	62.4	48.3	85.9
	overnight	100.0	83.5	83.5

[a]Trimethoxybenzene was used as an internal standard. [b]% C-adduct is relative to initial concentration of the starting enolate.

Computational Results. In order to understand why nitronates and enolates behave differently, DFT calculations (B3LYP/6-31+G*) were carried out for the reactions of nitronates (**1**-X) and enolates (**3**-X) with two methylating reagents (eqs 1 and 2). The calculated activation and reaction enthalpies for the reactions with MeCl and $MeOSO_2Me$ (MeOMs) are listed in Tables 4 and 5.



(1)



(2)

It is seen from Table 4 that the C-methylated products are more stable by 13 - 15 kcal/mol than the O-methylated ones, whereas the activation barriers are lower for the O-methylation by 2 - 4 kcal/mol for all substituted nitronates. The calculated kinetic O-preference is in line with the experimental selectivity mentioned above. Similar trends have previously been reported for the protonation of nitronates, where the C-protonated products were more stable than the O-protonated ones, whereas the O-protonation was kinetically favored for the reaction of $PhCHNO_2^-$ with various acids.[5] The C/O selectivity is similar for both methylating reagents, although the kinetic O-preference is slightly larger for the reactions with MeOMs than with MeCl.

The reactions of enolates in Table 5 showed the same trend as those of nitronates in that the C-methylation is favored thermodynamically, whereas the O-methylation is preferred kinetically. The calculated kinetic O-methylation preference in the enolate reactions did not reproduce the experimental results that only C-methylated product was observed for the reactions of **2**-X in THF. A possible origin of this discrepancy will be discussed later.

In Figure 4 and Supplementary Figure S2 are illustrated the Brønsted-type (rate-equilibrium) plots for the reactions with MeCl and with MeOMs, respectively.

These Brønsted-type plots gave normal α values of about 0.4 for all reactions. Several points are apparent from Figures 4 and S2: (1) The points of the C-methylation and the O-methylation gave separated Brønsted plots for both the nitronate and enolate series, indicating that the C-methylation and O-methylation reactions belong to different reaction families. (2) The lines for the O-methylation are located in lower-right positions relative to the lines for the C-methylation in both nitronates and enolates, reflecting the fact that although the C-methylated product is more stable the barrier for C-methylation is higher for a given anion. (3) In each C-attack and O-attack series, the Brønsted lines of nitronates and enolates are located close to each other, with the lines of nitronates being slightly above the enolate lines. This means that nitronates are less reactive than enolates at the same reaction energies. In relation to this, it is interesting to note that ΔH for the Me-transfer reactions of nitronates and enolates with MeCl gave excellent correlation against ΔH for the proton-transfer reaction of these anions with $CH_2(NO_2)_2$, with both nitronates and enolates being in the same correlation lines (Figure 5). On the basis of the fact that the carbon affinity and the proton affinity give an excellent single correlation line with a unity slope for each reacting site, the above Brønsted lines further mean that nitronates are less reactive than enolates at the same pK_a values. This, in turn, indicates that the kinetic barriers are larger for nitronates than for enolates.

A more quantitative means of interpreting the kinetic barrier is given by Marcus' equation (eq 3), in which $\Delta E^{\ddagger}$ and ΔE have their usual meanings and $\Delta E_0^{\ddagger}$ is the intrinsic barrier.[18] The intrinsic barrier is the barrier for the hypothetical thermoneutral step of a given reaction (kinetic barrier). Equation 3 indicates that a reaction barrier is controlled by the intrinsic barrier and the reaction endothermicity; the latter modifies the overall barrier in such a way that the barrier increases when the reaction is endothermic and decreases if it is an exothermic reaction (thermodynamic driving force).

$$\Delta E^{\ddagger} = \Delta E_0^{\ddagger} + 1/2\Delta E + (\Delta E)^2/16\Delta E_0^{\ddagger} \quad (3)$$

The intrinsic barrier of a given group-transfer reaction between R and X fragments ($\Delta E_{0\,R,X}^{\ddagger}$) can be calculated by the assumption of arithmetic mean of the intrinsic barriers of two symmetry reactions, eq 4.[18]

$$\Delta E_{0\,R,X}^{\ddagger} = 1/2[(\Delta E_{0\,R,R}^{\ddagger} + \Delta E_{0\,X,X}^{\ddagger})]] \quad (4)$$

