Theoretical Studies of Regioselectivity of *myo*-Inositol Derivatives: Importance of Solvent Dielectric Constants

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Understanding the origin of the regioselectivity of inositol derivatives is essential to the synthetic design of these biologically important molecules. We have undertaken a study of the regioselectivities displayed by the *myo*-inositol derivatives toward electrophiles using various levels of quantum mechanical calculation: Hartree−Fock (HF) theory, Möller-Plesset second-order perturbation (MP2) theory, density functional theory (DFT), and self-consistent reaction field (SCRF) theory. Various basis sets were also tested. The systems investigated here are 1,2:4,5-di-*O*-methylidene-*myo*-inositol and its probable intermediates (deprotonated and sodium-chelated species). In experiments the O3 position was the major site for derivatization of the molecule. However, the MP2 and DFT results could not explain the experiments. Taking into account that the *myo*-inositol derivatives were highly insoluble with the exception of some polar solvents, we performed the SCRF calculations using the dielectric constant (ϵ) of 40. These results show agreements with the experimental results. In the presence of solvents with large dielectric constants, the regioselectivity in favor of the O3 position is not only due to reduced Coulombic repulsion between the deprotonated oxygen and its vicinal oxygen but also due to reduced anisotropicity of the polarization from Na toward two vicinal oxygens.

I. Introduction

Inositol and its various derivatives are essential for various biofunctions related to the intracellular signal transduction.[1] A recent progress in understanding the intracellular signal transduction pathway utilizing inositol phosphate derivatives has stimulated the interest in *myo*-inositol chemistry since *myo*-inositol (**1**) is readily available.[2] Various reaction conditions have been investigated under which *myo*-inositol and its derivatives are regioselectively manipulated.[3] Generally, the selectivity is not very high because of the lack of distinctive difference between the six hydroxyl groups in the *myo*-inositol. Although a few theoretical studies discussed its conformation,[4] no theoretical study on the regioselectivity question of the molecule was reported. Owing to its large molecular size, the previous conformational studies resulted in different conclusions depending on the levels of theoretical method used. Our preliminary study of 1,2:4,5-di-*O*-methylidene-*myo*-inositol (**4**) showed a very consistent result without showing much dependency of the theoretical methods employed.[5] Therefore, we have undertaken the first *ab initio* theoretical investigation of the regioselectivity of *myo*-inositol derivatives.

Cyclic acetals such as cyclohexylidene and isopropylidene have routinely been used as protecting groups in the synthesis of the *myo*-inositol derivatives to differentiate the six hydroxyl groups.[6] The overall patterns of the reactivity for these acetals toward electrophiles are very similar. Therefore, it is reasonable to think that the bulkiness of the acetal groups does not affect the reactivities significantly. In the selective functionalization of *myo*-inositol, 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**2**) and

1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (**3**) have been most widely used (Figure 1).[7] The protecting groups in **2** and **3** impose the ring strain on the central cyclohexyl moiety, which makes it possible to differentiate the remaining two hydroxyl groups. The derivatization of the O3 position turns out to be the major product in all cases. Therefore, the selective functionalization has been assumed to have resulted from the compound itself. In spite of some proposed explanations,[8−11] the complexity of the molecules has made it difficult to understand the origin of the selectivity.

Chung and collaborators[9] have recently studied the regioselectivity of *myo*-inositol derivatives. In particular, they reported that **2** is regioselectively functionalized at O3 in preference to O6 in reactions including alkylation, acylation, and silylation. These experimental regioselectivities are listed in Table 1 to facilitate our discussion. Since the regioselectivity does not depend much on the size of cyclic ketals and the system is large, we investigated simplified model **4** to make our calculation more accurate and efficient. As a preliminary work before uncovering the origin of the regioselectivity, we reported the conformational stability of the molecule using *ab initio* calculations.[5] Since there are two hydroxyl groups in the molecule and each of them can form hydrogen bonds with one of two neighboring O atoms, there can be four different conformers depending on the orientation of the two OH groups. Among the four possible conformers, the lowest energy conformer was found to be **4** shown in Figure 1 regardless of the levels of calculation and basis set. On the basis of this conformer, it was possible to explain reasonably the NMR spectra related to the presence of intramolecular hydrogen bonds.[9] Thus we focus on the regioselectivity of **4**.
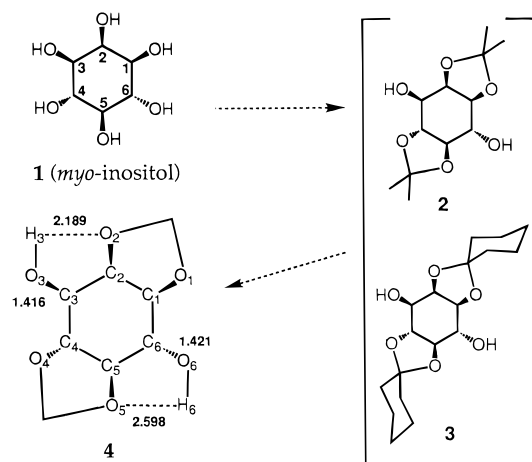
All experiments listed in Table 1 were performed in the presence of bases such as NaH, pyridine, imidazole, and

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Figure 1. *myo*-Inositol (**1**), its protected species (**2**, **3**), and model system (**4**). Selected distances in the MP2/6-31G* geometry of **4** are given in angstroms.

TABLE 1: Regioselectivity of Diol 2 (Figure 1)[a]

		products (isolated yield, %)	
entry	reaction conditions	O3	O6
1	BnBr (1.2 equiv), NaH (1.2 equiv), DMF, RT, 11 h	46	0
2	BnBr (1.2 equiv), NaH (1.2 equiv), toluene, reflux, 12 h	48.1	11.5
3	*p*-(CH$_3$O)BnCl (1.0 equiv), NaH (5.0 equiv), DMF, RT, 5 h	20	0
4	*p*-(CH$_3$O)BnCl (1.2 equiv), NaH (1.2 equiv), DMF, RT, 3 h	30.5	0
5	(CH$_3$)$_3$CC(O)Cl (1.8 equiv), pyridine, RT, 28 h	42.3	9.1
6	(CF$_3$SO$_2$)$_2$O (1.15 equiv), pyridine (2.0 equiv), CH$_2$Cl$_2$, −20 °C, 3 h	52.0	0
7	*t*-BuMe$_2$SiCl (1.1 equiv), imidazole (3.3 equiv), DMF, RT, 12 h	55.4	0
8	(PhO)$_2$P(O)Cl (1.2 equiv), TEA (3.0 equiv), cat. DMAP, CH$_2$Cl$_2$, RT, 4 h	30	trace

