Friedel-Crafts-Type Reactions Involving Di- and Tricationic Species. Onium-Allyl Dications and O,O-Diprotonated *aci*-Nitro Species Bearing a Protonated Carbonyl Group

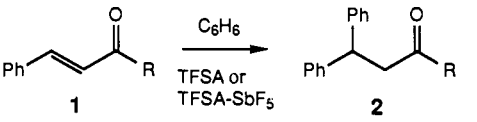
Tomohiko Ohwada, Naoko Yamagata, and Koichi Shudo*

Contribution from the Faculty of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan. *Received May 30, 1990*

Abstract: Stable carbocations do not react with nonactivated benzenes. For example, acetophenone does not react with benzene in the presence of trifluoromethanesulfonic acid (TFSA), while trifluoroacetophenone does do so under acidic conditions owing to activation of the electrophilicity of the hydroxycarbenium cation by the trifluoromethyl group. This and other studies suggest that an electron-withdrawing substituent on the cationic center increases the reactivity toward benzenes. In this paper, involvement of multiply positively charged (dicationic and tricationic) species, which have sufficient electrophilicity toward benzene, is demonstrated in the acid-catalyzed reactions of cinnamaldehyde and its derivatives and also in the acid-catalyzed reactions of nitromethanes. The species formed from cinnamaldehyde, cinnamaldimine, cinnamaldoxime, and their derivatives in TFSA or TFSA-SbF_5 have an adequate reactivity toward benzene. O-Protonated cinnamaldehyde and its derivatives, N-protonated cinnamaldimine, and *N,N*-dimethylcinnamaldiminium salt do not react with benzene. Since a strong acid catalyst is required for the reactions, participation of doubly protonated species, onium-allyl dications, is proposed. Ab initio calculations of (1) the donor-acceptor interaction energies of a neutral donor (such as water and ammonia) and a doubly charged allyl dication and (2) proton affinities demonstrated that the ammonium-allyl dication is more stable than the oxonium-allyl dication, in accordance with the experimental observation. Nitronic acids also react with benzene at the ipso position with respect to the nitro group to give the phenylated oximes in the presence of TFSA. The reaction with benzene is not catalyzed by trifluoroacetic acid, which is sufficiently acidic to monoprotonate a nitronic acid to the protonated *aci*-nitro form. The reaction requires a stronger acid, trifluoromethanesulfonic acid, suggesting intervention of the dication formed by O,O-diprotonation of *aci*-nitroalkanes rather than the monoprotonated *aci*-nitroalkane. As a result of further study on the phenylation reactions, we found a facile phenylation reaction of nitromethanes substituted with an electron-withdrawing group, catalyzed by TFSA, to give phenylated α-carbonyloximes in high yields. A triply positively charged cation, an O,O-diprotonated *aci*-nitro species bearing a protonated ethoxycarbonyl group, which can react with nonactivated benzene, is proposed to be an intermediate in this reaction.

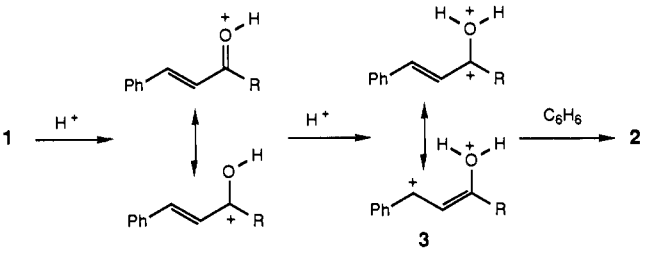
Friedel-Crafts and related reactions are most important in the chemistry of aromatic compounds. Such carbon-carbon bond-forming reactions between aromatic compounds and carbon electrophiles are well documented in excellent reviews.[1] A great variety of reactivities and mechanisms have been identified and discussed. Some stable carbocations do not react with nonactivated benzenes. For example, acetophenone does not react with benzene in the presence of trifluoromethanesulfonic acid (TFSA), while trifluoroacetophenone does do so under acidic conditions.[2] The trifluoromethyl group activates the electrophilicity of the hydroxycarbenium cation.[3] On the other hand, experimental and theoretical studies of carbocations with electron-withdrawing substituents, involving carbonyl[4,5a] and cyano[5a,6] groups, have demonstrated a facile formation of these electron-deficient carbonium ions, leading to the postulation that substitution by such groups in place of hydrogen on a cationic center is not destabilizing, but rather stabilizing.[4,6] In the case of the reactions of the diphenylmethyl cations, substitution with a protonated carbonyl group (not merely a carbonyl group) on the cation center is sufficiently activating to allow a facile 4π electrocyclization to form the fluorene.[5] These results can be interpreted in terms of a comparable electron-withdrawing ability of a protonated carbonyl (or a protonated cyano) group to that of the trifluoromethyl group. Accumulation of these and related observations has led to the general premise that a *genuine* electron-withdrawing substituent on the cationic center increases the electrophilicity toward benzenes. In this paper we demonstrate the involvement of multiply positively charged (dicationic and tricationic) species, which have sufficient electrophilicity toward benzene, in the acid-catalyzed reactions of cinnamaldehyde and its derivatives and in the acid-catalyzed reactions of nitromethanes.