In Tables 6 and 7 are listed the calculated intrinsic barriers for the methylating reactions of three ring-substituted phenylmethanenitronates and phenylacetaldehyde enolates, respectively. Here, $\Delta H_0^{\ddagger}$(Y,Y) is the barrier of a methyl-transfer reaction between Y's, $\Delta H_0^{\ddagger}$(X,X) is the barrier of a methyl-transfer reaction between nitronates (or enolates) at the C or the O position, and $\Delta H_0^{\ddagger}$(X,Y) is the intrinsic barrier for the methylation of a nitronate (or an enolate).

The data in Tables 6 and 7 show that the intrinsic barriers were much smaller (9−10 kcal/mol) for the O-methylation than for the C-methylation both for the nitronate and enolate reactions. The smaller intrinsic barriers for the O-methylation arise from smaller barriers for the symmetrical methyl-transfer reactions ($\Delta H_0^{\ddagger}$(X,X)) at O compared to those at C. This explains the strong preference for O-

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Table 4. Calculated Activation and Reaction Enthalpies for the Reactions of $XC_6H_4CH{=}NO_2^-$ and Methylation Reagents at B3LYP/6-31+G*[a]

		MeCl				MeOMs			
		C-methylation		O-methylation		C-methylation		O-methylation	
no.	X	$\Delta H^{\ddagger}$	ΔH	$\Delta H^{\ddagger}$	ΔH	$\Delta H^{\ddagger}$	ΔH	$\Delta H^{\ddagger}$	ΔH
1	*p*-NH_2	6.7	−19.7	4.3	−4.6	5.3	−32.1	1.3	−17.0
2	*p*-MeO	7.2	−17.1	5.0	−1.5	6.0	−29.9	1.8	−14.9
3	*p*-OH	7.3	−16.5	5.0	−2.0	6.4	−28.9	2.2	−13.9
4	*p*-Me	7.7	−15.9	5.6	−0.7	6.8	−28.3	2.8	−13.1
5	*m*-Me	8.0	−15.2	5.9	0.1	7.0	−27.6	3.1	−12.4
6	H	8.0	−14.6	6.0	0.6	7.2	−27.0	3.1	−11.9
7	*p*-Cl	9.7	−9.7	7.7	5.0	8.9	−22.1	4.8	−7.4
8	*m*-Cl	10.2	−8.9	8.1	5.8	9.2	−21.5	5.2	−6.9
9	*p*-CN	13.5	0.1	11.5	13.7	12.9	−12.4	8.6	1.3
10	*p*-NO_2	16.2	5.4	14.1	18.7	15.9	−7.0	11.1	6.2

[a]Energies are relative to the separated reactants in kcal/mol.

Table 5. Calculated Activation and Reaction Enthalpies for the Reactions of $XC_6H_4CH{=}CHO^-$ and Methylation Reagents at B3LYP/6-31+G*[a]

		MeCl				MeOMs			
		C-methylation		O-methylation		C-methylation		O-methylation	
no.	X	$\Delta H^{\ddagger}$	ΔH	$\Delta H^{\ddagger}$	ΔH	$\Delta H^{\ddagger}$	ΔH	$\Delta H^{\ddagger}$	ΔH
1	*p*-NH_2	3.5	−25.4	1.0	−11.0	2.3	−37.7	−0.3	−21.3
2	*p*-MeO	4.0	−22.8	1.5	−8.8	3.2	−33.4	0.1	−19.1
3	*p*-OH	4.0	−22.2	1.5	−8.4	2.9	−35.0	−0.2	−18.9
4	*p*-Me	4.5	−21.7	2.1	−7.3	3.7	−34.1	0.7	−18.2
5	*m*-Me	4.8	−21.7	1.9	−6.5	2.6	−33.9	−0.4	−18.9
6	H	4.8	−20.5	2.4	−6.1	2.7	−34.2	−0.4	−18.5
7	*p*-Cl	6.7	−15.0	3.9	−1.5	5.8	−27.4	2.4	−12.1
8	*m*-Cl	7.0	−14.4	5.2	0.9	4.9	−28.1	1.3	−13.2
9	*p*-CN	10.8	−4.5	7.1	8.4	10.1	−16.9	5.7	−3.0
10	*p*-NO_2	14.1	1.7	10.7	14.6	13.1	−10.6	8.2	2.5

[a]Energies are relative to the separated reactants in kcal/mol.