[a] Reference 9; RT denotes room temperature.

tetraethylamine (TEA). The regioselectivity at the O3 position relative to O6 is evident for all derivatizations studied. Thus, we focused on the regioselectivity of **4** in the case where NaH was employed as a base. The first four entries in Table 1 belong to this category. The most simple and representative reaction for this category would be alkylation of **4** in the presence of NaH and CH$_3$Cl. To elucidate the origin of this regioselectivity, we performed quantum mechanical *ab initio* calculations for **4**, and its anions (Ion3, Ion6), sodium alkoxides (Na32, Na34, Na65, Na61), and the transition states (TS) for alkylation in the presence of NaH and CH$_3$Cl (TS32, TS65), as shown in Figure 2.

II. Calculation Method

To investigate the regioselectivity, we studied **4** and the model species in Figure 2 at various levels of theory: HF, MP2, DFT, and SCRF. The basis sets tested here are STO-3G, 3-21G, 6-31G, 6-31G*, and 6-31+G*. In general, it is known that the conformational study dealing with the relative energies of internally hydrogen-bonded structures requires high levels of theory.[12] Since the conformation of *myo*-inositol is related to the internal hydrogen bonding, we examined the consistency between different calculational methods and that between different basis sets. Since the present calculation includes
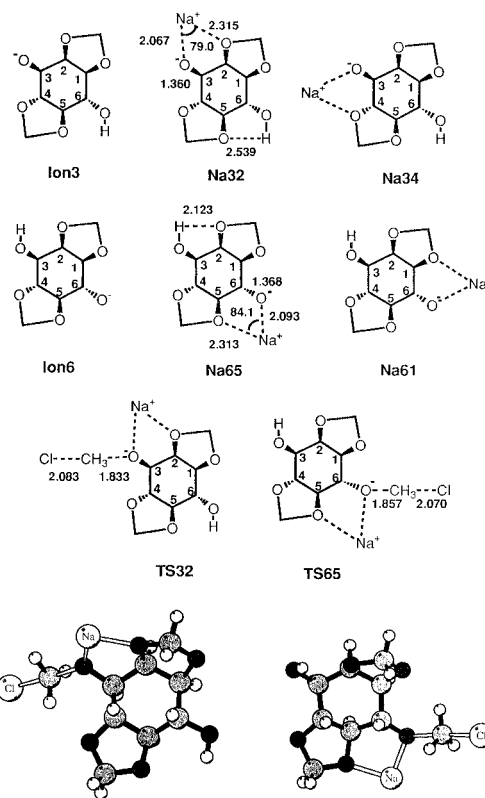
Figure 2. Schematic views of anionic species (Ion3 and Ion6), sodium-chelated species (Na32, Na34, Na65, and Na61), and transition states for the reaction of sodium alkoxides with CH$_3$Cl (TS32 and TS65). Three-dimensional views of TS32 and TS65 are also presented. Selected distances and angles for MP2/6-31G* geometries of Na32 and Na65 and HF/STO-3G geometries of TS32 and TS65 are given in angstroms and degrees, respectively.

anionic species, a diffuse basis set of 6-31+G* was also considered.[13] In the case of the DFT method, we used both Becke−Lee−Yang−Parr (B-LYP) and B3-LYP functionals,[14] the latter of which is known to be one of the most reliable functionals.[15] All the geometries were fully optimized using a GAUSSIAN 94 suite.[16] The local minima were confirmed by harmonic frequency analyses based on the HF theory. The frequencies were also utilized to obtain zero-point energies (ZPE) and relative free energies at 298 K and 1 atm (ΔG_{298}^{rel}).[17] Although HF geometry optimization was performed up to the level employing the 6-31+G* basis set, the MP2 geometry optimization was performed using the 6-31G* basis set, followed by a single-point calculation of MP2/6-31+G*. We also carried out the SCRF(HF) and SCRF(MP2) calculations in consideration of the solvent effect.

III. Results and Discussion

(a) Geometries and Energies of Reactants and Intermediates. From Table 1, the selective derivatizations of the O3 position are obvious in contrast to those of the O6 position, regardless of the bases and electrophiles in experiment. It is expected that the reaction proceeds through intermediates of either ions (Ion3, Ion6) of sodium-chelated species (Na32, Na43, Na65, Na61) in Figure 2. In Ion3 H3 is deprotonated from **4**, and in Ion6 H6 is deprotonated. Likewise, Na32 is denoted after the species where a sodium cation is coordinated to both O2 and O3 of Ion3; in Na34 a sodium ion is coordinated to both O3 and O4 of Ion3, etc. For alkylation in the presence of NaH and CHCl$_3$, the transition states, TS32 and TS65, are also shown in Figure 2.

TABLE 2: Calculated Energies[a]

| | STO-3G HF | 6-31G* | | | | 6-31+G* | | 6-31G* | |
		DFT(BLYP)	DFT(B3LYP)	HF(6d)	MP2	HF	MP2/HF[b]	SCRF(HF)//HF[c]	SCRF(MP2)//MP2[c]
Diol **4**	−748.357 33	−763.088 36	−763.327 10	−759.044 91	−761.139 17	−759.068 29			
Ion3	−748.564 30	−762.487 54	−762.720 38	−758.431 13	−760.533 51	−758.466 79	−760.577 49	−758.439 05	−760.540 19
Ion6	−748.565 31	−762.490 46	−762.723 12	−758.432 73	−760.535 53	−758.468 53	−760.579 23	−758.439 49	−760.540 73
Na32	−908.669 48	−924.811 23	−925.055 71	−902.338 68	−922.447 47	−920.339 16	−922.489 96	−920.346 23	−922.455 90
Na65	−908.666 46	−924.811 97	−925.056 14	−920.338 30	−922.449 10	−920.358 70	−922.491 61	−920.343 45	−922.454 73
Na34	−908.665 23	−924.809 23	−925.053 49	−920.336 50	−922.446 41	−920.356 93			
Na61	−908.664 36	−924.806 55	−925.050 65	−920.332 67	−922.443 04	−920.353 12			
relative energies									
Ion3 − Ion6									
ΔE_e	0.64	1.83	1.72	1.01	1.24	1.09	1.09	0.28	0.34
ΔE_0	0.39			0.77		0.82			
ΔG_{298}	0.47			0.80		0.89			
Na32 − Na34	−2.66	−1.36	−1.39	−1.37	−0.67	−1.40			
Na32 − Na61	−3.21	−2.94	−3.18	−3.77	−2.78	−3.79			
Na32 − Na65									
ΔE_e	−1.89	0.46	0.27	−0.24	1.02	−0.29	1.04	−1.74	−0.85
ΔE_0	−2.20			−0.52					
ΔG_{298}	−2.67			−0.95					
TS32 − TS65	−1.52								