Scheme I



a: R = H, **b**: R = CH_3, **c**: R = Ph, **d**: CH=CHPh

Scheme II



Allyl Cations Substituted with an Onium Group React with Benzenes. Onium-Allyl Dications

Acid-Catalyzed Reactions of Cinnamaldehyde and Its Derivatives. Cinnamaldehyde (**1a**), 4-phenyl-3-buten-2-one (**1b**), chalcone (**1c**), and 1,5-diphenyl-1,4-pentadien-3-one (**1d**) did not react with benzene in trifluoroacetic acid. In TFSA (10 or 100 equiv with respect to the substrate), they reacted with benzene at 23 °C to give the corresponding monophenylated compound **2a-d** (and compounds secondarily derived from it) (Scheme I), though the yields were variable (Table I). The parent compound, cinnam-

(1) *Friedel-Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley: New York, 1964; Vol. II, Chapter XV (Koncos, R.; Friedman, B. S.); and Vol. II, Chapter XIX (Hofmann, J. E.; Schriesheim, A.).
(2) Kray, W. D.; Rosser, R. W. *J. Org. Chem.* **1977**, *42*, 1186.
(3) Koshy, K. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1980**, *102*, 1216. Liu, K.-T.; Sheu, C.-F. *Tetrahedron Lett.* **1980**, *21*, 4091. Allen, A. D.; Kanagasabapathy, V. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1983**, *105*, 5961. Kwong-Chip, J. M.; Tidwell, T. T. *Tetrahedron Lett.* **1989**, *30*, 1319.
(4) (a) Creary, X. *Acc. Chem. Res.* **1985**, *18*, 3. (b) Takeuchi, K.; Kitagawa, T.; Okamoto, K. *J. Chem. Soc., Chem. Commun.* **1983**, 7.
(5) (a) Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1988**, *110*, 1862. Ohwada, T.; Shudo, K. *J. Org. Chem.* **1989**, *54*, 5227. (b) Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1989**, *111*, 34.
(6) Review: Gassman, P. G.; Tidwell, T. T. *Acc. Chem. Res.* **1983**, *16*, 279. Tidwell, T. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 20.