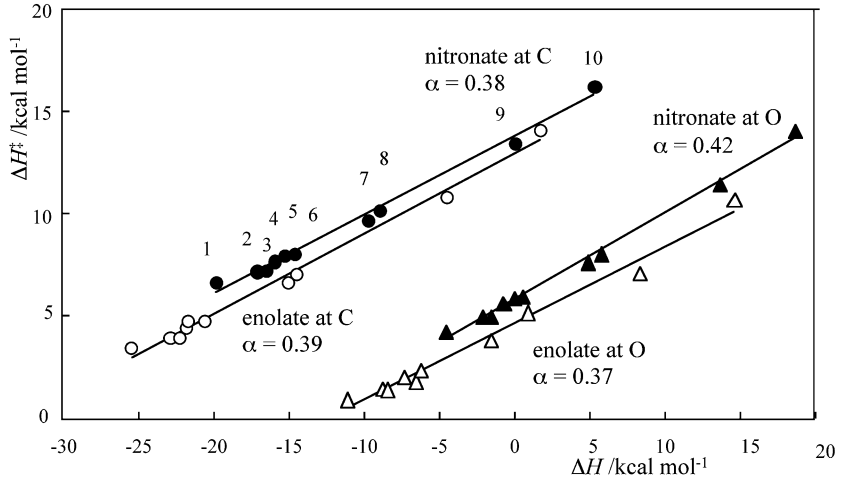

Figure 4. Brønsted-type plots for the reactions of nitronates and enolates with MeCl at B3LYP/6-31+G*. Closed symbols are for nitronates and open symbols are for enolates. Circles are for C-methylation and triangles are for O-methylation. Numbers correspond to the substituent in Table 4.

alkylation observed for the nitronate reactions and for the gas-phase enolate reactions. It is interesting to note that the substituent effect on $\Delta H_0^{\ddagger}(X,X)$ is small, because a substituent that makes the anion a better nucleophile makes it a poorer leaving group at the same time. On the other hand, the size of $\Delta H_0^{\ddagger}(Y,Y)$ depends on the identity of Y, reflecting, for example, that Br^- and Cl^- are reactive both as a nucleophile and a leaving group.

If the O-alkylation selectivity in the nitronate reactions arises from the intrinsic barrier difference between the O- and C-alkylation steps, the C/O selectivity for a reaction with a very small intrinsic barrier should become controlled by the thermodynamic driving force. This argument may apply to the reported kinetic C-alkylation selectivity for the cation−anion combination reactions of nitronates with carbocations.[6]

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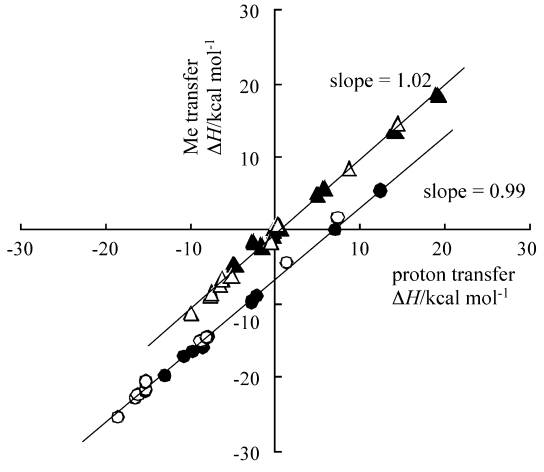

Figure 5. Correlation between carbon affinity (vs MeCl) and proton affinity (vs $CH_2(NO_2)_2$) of nitronates (closed symbol) and enolates (open symbol) at the carbon (circle) and the oxygen (triangle) reaction center.