[a] All the polarization basis sets used a set of 5d functions in the above calculations except for the cases of HF/6-31G*(6d) which used a set of 6d functions. Total and relative energies are in hartrees and kcal/mol, respectively. E_e and E_0 are the interaction energies without and with ZPE correction, respectively. G_{298} are the Gibbs free energies at 298K and 1 atm. [b] Single-point calculation at the HF optimization geometry. [c] Dielectric constant: $\epsilon = 40$.

To discuss the geometries of the reactants, intermediates, and transition states, it is important to compare the predicted geometries of the diol species with the X-ray structure.[11] As noted earlier, we previously investigated the structures and conformational stability of 1,2:4,5-di-*O*-methylidene-*myo*-inositol.[5] Four different conformers depending on the two OH orientations to form two intramolecular hydrogen bonds (one from H3···O2 and H3···O4, and the other from H6···O5 and H6···O1) were investigated. Among the four conformers, **4** (which has two hydrogen bonds of H3···O2 and H6···O5) was found to be the most stable by 1−2 kcal/mol. All calculational levels (HF, MP2, DFT, and SCRF) predicted almost the same relative stability among the different conformers. The conformational stability was understood in terms of its short hydrogen bond distances. Conformer **4** was fit for the NMR experiment regarding to the OH orientation.

The HF and DFT geometries of **4** on the whole were in good agreement with the X-ray structure; in particular, the MP2 geometries obtained with a reasonable size of basis set such as 6-31G* were in excellent agreement. Since there was no significant difference in geometry between the 6-31G* and 6-31+G* basis sets, the incomplete basis set problem is considered to be insignificant with such basis set size. However, the methodological difference gave a slight difference in geometry. Based on the 6-31G* basis set, the HF results showed that the bond lengths between ring carbons and vicinal oxygens are too short (by ∼0.03 Å), while those between ring carbons are in good agreement with the X-ray bond lengths. In the case of the DFT/B3-LYP method, the bond lengths between ring carbons are too long (by ∼0.03 Å), and those between ring carbons and vicinal oxygens are somewhat long (by ∼0.01 Å). In this respect, the DFT functional may not be accurate enough to predict exact bond lengths for this molecular system. A somewhat larger basis set such as 6-31+G* did not improve such errors in both HF and DFT calculations. On the other hand, the MP2 results using the 6-31G* basis set are in good agreement with all the experimental bond lengths (within 0.015 Å). As to the 12 bond lengths of C−C of the ring and C−O of the ring carbons and vicinal oxygens, the standard deviation of the MP2/6-31G* values from the X-ray data was within 0.01 Å.

TABLE 3: HF/STO-3G Predicted Structures of 4, Its Anionic and Sodium-Chelated Species, and Transition States[a]

	Diol **4**	Ion3	Ion6	Na32	Na65	TS32	TS65
d(C3−O3)	1.430	1.302	1.436	1.382	1.431	1.407	1.430
d(C6−O6)	1.433	1.438	1.304	1.434	1.391	1.432	1.412
d(O3···O2)	2.715	2.954	2.660	2.784	2.684	2.729	2.713
d(O3···O4)	3.083	3.160	3.024	3.109	3.136	3.089	3.146
d(O6···O5)	3.071	2.990	3.137	3.045	2.931	3.073	2.891
d(O6···O1)	3.072	3.039	3.202	3.058	3.186	3.081	3.167
d(Na/H3···O2/O4)	2.186		2.061	2.046	2.093	2.041	2.141
d(Na/H6···O5/O1)	2.697	2.517		2.628	2.066	2.676	2.053
d(Na/H3···O3)	0.991		0.991	1.904	0.991	1.932	0.991
d(Na/H6···O6)	0.991	0.992		0.991	1.914	0.991	1.951
∠O2/O4···Na/H3−O3	111.8		116.9	89.6	116.3	86.7	115.0
∠O5/O1···Na/H6−O6	102.7	108.9		105.4	94.8	104.2	92.4

	TS32	TS65		TS32	TS65
d(Cl···Me)	2.083	2.070	∠O3···Me···Cl	177.4	
d(O3/O6···Me)	1.833	1.857	∠O6···Me···Cl		176.7
∠C3−O3···Me	114.5		φ(Cl···Me···O3···Na)	23.7	
∠C6−O6···Me		176.7	φ(Cl···Me···O6···Na)		21.5
∠Na···O3···Me	134.7		φ(Cl···Me···O3···C3)	−15.6	
∠Na···O6···Me		114.6	φ(Cl···Me···O6···C6)		39.9

[a] Distances are in Å, angles in deg.

As a result, the geometries and energetics predicted by MP2/6-31G* and MP2/6-31+G* are expected to be very close to the experimental results. Nevertheless, even the HF/STO-3G calculations are good enough to give meaningful results. These results are necessary for understanding of the transition states, since other levels of calculation were not successful to locate the transition states.

We investigated the energies and geometries of **4** (Diol 4), anions (Ion3, Ion6), sodium-alkoxides (Na32, Na65, Na34, Na61), and transition states (TS32, TS65) shown in Figure 2, using HF, MP2, and DFT employing the STO-3G, 6-31G*, and 6-31+G* basis sets. The TS structures are only available at the HF/STO-3G level. Table 2 lists all the predicted energies. Tables 3 and 4 report the HF/STO-3G and MP2/6-31G* structures, respectively. The geometries predicted by other methods are reported in the Supporting Information. The HF6-31+G* geometries are very similar to the HF/6-31G* geometries even for the anionic species (see Supporting Information).