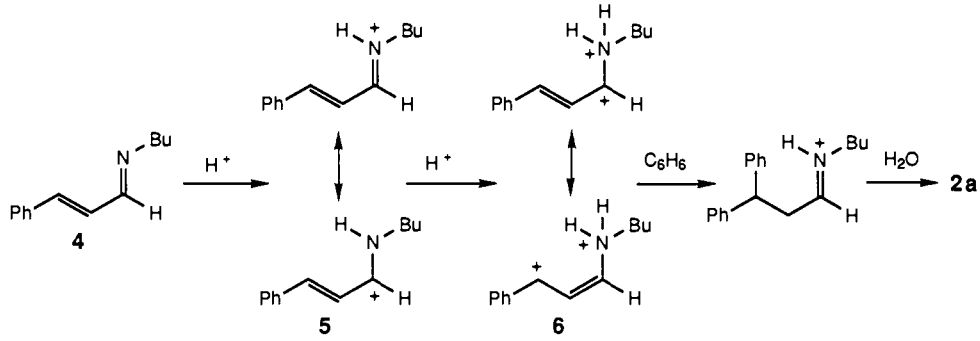
0002-7863/91/1513-1364$02.50/0

Table I. Acid-Catalyzed Reactions of PhCH=CH(=X)—R

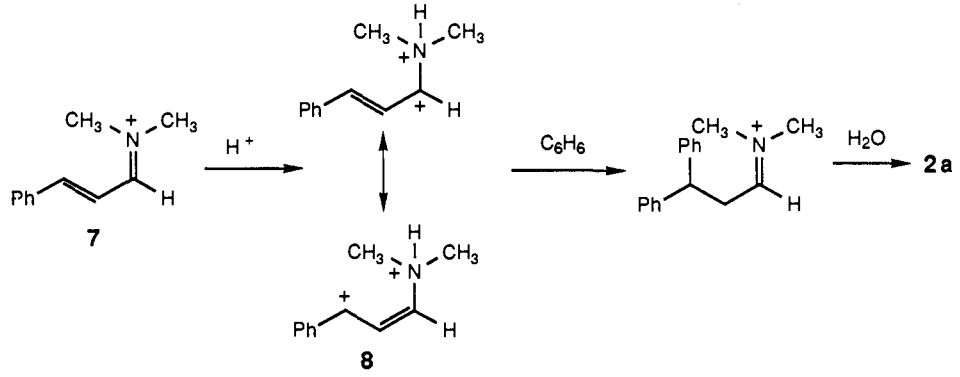
	X	R	acid	time,[a] h	product, %	recovery, %
1a	O	H	TFSA[b]	24	6[f]	87
1b	O	CH_3	TFSA[b]	24	60[g]	18
1b	O	CH_3	TFSA-SbF_5[b,d]	8	46[h]	29
1c	O	Ph	TFSA[b]	24	83[i]	7
1c	O	Ph	TFSA-SbF_5[b,d]	8	89[j]	9
1d	O	CH=CHPh	TFSA[b]	1.5	98	0
4	NBu	H	TFSA[c]	24	39	2[k]
7	$N(CH_3)_2$	H	TFSA[c]	24	83	16[k]
15a	NOH	H	TFSA[c]	24	92	2
15b	NOH	CH_3	TFSA[c]	6	90	2
15b	NOH	CH_3	TFSA-SbF_5[c,e]	3	91	3
15c	NOH	Ph	TFSA[b]	1.5	99	0
15c	NOH	Ph	TFSA-SbF_5[b,d]	0.25	65	0

[a] All the reactions were performed at 23 °C. [b] A 100-fold molar excess of the acid was used. [c] A 10-fold molar excess of the acid was used. [d] TFSA-SbF_5 mole ratio 95:5. [e] TFSA-SbF_5 (mole ratio 2.5:1). [f] 3-Phenylindene (6%). [g] Indenes (60%). [h] Indenes (46%). [i] **2c** (76%) and indenes (7%). [j] **2c** (80%) and indenes (9%). [k] Cinnamaldehyde.

Scheme III



Scheme IV



aldehyde (**1a**), yielded 3-phenylindene, and 4-phenyl-3-buten-2-one (**1b**) yielded 1-methyl-3-phenyl- and 1-phenyl-3-methylindenes. These products were formed from **2a** and **2b** under the reaction conditions. Chalcone (**1c**) gave the phenylated ketone **2c** in a high yield (76%) in the reaction, together with a 7% yield of 1,3-diphenylindene. 1,5-Diphenyl-1,4-pentadien-3-one (**1d**) also gave the monophenylated ketone **2d** in 98% yield. If the acidity was increased by the addition of SbF_5, the reaction was accelerated, indicating a requirement for a strong acid (Table I and Scheme II).[7] This suggests the participation of the O-protonated allyl cation (**3**).