Table 6. Intrinsic Barriers ($\Delta H_0^{\ddagger}$(X,Y), in kcal/mol) for the S_N2 Reactions of $XC_6H_4CH{=}NO_2^-$ and Methylation Reagents at B3LYP/6-31+G*

		p-NH_2		H		*p*-NO_2	
Me-Y	$\Delta H_0^{\ddagger}$(Y,Y)	at C	at O	at C	at O	at C	at O
				$\Delta H_0^{\ddagger}$(X,X)			
		31.5	13.5	30.8	12.1	30.4	10.5
				$\Delta H_0^{\ddagger}$(X,Y)			
Me-OMe_2^+	4.2	17.9	8.8	17.5	8.2	17.3	7.4
Me-OMs	5.4	18.5	9.5	18.1	8.8	17.9	8.0
Me-Br	−5.7	12.9	3.9	12.5	3.2	12.3	2.4
Me-Cl	−1.7	14.9	5.9	14.6	5.2	14.4	4.4
Me-ONO	3.5	17.5	8.5	17.2	7.8	16.9	7.0
Me-CN	27.4	29.5	20.4	29.1	19.8	28.9	19.0

Table 7. Intrinsic Barriers ($\Delta H_0^{\ddagger}$(X,Y), in kcal/mol) for the S_N2 Reactions of $XC_6H_4CHCHO^-$ and Methylation Reagents at B3LYP/6-31+G*

		p-NH_2		H		*p*-NO_2	
Me-Y	$\Delta H_0^{\ddagger}$(Y,Y)	at C	at O	at C	at O	at C	at O
				$\Delta H_0^{\ddagger}$(X,X)			
		31.3	10.7	29.1	8.3	28.9	8.5
				$\Delta H_0^{\ddagger}$(X,Y)			
Me-OMe_2^+	4.2	17.8	7.5	16.7	6.3	16.6	6.3
Me-OMs	5.4	18.4	8.1	17.3	6.9	17.2	7.0
Me-Br	−5.7	12.8	2.5	11.7	1.3	11.6	1.4
Me-Cl	−1.7	14.8	4.5	13.7	3.3	13.6	3.4
Me-ONO	3.5	17.4	7.1	16.3	5.9	16.2	6.0
Me-CN	27.4	29.4	19.0	28.3	17.9	28.2	17.9

Although the intrinsic preference for the O-alkylation was observed in the gas-phase enolate reaction, the enolates of simple ketones and aldehydes give exclusively the C-alkylated products in polar aprotic solvents, and the enolates of diketones and ketoesters, which can exist in protic solvents, give the mixture of the C- and O-alkylated products with more C-isomer in protic solvents than in aprotic solvents. The preference for the C-alkylation for less stable and more reactive enolates is in line with the above intrinsic barrier argument in that the reactivities of more reactive enolates is controlled by the thermodynamic driving force to a larger extent. However, the different behavior in the gas-phase and in solution and the solvent effect on the C/O selection in the enolate reactions cannot be explained by the intrinsic barrier argument alone.

Since the C/O selectivity has been shown to depend on the existence of a countercation, we have then examine the effect of a metal cation on the C/O selectivity for the Me-transfer reactions of aliphatic nitronates and enolates. Calculations were carried out for the S_N2 reactions of MeCl with $CH_2{=}NO_2^-$ and $CH_2{=}CHO^-$ with and without Li^+ solvated by three Me_2O. The results are summarized in Table 8.

Since the reactant states are stabilized by the strong interaction between the anions and Li^+, the activation enthalpies greatly increased for all reactions upon complexation. In the absence of the cation, the C/O selectivity is very low for the simple aliphatic nitronate. This is because the O-alkylated alkenes in these reactions do not have a stabilizing group on the $CH_2{=}$ end of the molecules and are thus relatively unstable compared to the aromatic counterparts. This can be seen in the difference of the reaction enthalpies between C-methylation and O-methylation, which are much larger for the simple aliphatic nitronate and enolate (20−24 kcal/mol, Table 8) than for aromatic counterparts (14−15 kcal/mol, Tables 4 and 5). Under these circumstances, we only focus on the change of the C/O selectivity upon metal coordination.