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TABLE 4: MP2/6-31G* Structures of 4 and Its Anionic and Sodium-Chelated Species[a]

	Diol **4**	Ion3	Ion6	Na32	Na65	Na34	Na61
d(C3$-$O3)	1.416	1.308	1.429	1.360	1.418	1.362	1.419
d(C6$-$O6)	1.421	1.434	1.315	1.423	1.368	1.423	1.366
d(O3$\cdots$O2)	2.710	2.848	2.664	2.794	2.683	2.892	2.743
d(O3$\cdots$O4)	3.085	3.118	3.017	3.067	3.078	2.991	3.045
d(O6$\cdots$O5)	2.977	2.915	3.068	2.960	2.956	3.037	3.057
d(O6$\cdots$O1)	3.040	3.033	3.131	2.999	3.111	3.018	2.959
d(Na/H3$\cdots$O2/O4)	2.189		2.082	2.315	2.123	2.322	2.272
d(Na/H6$\cdots$O5/O1)	2.598	2.416		2.539	2.313	2.713	2.372
d(Na/H3$\cdots$O3)	0.976		0.977	2.067	0.977	2.094	0.975
d(Na/H6$\cdots$O6)	0.975	0.975		0.975	2.093	0.974	2.096
$\angle$O2/O4$\cdots$Na/H3$\cdots$O3	112.0		116.4	79.0	114.8	85.1	108.6
$\angle$O5/O1$\cdots$Na/H6$\cdots$O6	103.2	111.3		106.0	84.1	100.0	82.7

[a] Distances are in Å; angles in deg.

For the structures of HF/6-31+G* with respect to those of HF/6-31G*, the only notable difference is the C3$-$O3 bond in Ion3 which is lengthened by 0.013 Å and the C6$-$O6 bond in Ion6 lengthened by 0.014 Å. In the sodium-chelated species, the bond length increments in C3$-$O3 of Na32 and in C6$-$O6 of Na65 are only 0.02 Å. All the other bond length changes are within 0.001 Å. The MP2 geometry optimization was performed using the 6-31G* basis set, followed by a single-point calculation of MP2/6-31+G*. The MP2/6-31+G* geometries should be similar to the MP2/6-31G* geometries.

(b) Transition State Structures. The most conventional way to study regioselectivity by means of theoretical calculations is to investigate the transition state structures. Although various electrophiles were investigated in the experiments, CH$_3$Cl can be considered as the simplest and most representative electrophile. This reaction would proceed via intermediates of either ionic species or sodium complexes, as shown in Figure 3. The reaction of Ion3 with CH$_3$Cl was found to be exothermic by over 81 kcal/mol at the HF/STO-3G level and proceeded to products with no activation barrier. The reactions with naked ionic species are too exothermic to have transition states. Furthermore, deprotonating **4**, i.e., generating Ion3 and Ion6 without binding Na$^+$, would not be an easy reaction step. The sodium complexes are much more stable than separated ionic species. Through sodium chelation, the nucleophilicity of the negatively charged oxygen is reduced. Since the reaction in reality does not proceed fast enough, there must be a transition state with activation barrier. Therefore, it seems that the intermediates of sodium complexes take part in the reaction. Among the four probable structures of the sodium alkoxides, Na32 is ~1 kcal/mol more stable than Na34, and Na65 is ~3 kcal/mol more stable than Na61 (Table 2). For the reactions of Na32 and Na65 with CH$_3$Cl, we have further proceeded to locate the transition state structures (TS32, TS65). This procedure was very time consuming because of the large size of the system. The transition state geometries were not readily optimized, possibly because these systems are composed of multifused rings. We were able to locate the transition state structures only for the HF/STO-3G calculations. These structures are compared with diol **4** and its naked anions and sodium alkoxides in Table 3. The forming bond distances of C$\cdots$O and breaking bond distances of Cl$\cdots$C in TS32 are 1.833 and 2.083 Å, respectively, and those in TS65 are 1.857 and 2.070 Å, respectively. Although anionic structures are somewhat different from the TS structures, the sodium-chelated structures are very similar to the TS structures, suggesting early transition states for the reaction.

The reactions of the sodium complexes (Na32 or Na65) with CH$_3$Cl (MeCl) are also highly exothermic at the HF/STO-3G level. As shown in Figure 3, the reactants with Na32 are 45

kcal/mol less stable than the products, and those with Na65 are 49 kcal/mol less stable. The forward activation barriers of 16 kcal/mol in TS32 and 15 kcal/mol in TS65 are not great compared with their backward activation barriers which are over 60 kcal/mol. Since the backward reaction is not practically possible, the reaction is governed kinetically.[18] The reaction proceeds via early transition state structures that resemble the reactant-like transition state structures. As noted before, the structures of the two TS states (TS32 and TS65) are very close to those of the two sodium complexes (Na32 and Na65), because addition of a stable compound CH$_3$Cl to a sodium complex would have little effect on the structural change (see Figure 2 and Table 3). It is evident from the HF/STO-3G result that the energy difference between the two TS states (1.52 kcal/mol) is also very close to that between the two sodium complexes (1.89 kcal/mol), as listed in Table 2. This tendency would have little change even at higher levels of calculation using larger basis sets. That is, the energy difference between the two states is expected to be very close to that between the two TSs at any higher level of calculation. Therefore, the former can be replaced by the latter to a certain degree, which is in accord with Hammond's postulate.[19] Since TS32 has a lower energy than TS65 at the HF/STO-3G level, the Curtin$-$Hammett principle[18] would conclude that the O3 position is the major reaction site. However, the HF/STO-3G results would not be accurate enough to study the origin of the regioselectivity which might be somewhat sensitive to the calculational level used. It should be noted that the relative stability between two TSs and between two intermediates can be changed at a higher level of calculation, which will be seen later. Since the location of TSs was not possible at higher levels of calculation and the TSs are reactant-like, we studied the energies and structures of the reactants (or the possible intermediates, in particular, the sodium complexes) with higher levels of calculation using larger basis sets, which are listed in Tables 2 and 4 and Supporting Information.