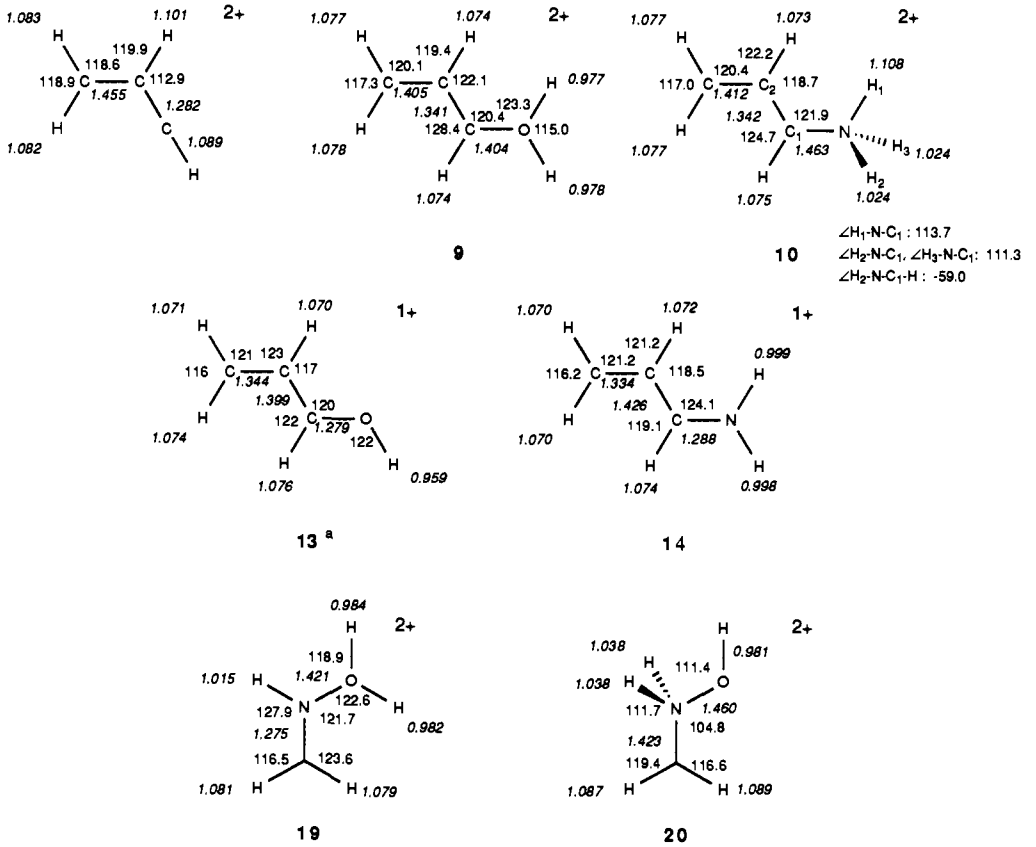
Cinnamaldimine (**4**) in TFSA also reacted with benzene at 23 °C to give 3,3-diphenylpropaldehyde (**2a**) in 39% yield after hydrolysis during aqueous workup. The same product was not formed at all, but cinnamaldehyde was recovered after hydrolysis, when the acid was replaced by trifluoroacetic acid, which is sufficiently acidic to protonate the imine.[8] The monoprotonation in TFA has been confirmed by the observation of the signal of a protonated species (**5**) in the ^1H NMR spectrum (an NH proton at 10.4 ppm). This clearly shows that the further protonation of **5** is required for the phenylation reaction (Scheme III). This conclusion is confirmed by the observation that the *N,N*-dimethyliminium salt (**7**), which corresponds to monoprotonated **4**, i.e., **5**, did not react with benzene in TFA, whereas in the presence of TFSA it gave diphenylpropaldehyde (**2a**) in good yield (83%) after hydrolysis (Scheme IV). It is not surprising that **5** and **7** (and, by deduction, protonated **1**) are stable and do not react with nonactivated benzene, because they can be regarded as allyl cations stabilized by a phenyl group and an amino or a hydroxyl group. All the experimental results favor the postulation that the reactive species are formed by an additional protonation of the monocationic species.