The calculations showed that the relative activation enthalpies ($\delta\Delta H^{\ddagger}$) for the C- vs the O-methylation of the nitronate changed little upon Li^+ coordination to the nitronate. By contrast, the C/O selectivity dramatically changed upon Li^+ coordination for the enolate reactions. Thus, the preference of enolates for O-alkylation switches to C-alkylation in the presence of the countercation. Furthermore, the coordination may introduce a larger effect if enolates react as aggregates. Lithium enolates and other alkyl lithium reagents are known to exist as aggregates, which introduce a larger steric hindrance than a monomer,[19] although whether these reagents react as an aggregate or as a monomer that exists in equilibrium with the aggregate is not well understood.[20]

The coordination effect explains the experimental observations that the gas-phase reaction of the cyclohexanone enolate gave only the O-alkylated product whereas the C-alkylation was preferred in solution reactions. The fact that more C-alkylation occurs in protic solvents than in polar aprotic solvents may also be explained partly as arises from the coordination effect, since a polar aprotic solvent interacts strongly with a metal cation, leaving an enolate anion less coordinated. Another contribution from solvents is an anion solvation by protic solvents, which tends to inhibit O-methylation.

The origin of the dramatic difference in the Li^+ coordination effect for the enolate and the nitronate likely resides in the fact that enolates have one negative oxygen in the molecule whereas nitronates have two. Thus, the countercation coordination blocks the oxygen reaction center leading to the enhanced C-selectivity for enolates, whereas one oxygen atom is still reactive leaving the C/O selectivity nearly unchanged upon cation coordination for nitronates. The calculated transition structures for the O-methylation of the Li^+-coordinated nitronate and enolate clearly illustrate the situation (Figure 6).

In summary, the reactions of nitronates (**1**-X) of ring-substituted phenylnitromethanes with MeOBs gave the O-methylated product in nearly quantitative yields both in aqueous and nonaqueous solvents. Analogous reactions of enolates (**2**-X) of ring-substituted 1-phenyl-2-propanones in THF gave the C-methylated product exclusively. Thus, the alkylation reactions of nitronates and enolates showed clear difference in the C/O regioselectivity. The Brønsted plots for the reactions of **1**-X with MeOBs showed no nitroalkane anomaly.

DFT calculations for the reactions of **1**-X and **3**-X with MeCl and MeOMs revealed that for both nucleophiles O-methylation is kinetically favored, whereas C-methylation is thermodynamically preferred in the gas phase. Two factors were considered to control the C/O selectivity, namely the intrinsic barriers and the metal-cation coordination. The kinetic preference for O-methylation for the nitronate reactions arises from the difference of the intrinsic barriers, which are ca. 10 kcal/mol lower for the O-methylation than for the C-methylation. The same applies to the O-methylation in the gas-phase reaction of an enolate. The experimentally observed C-selectivity of

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Table 8. Activation and Reaction Enthalpies for the S_N2 Reactions of MeCl with $CH_2{=}NO_2^-$ and $CH_2{=}CHO^-$ with and without $Li^+(Me_2O)_3$ at B3LYP/6-31+G*[a]

		$CH_2{=}NO_2^-$				$CH_2{=}CHO^-$	
	cation	$\Delta H^{\ddagger}$	ΔH	$\delta\Delta H^{\ddagger b}$	$\Delta H^{\ddagger}$	ΔH	$\delta\Delta H^{\ddagger b}$
C-methylation	no	−1.3	−32.3	−1.5	−4.6	−41.3	0.1
O-methylation	no	0.2	−8.5		−4.7	−20.7	
C-methylation	yes	20.7	−25.8	−2.2	13.5	−31.3	−7.5
O-methylation	yes	22.9	−2.1		21.0	−14.7	

[a]Energies are relative to the separated reactants (anion + MeCl, or anion-Li$(OMe)_2$ complex + MeCl) in kcal/mol. Product states are C- or O-methylated product + LiCl. [b]Relative activation enthalpy for C-methylation over O-methylation.