(c) Relative Stabilities of the Intermediates in Isolated States. As stated above, we focus our attention on the sodium-chelated species which is in an environment very similar to the TS states. However, for comparison with as well as better understanding of the Na-chelated species, the relative stability of Ion3 with respect to Ion6 is also reported. As shown in Table 2, at the HF/STO-3G level, Ion6 is more stable than Ion3 by 0.64 kcal/mol in terms of the energy (E_e) without ZPE correction at 0 K, and by 0.47 kcal/mol in terms of Gibbs free energy (G_{298}) at 298 K and 1 atm. The two corresponding values by HF/6-31+G* are 1.09 and 0.89 kcal/mol, respectively. The difference between the energies predicted by HF/STO-3G and HF/6-31+G* is not great. This relative stability does not change much in the MP2 calculations, either. The single-point MP2/STO-3G calculations at the HF/STO-3G optimized geometries predict that Ion6 is more stable than Ion3 by 0.97 kcal/mol. This relative energy is predicted to be 1.24 kcal/mol for MP2/6-31G* and 1.09 kcal/mol for MP2/6-31+G*//HF/6-31+G*. Therefore, for the anionic species the relative stability of Ion6 with respect to Ion3 does not change with the basis sets and the methods employed.

Among the four sodium complexes, the most stable complex is Na32. It is apparent that the HF prediction of the relative stability of Na32 with respect to Na65 is consistent with the experimental observation. For HF/STO-3G, Na32 is 1.9 kcal/mol more stable than Na65, and for HF/6-31G* and HF/6-31+G*, 0.2$-$0.3 kcal/mol more stable in terms of E_e, which increases to 1.0 kcal/mol in terms of G_{298}. However, the MP2 calculations using the 6-31G* or 6-31+G* basis set lead to a
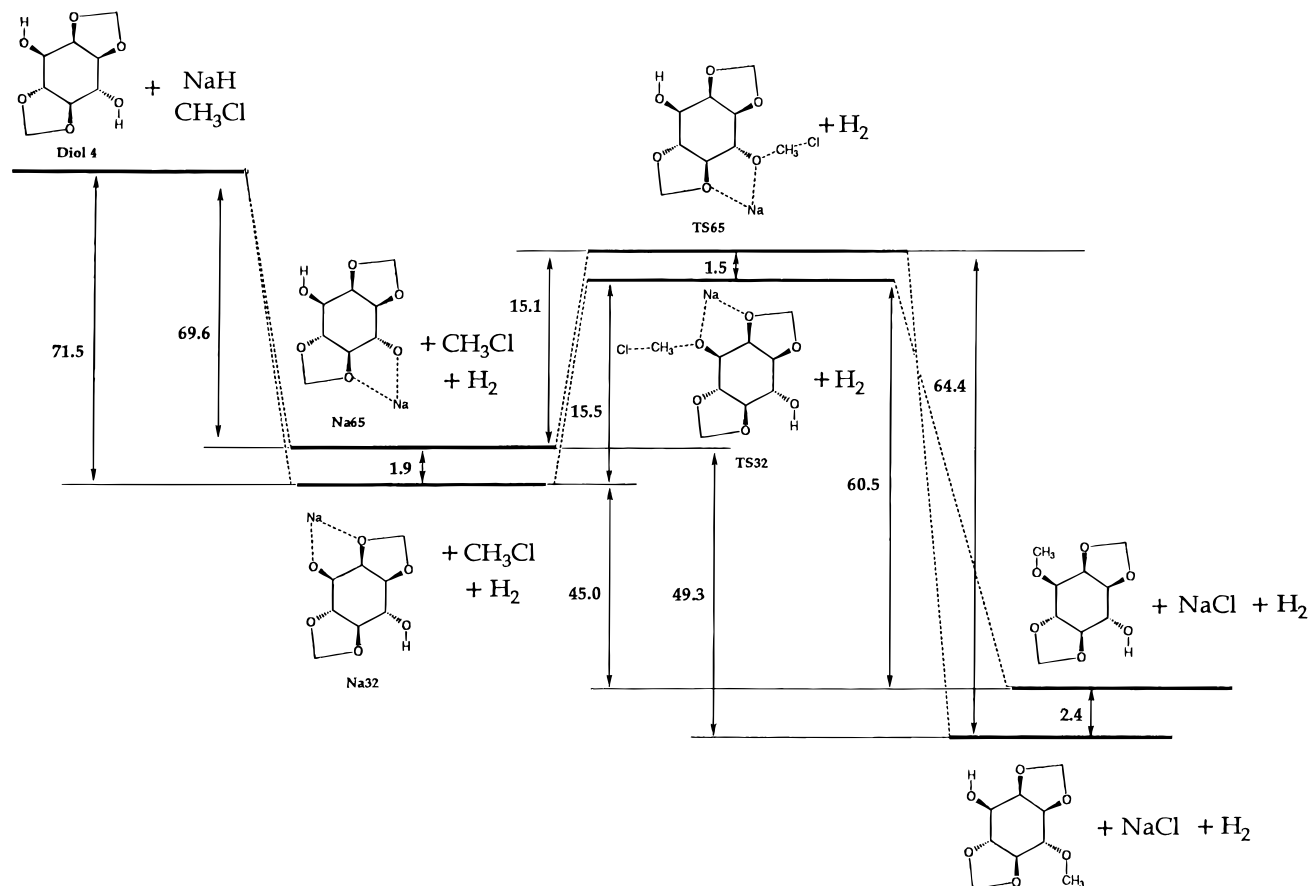
Figure 3. Schematics of TS energy profiles.

totally different conclusion. That is, the relative stability has been reversed: Na32 is 1.0 kcal/mol less stable than Na65. The MP2 results using larger basis sets should be considered more reliable, so we now have a dilemma that the reliable results are in contradiction to the experimental observation. Therefore, we analyzed their structures. First, the analysis of the geometrical changes of the deprotonated intermediates relative to **4** shows that the greatest difference comes from the distance between negatively charged oxygen and nearby vicinal ether oxygens. For MP2/6-31G*, the bond length of C3—O3 in Ion3 and that of C6—O6 in Ion6 are shortened by 0.11 Å, so that the C—O bonds in the anionic intermediates have the double bond character, while the C—O bonds in **4** have the single bond character. The atomic charges of the anionic O3 in Ion3 and O6 in Ion6 are −0.8 au in contrast to −0.7 au for the atomic charge of O3/O6 in **4**. The O3···O2 distance is lengthened in Ion3 by 0.14 Å, and the O6···O5 distance is lengthened in Ion6 by 0.09 Å. This implies that the Coulombic repulsion between O3 and O2 in Ion3 is greater than that between O6 and O5 in Ion6. In addition, the H···O distances in Ion3 and Ion6 are shortened by 0.1−0.2 Å. This indicates that the interoxygen repulsions (O3···O2, O6···O5) and intramolecular hydrogen bonding interactions (H6···O5, H3···O2) give the major effect on the relative stability of the anionic species. In the anionic species the interoxygen distance needs to be much greater to reduce the Coulombic repulsion between the highly negatively charged O3/O6 and the neighboring oxygen O2/O5. At the same time, the remaining OH group needs to be utilized to strengthen the hydrogen bond interaction by shortening the hydrogen bond length. Ion3 is less stable than Ion6 due to stronger interoxygen repulsion as well as weaker hydrogen bond interaction. It is certain that in the presence of solvents with high dielectric constants the weakened coulombic forces stabilize Ion3 more than Ion6.