Since the cinnamaldehyde and its imine derivatives in CF_3SO_3D did not show any indication of deuterium exchange of the olefinic and aromatic protons, the additional protonation must occur on the oxygen or the nitrogen atom. Thus, we propose the participation of onium–carbenium dications or strongly destabilized allyl cations (**3**, **6**, and **8**) as the reactive intermediates.[9,10]

(7) Paspaleev, E.; Kojucharova, A. *Monatsh. Chem.* **1969**, *100*, 1213.
(8) Childs, R. F.; Dickie, B. D. *J. Am. Chem. Soc.* **1983**, *105*, 5041.

(9) Attempts to observe directly the dicationic species in super acids (TFSA-SbF_5) failed owing to rapid polymerization. Species predominantly formed in TFSA at low temperature can be assigned as the monocations.

Chart I. 4-31G Optimized Geometries of Ions (Bond Lengths Are in Angstroms and Angles Are in Degrees)



[a] Taken from ref 15.

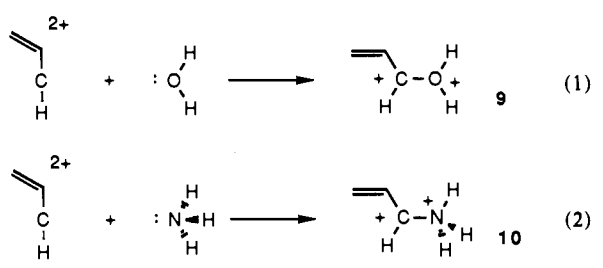
Table II. Calculated Proton Affinities to Allyl–Onium Dications

	total energy, au		proton affinity, kcal/mol	total energy, au		proton affinity, kcal/mol
	13	**9**		**14**	**10**	
4-31G//4-31G	−190.80588[a]	−190.88411	49.1	−171.05442	−171.14298	55.5
6-31G*//4-31G	−191.08543	−191.14406	36.8	−171.29674	−171.38594	55.9

[a] Reference 15.

Calculational Estimate of Relative Stabilities of Onium–Carbenium Dications. Stability and relative ease of formation of these dicationic species were estimated by molecular orbital calculations in terms of differences in (1) energies of donor–acceptor interactions of a neutral donor and a doubly charged acceptor molecule and (2) proton affinities. To simplify the calculations, we considered corresponding model dications correspondingly formed from acrolein and its imine.[11]

The first calculations were based on the conceptual assumption that such species (**9** and **10**) can be formed from allyl dication ($C_3H_4^{2+}$) and water (eq 1) or ammonia (eq 2).[12a] The optimized geometries (based on 4-31G full optimization[13]) of the fragment molecule ($C_3H_4^{2+}$) and combined molecules are shown in Chart I. The (exothermic) reaction energies (4-31G//4-31G) of these reactions are −107.7 (for eq 1) and −145.8 kcal/mol (for eq 2).[14] The larger interaction energy of the N analogue indicates the stronger C–N bonding. Donation of electrons from the stronger donor to the allyl dication leads to strong bonding, resulting in stabilization of the system. Thus, the ammonium–allyl system (**10**) is more stable and easily formed than the oxonium–allyl system (**9**): this may reflect the more facile reactions of cinnamaldimines as compared with cinnamaldehyde. The calculations (based on the 4-31G basis set)[14] on simple methylium–onium ions



(10) Olah, G. A.; Prakash, G. K. S.; Barzaghi, H.; Lammertsma, K.; Schleyer, P. v. R.; Pople, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 1032. Olah, G. A.; Prakash, G. K. S.; Lammertsma, K. *Res. Chem. Intermed.* **1989**, *12*, 141.

(11) Zalewski, R. I.; Dunn, G. E. *Can. J. Chem.* **1969**, *47*, 2263.

(12) (a) Koch, W.; Frenking, G.; Causs, J.; Cremer, D. *J. Am. Chem. Soc.* **1986**, *108*, 5808. (b) Maquin, F.; Stahl, D.; Sawaryn, A.; Schleyer, P. v. R.; Koch, W.; Frenking, G.; Schwarz, H. *J. Chem. Soc., Chem. Commun.* **1984**, 504. Higher level calculations on the cations **11** and **12** are reported in the following: (c) Lammertsma, K. *J. Am. Chem. Soc.* **1984**, *106*, 4619. (d) Paddon-Raw, M. N.; Santiga, C.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6561. (e) Yates, B. F.; Bouna, W. J.; Radom, L. *J. Am. Chem. Soc.* **1986**, *108*, 6545.