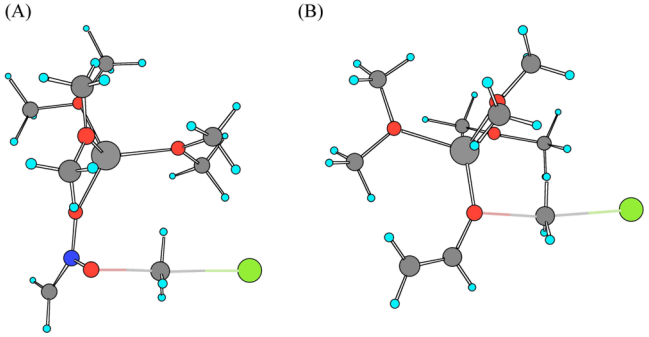

Figure 6. Transition structures for the O-methylation of the Li^+-coordinated (A) nitronate and (B) enolate calculated at B3LYP/6-31+G*.

enolate reactions is due to the metal-cation coordination, which hinders O-methylation for enolates. Variation in the C/O selectivity with an enolate stability is rationalized by a variable relative importance of the thermodynamic driving force over the kinetic barrier in enolate reactions.

EXPERIMENTAL SECTION

Materials. DMF was distilled over MS 4A. Deuterated solvents were used as received: DMF-d_7 (ACROS, 99.5% atom D), D_2O (Merck, 99.9% atom D), and CD_3OD (ACROS, 99.8% atom D). CD_3OH was prepared by mixing CD_3OD and H_2O and fractionally distilled. Ring-substituted phenylnitromethanes and 1-phenyl-2-propanones were prepared as reported previously.[14,21] A series of sodium nitronates (**1**-X, X = *p*-MeO, *p*-Me, *m*-Me, H, *p*-Cl, *m*-F, *m*-Cl, *p*-CF_3, *m*-NO_2) were prepared from the reactions of ring-substituted phenylnitromethanes and NaOEt in diethyl ether.

Sodium Nitronate (1-X). In a 100 mL flask were placed ethanol (3 mL), dry ether (3 mL), and sodium (0.25 g, 0.011 mol). After the sodium dissolved completely, the solution was diluted with dry ether (30 mL), and then phenylnitromethane (1.189 g, 8.68 mmol) in dry ether (10 mL) was added dropwise with stirring. The resultant precipitate was collected, washed with dry ether, and dried. Yield, 82.2%. Other substituted salts (**1**-X) were prepared in a similar manner.

Sodium Enolate (2-X). **2**-X (X = *p*-MeO, *p*-Me, *m*-Me, H, *p*-Cl, *p*-CF_3) was prepared by mixing a preset amount of substituted 1-phenyl-2-propanone and NaHMDS in THF and stirred for 1 h under N_2 at 25 °C, and used without isolation.

Kinetics. The rates of the reactions **1**-X in DMF were studied photometrically at 25.0 ± 0.1 °C with the substrate concentration of 0.046 mmol/L in the presence of 10 equiv of MeOBs. The decay of absorbance of **1**-X at λ_{max} (332−370 nm, depending on the substituent) was followed. Excellent pseudo-first-order rate plots (R^2 > 0.9997) were obtained. Reactions in 80% (v/v) aqueous DMF were carried out with the substrate concentration of 0.10 mmol/L in the presence of 50 equiv of MeOBs. Rates were measured at least 3 times, and the reproducibility is listed in Table 2.

Product Analysis. The reaction of **1**-X (ca. 50 mmol/L), a slightly excess amount of MeOBs, and a drop of toluene dissolved in DMF-d_7 was carried out at 25 °C in an NMR sample tube. At preset intervals, the NMR spectra were recorded and the remaining **1**-X and the O-methylated products were quantified with toluene as an internal standard. Assignment of *E*- and *Z*-methylated products was made according to the literature.[4] Reactions in other solvents were carried out similarly. The reaction of **2**-X (ca. 40 mmol/L) with 2 equiv of MeOBs in THF was carried out at 25 °C under N_2 in a flask. At preset intervals, a part of the reaction solution was quenched with water and the organic layer was extracted with ether and subject to NMR analysis. Trimethoxybenzene was used as an internal standard.

Computational Methods. Electronic structure calculations were carried out with the Gaussian 03 program suite.[22] Geometries were fully optimized at the B3LYP/6-31+G* level of theory. Vibrational normal-mode analyses were performed to ensure that each optimized structure was a true minimum or a saddle point on the PES. Unscaled frequencies were used to obtain thermochemical quantities, the thermal enthalpies at 298 K.

ASSOCIATED CONTENT

Supporting Information

Tables (S1−S3), Figures (S1, S2), and calculated geometrical coordinates and energies of the species discussed. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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