Second, we turn our attention to the structures of the sodium-chelated intermediates. At the MP2/6-31G* level, the bond length of C3—O3 in Na32 is 1.36 Å. This bond length is 0.05 Å longer than that in Ion3 which has some of the double bond character due to the deprotonation, and 0.05 Å shorter than that in **4** which has the single bond character. The same tendency is found for the C6—O6 distance in Na65. The sodium chelation plays an important role to stabilize the intermediate by the interaction between the sodium ion and the neighboring oxygens. Therefore, the sodium intermediates should be much more stable than the naked anionic species, and the reaction would proceed via sodium chelation instead of the anionic species, as discussed earlier. Nevertheless, while the HF/6-31G* results are slightly in favor of experiments, the more reliable MP2/6-31G* results are in disagreement with experiments.

Comparing the HF/6-31G* and MP2/6-31G* structures, the interoxygen distances of O2···O3 and O6···O5 are found to show the most significant changes. For the MP2 structures relative to the HF structures, the O3···O2 distance is lengthened in Na32 by 0.046 Å and the O5···O6 distance in Na65 by 0.045 Å. This lengthening arises because the Coulombic repulsion between O2 and O3 or between O5 and O6 is much stronger at the MP2 level than that at the HF level. At the HF/6-31G* level, the notable structural change of Na32 from **4** is the distance increment in O3···O2 (by 0.046 Å), while that of Na65 from **4** is the distance decrement in O6···O5 (by 0.064 Å). Therefore, the interoxygen distance change is slightly greater in Na65 than in Na32. This would imply that Na65 is slightly less stable than Na32, which is in agreement with the calculated relative stability. On the other hand, at the MP2/6-31G* level, a large O3···O2 distance increment was needed in Na32 (from 2.710 to 2.801 Å), while the O6···O5 distance in Na65 was slightly reduced from 2.977 to 2.960 Å. In Na32 the angle of O3···Na···O2 became 79.0° after the O3···O2 distance was

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lengthened by 0.084 Å, while in Na65 the angle of O6···Na··· O5 became 84.1° after the O6···O5 distance was shortened by 0.021 Å. Therefore, at the MP2/6-31G* level the O3···O2 distance of **4** (2.710 Å) is short for a sodium ion to fit in a space around O3 and O2, while the O6···O5 distance of **4** (2.977 Å) is reasonably optimal for a sodium ion to fit in a space around O6 and O5. The O6···O5 distance in **4** was already large enough to compensate the O6···O5 Coulombic repulsion with the Na···O6/O5 interactions. Although there is a strong interaction between the sodium ion and O3/O2, the O3···O2 distance in Na32 is too short after deprotonating H3 from **4** because the Coulombic repulsion between O3 and O2 is too large. This would make Na32 be less stable than Na65 at the MP2/6-31G* level. However, this MP2 result cannot explain the experimental regioselectivity. Since the MP2 geometries of **4** are in excellent agreement with X-ray experiment, further higher levels of calculation should not change the MP2 geometry and relative stability significantly. Then, this implies that an important factor is missing in our investigation.

(d) Possible Factors To Determine the Regioselectivity. We investigated possible main factors to determine the regio-selectivity, for example, charge, HOMO/LUMO, and polarizability. However, we could not find any significant difference in those physical and chemical properties between Ion3 and Ion6 and between Na32 and Na65. The atomic charges of these species were investigated by both Mullikan population analysis (Mullikan charges) and natural bond orbital population analysis (NBO charges)[20] at the HF/6-31G* level. These charges are listed in the Supporting Information. The most important charges that can affect regioselectivity are the alkoxide oxygen charges. Compared to **4**, the anionic species has more negative charges on the alkoxide oxygens. The charge of O3 in Ion3 (−0.83 au in Mulliken charge, −1.02 au in NBO charge) is almost the same as or 0.01 au less negative than that of O6 in Ion6. The very small difference as well as the wrong prediction of the selectivity is not consistent with the experimental regioselectivity. In the sodium complexes (Na32, Na65), their charge difference is also negligible. The charge of O3 in Na32 (−0.83 au in Mulliken charge, −1.10 au in NBO charge) is again 0.02 au less negative than or almost the same as that of O6 in Na65. Because the O3 position was the major site to be derivatized, this cannot be the origin of the observed regiose-lectivity. The charge difference does not seem to be responsible for the observed regioselectivity.

Because the inositol species acts as a nucleophile in the derivatization reactions, the HOMO energy level can be important. As nucleophilicity increases, the HOMO energy level tends to be higher. For the deprotonated species, the HOMO energy level of Ion3 is almost the same as that of Ion6 (−4.2 eV for HF/6-31+G*). For sodium complexes, the HOMO level of Na32 is almost the same as that of Na65 (−9.0 eV for HF/6-31+G*). Thus, the HOMO energy cannot explain the experimentally observed regioselectivity.

As another possible factor to determine the regioselectivity, we investigated polarizabilities of the intermediates. The calculated polarizabilities, which show a slight dependence of the basis set used, are listed in Table 5. For the anionic species, the polarizability of Ion3 is greater than that of Ion6 by 0.60, 0.41, and 0.70 au for HF/STO-3G, HF/6-31G*, and HF/6-31+G*, respectively. The HF/6-31+G*-predicted polarizabilities of Ion3 and Ion6 are 102.99 and 102.29 au, respectively. For sodium-chelated complexes, Na32 has a polarizability larger than Na65 by 0.53 and 0.14 for HF/STO-3G and HF/6-31G*, respectively. For all the calculated results, the O3-alkoxide has a larger polarizability than the O6-alkoxide: a larger polariz-

TABLE 5: Average Polarizabilities (α) and Distances between Oxide Oxygen and Nearest Vicinal Oxygen[a]

	α	Δα	d(O···O)
HF/STO-3G			
Ion3	57.49	0.60	2.954
Ion6	56.89		3.137
Na32	58.27	0.53	2.784
Na5	57.74		2.931
TS32	77.08	0.95	2.729
TS65	76.13		2.891
HF/6-31G*			
Ion3	89.45	0.41	2.852
Ion6	89.04		3.046
Na32	92.25	0.14	2.744
Na65	92.11		2.912
HF/6-31+G*			
Ion3	102.99	0.70	2.877
Ion6	102.29		3.046

[a] Δα is relative polarizability. Polarizabilities are in au; distances in Å.

ability is found for the shorter O···O distance between the oxide oxygen and the nearest vicinal oxygen. Similarly, the polarizability difference between Na32 and Na65 is smaller than that between Ion3 and Ion6, as the O···O distance is shorter in the sodium complexes than in the ionic species. Therefore, the sodium plays a role to reduce the polarizability difference of the intermediates, in particular for the ionic species. This is likely due to the through-space α-effect arising from the repulsion between the lone pair electrons of the alkoxide oxygen and those of the nearest vicinal oxygen. Although the data do not show the linear dependence between the polarizability difference and the O···O distance difference, they seem to be somewhat related. However, the polarization difference in the ionic species is much greater than that in the sodium complexes. If this were the dominating factor, the anionic species rather than the sodium complex should be more prominantly involved in the reaction. In fact, the sodium chelation is expected to give an adverse effect on the regioselectivity, which is contrary to the experimental observation. Therefore, the polarizability cannot be the most important factor determining the regiose-lectivity. Furthermore, from the experimental regioselectivity found in 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol which is an isomer of **2**, we find that the regioselectivity is altered with changes of solvents and catalysts used, while the polarization of the intermediates does not change because the molecular structure does not change.[7b,1,9] Therefore, instead of the polarization of the intermediates, the polarized medium, i.e., solvent, may affect the regioselectivity. Furthermore, as discussed already, our structural analysis implied that the highly polarized medium would stabilize Ion3 more than Ion6, and Na32 more than Na65, because the interoxygen repulsions would be substantially reduced. This implication leads us to study the solvent effects on the intermediates.

(e) Solvent Effects on the Regioselectivity. At first sight, the regioselectivity does not appear to be dependent on the solvents for the experiments shown in Table 1. Nevertheless, most of the solvents used in the experiments were polar. The dielectric constants (ε) of the solvents used in the experiments (Table 1) are ε(DMF = *N*,*N*-dimethylformamide) = 36.7, ε(pyridine) = 12.3, ε(CH₂Cl₂) = 9.0, and ε(toluene) = 2.4.[21] The toluene solvent in entry 2 of Table 1 has small ε, and thus, it is considered as almost nonpolar solvent. In most cases, the solvent used in the experiments was DMF. Therefore, we have performed SCRF calculations using both HF and MP2 methods with ε = 40. In going from ε = 1 to ε = 40 the stability of Na32 with respect to Na65 is enhanced by 1.5 and 1.8 kcal/ mol at the SCRF(HF)/6-31G* and SCRF(MP2)/6-31G* levels,

respectively; thus, Na32 is more stable than Na65 by 1.74 and 0.85 kcal/mol, respectively. Therefore, not only SCRF(HF) but also SCRF(MP2) predicts that Na32 is slightly more stable than Na65, in contrast to the MP2 results on the isolated state. The correction of zero-point vibrational, thermal, and entropic energies is 0.71 kcal/mol at the HF/6-31G* level. The value to be corrected does not change much with the basis sets employed, as can be noted from the HF/STO-3G, HF/6-31G*, and HF/6-31+G* results for the relative energy differences of Ion3-Ion6 and of Na32−Na65. It has been noted and discussed that such a value to be corrected does not change much with the basis sets and with the levels of calculation employed in the water cluster and ion−water cluster systems; the correction is not significant unless the binding energy change is drastic.[17,22,23] Similarly, we expect that in solvent, the correction would be reduced slightly, but not by much. This correction would make Na32 be more stable than Na65 by 2.45 (for SCRF-(HF)) and 1.56 (for SCRF(MP2)) kcal/mol in terms of free energy ΔG_{298}, which would give the product ratios of 98:2 and 93:7, respectively. This partly explains the experimental regioselectivity of the reaction, in which the product derivatized at the O6 position is much smaller compared with those derivatized at the O3 position. Now the MP2/6-31G* results with $\epsilon = 40$ are in reasonable agreement with experiments. In the case of the anionic intermediates, the MP2/6-31G* calculations with $\epsilon = 40$ predict that Ion3 is still less stable than Ion 6, but the energy difference has been reduced down to 0.34 kcal/mol from 1.24 kcal/mol (for $\epsilon = 1$). If the zero-point vibrational, thermal, and entropic energy correction (0.21 kcal/mol) predicted by HF/6-31G* or HF/6-31+G* is made, the free energy difference is further reduced down to 0.13 kcal/mol, so that the two anionic species (Ion3, Ion6) would be almost isoenergetic. Nevertheless, the anionic species may not play an important role in the formation of the transition states. Only the sodium-chelated intermediates can explain the regioselectivity in favor of the O3 position in the presence of polar solvents.

In a previous section, we noted that at the MP2/6-31G* level the O3···O2 distance is somewhat short for a sodium ion to fit in the space around O3 and O2, as can be seen from the angle of O−Na−O (79.0°). The aqua-Na(I) complexes favor the coordination number between 4 and 6.[24] This indicates that the angle of 79.0° seems to be too small. This, in turn, implies that the anisotropic polarization of Na toward a cone-shaped space with a somewhat small angle formed by O3 and O2 would stabilize Na32 less than Na65 in which the cone-shaped space has a reasonably wide angle formed by O6 and O5 (84.4° for the angle O6···Na···O5). In the presence of polar solvents, the anisotropicity of the polarization of Na toward two vicinal oxygens will be much reduced because the polarization toward the polar solvent molecules is needed. Then, the polar solvents stabilize Na32 much more than Na65.

The experiments still show the regioselectivity at the O3 position with bases much weaker than NaH (entries 5−8 in Table 1). These weaker bases are also expected to interact with **4**, forming a complex of its conjugate acid (having a protonated nitrogen atom) and the anionic species of **4** (Ion3, Ion6). The conjugated acid and base species, i.e., both protonated and deprotonated species, cannot be in their isolated forms which are energetically much unstable. Therefore, their complex would be similar to the sodium-chelated species. That is, the positively charged H atom of the protonated species would play a role similar to that shown by Na⁺ (which would be partially hydrated) in the sodium-chelated reaction pathway. Therefore,
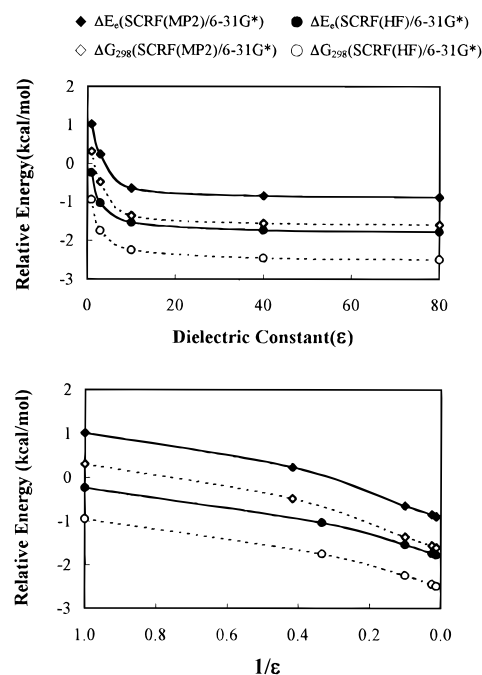
Figure 4. Dependency of the relative energy of Na32 with respect to Na65 on the solvent dielectric constant ϵ (SCRF/6-31G*).

the regioselectivity for the four entries 5−8 in Table 1 may be similarly understood.

Next, we need to explain the regioselectivity of the reaction in toluene (entry 2 in Table 1) which has small ϵ. In this case, the selectivity is not as pronounced, with the product ratio of 48.1−11.5% for the O3 and O6 derivatives. This corresponds to the Gibbs free energy difference of only 0.85 kcal/mol. We have performed the SCRF calculations for different values of ϵ. The relative stability of Na32 with respect to Na65 by SCRF-(HF) and SCRF(MP2) is given in Figure 4. As long as the primary origin of the relative stability comes from the Coulombic interaction, the relative stability would change almost linearly with ϵ^{-1}. The figure indeed shows the almost linear relationship. Thus, even toluene ($\epsilon = 2.4$) shows a significant solvent effect on the relative stability. The SCRF(MP2) predicts that Na32 is 0.2 kcal/mol less stable than Na65. An approximate zero-point vibrational, thermal, and entropic energy correction would make Na32 more stable than Na65 by 0.5 kcal/mol, leading to the regioselectivity ratio of 42:18 for O3:O6, which is in good agreement with the experimental ratio of 48.1:11.5. This result should be compared with the alkylation reaction in DMF in which the product ratio of 93:7. Therefore, our results indeed show that in the presence of NaH, the alkylation reaction in toluene has a much lower regioselectivity than that in DMF, in agreement with the experimental regioselectivity (entries 1 and 2 in Table 1). In this case, the SCRF(HF) predicts that the regioselectivity ratio of 56:4, which is in somewhat less agreement with the experiment than the SCRF(MP2). Of course, the SCRF(MP2) results would not be accurate enough to predict the accurate product ratio. However, the prediction of the solvent effect on the regioselectivity in favor of the O3 position should be reliable, because both SCRF(HF) and SCRF-(MP2) lead to the same conclusion.

IV. Conclusion

The probable pathways for alkylation of **4** in the presence of bases such as NaH, pyridine, and amine would might proceed through intermediates of either naked anionic species or sodium-chelated species (or corresponding ammonium-chelated com-

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plexes). The reactions with naked anionic species are too exothermic to have transition states. Since the reactions do not proceed fast enough, there must be activation barriers in reality, implying that the reactions would be initiated by the attack of sodium hydride (or a nitrogen base) on the alcoholic hydrogen. Sodium chelation (or ammonium ion chelation) with the anionic species plays an important role to stabilize the intermediates by the interaction between the sodium (or proton) and the neighboring oxygens. Therefore, the intermediates of the sodium-chelated complexes (or ammonium ion complexes) should be much more stable than the naked anionic intermediates.

The alkylation reaction of **4** in the presence of NaH is found to proceed via early transition states, on the basis of our *ab initio* calculations. However, the TSs were located only at the HF/STO-3G level. These results would not be reliable enough to study the origin of the regioselectivity of **4** in favor of the O3 position rather than O6. Since early TS structures are similar to those of the initial reactive intermediates, we investigated the intermediates with higher levels of theory using larger basis sets. Among four sodium-chelated species, Na32 is more stable than Na34, and Na65 is more stable than Na61. In isolated systems, Na32 is less stable than Na65. This is in contradiction to the experimental observation. We tried to find the dominating factor to determine the regioselectivity. Atomic charges, HOMO energies, and polarizabilities could not explain the experimental observation. However, it was found that polar solvents help stabilize Ion3 and Na32 much more than Ion6 and Na65, respectively. At the most reliable SCRF(MP2)/6-31G* level, for $\epsilon = 1$, Na32 is less stable than Na65; for $\epsilon > 1.5$, Na32 becomes more stable than Na65 in terms of free energy; for $\epsilon = 40$, Na32 turns out to be the dominating species, while Na65 makes a negligible contribution. Thus, the solvent effect which reduces the interoxygen repulsions and the anisotropicity of the polarization of Na toward two vicinal oxygens is highly responsible for the regioselectivity in favor of the derivatization to the O3 position. This solvent effect was demonstrated by both SCRF(HF) and SCRF(MP2) results which showed that in the presence of NaH, the alkylation reaction in toluene has a much lower regioselectivity than that in DMF. This is in agreement with experiment. However, the SCRF-(HF) results could not explain the absolute regioselectivity, while the SCRF(MP2) results are close to the experimental regioselectivity, implying that these results are not far from the asymptotic values to be predicted by higher levels of theoretical calculation. Nevertheless, our results should be interpreted only qualitatively because our approximations made on the SCRF-(MP2) results are not reliable enough to predict the accurate product ratio.

Supporting Information Available: Table of HF/6-31G*, HF/6-31+G*, and DFT(B3-LYP)/6-31G* structures of **4** and its anionic and sodium-chelated species, and table of Mulliken and NBO charges (2 pages). Ordering information is given on any current masthead page.

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