(13) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.

(14) Total energies (4-31G//4-31G, au) of allyl dication ($C_3H_4^{2+}$), H_2O, NH_3, allyl–onium dications **9** and **10**, and carbenium–onium dications **11** and **12** are as follows: allyl dication, −114.80372; H_2O, −75.90864; NH_3, −56.10669; **9**, −190.88411; **10**, −171.14298; methylene dication (CH_2^{2+}) ($C_{\infty h}$), −37.74782; **11**, −113.97380; **12**, −94.22705. The interaction energies leading to **11** and **12** were −199.0 and −233.6 kcal/mol, respectively, on the basis of the 4-31G basis set.

Table III. Acid-Catalyzed Reactions of Sodium Salts of *aci*-Nitroalkanes with Benzene

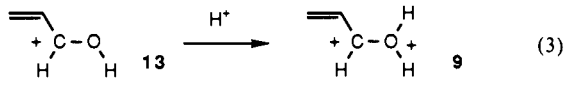
nitro	R	acid	temp, °C	time, h	oxime (**22**), %
21a	H	TFSA[a]	4	0.5	33
21a	H	TFSA-TFA[b,c]	2	1	35
21b	CH_3	TFSA[d]	5	2	40[e]
21b	CH_3	TFSA-TFA[b,c]	4	1.5	63[f]
21c	C_2H_5	TFSA[d]	5	2	54[g]
21c	C_2H_5	TFSA-TFA[b,c]	5	1.5	68[h]
21d	$PhCH_2$	TFSA[c]	4	1	33[i]
21d	$PhCH_2$	TFSA-TFA[b,c]	4	1	74[j]

[a] A 500-fold molar excess of the acid was used. [b] A mixture of TFSA and TFA (weight ratio 1:9) was used. [c] A 30-fold molar excess of the acid was used. [d] A 10-fold molar excess of the acid was used. [e] Accompanied with acetophenone (3%). [f] Accompanied with acetophenone (2%). [g] Accompanied with propiophenone (2%). [h] Accompanied with propiophenone (4%). [i] Accompanied with 2-phenyl-1-nitroethane (22%). [j] Accompanied with 2-phenyl-1-nitroethane (12%).

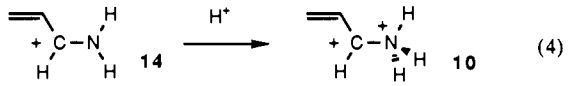
showed a larger exothermic reaction energy of the methylium–ammonium dication **12** as compared with that of the methylium–oxonium dication **11**, which is in accordance with the case

of the allyl–onium dications (**9** and **10**). The results of the reported higher level ab initio calculations[12a-e] on **11** and **12** are consistent with this trend. In the series of carbonyl compounds (**1**), the reactions are increasingly smooth in the order R = H, CH_3, Ph, and CH=CH—Ph. This order reflects the degree of diprotonation of the carbonyl moieties under the conditions used.

The second method estimates protonation energy leading to the dications (**9** and **10**) in terms of the differences in proton affinities of the monocations (**13** and **14**) (eqs 3 and 4). Previous calcu-



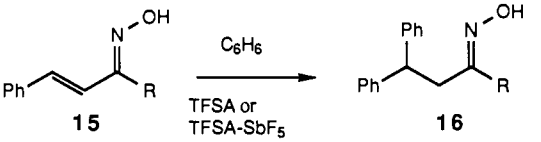
(3)



(4)

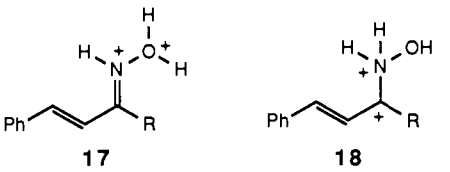
lations on O-protonated acrolein showed that protonation anti to the C–C single bond of the s-trans conformation (like **13**) is most favorable.[15] The optimization of the geometries of the monocations **13** and **14** was performed on the 4-31G basis sets, and the optimized geometries are shown in Chart I.[15] For accurate estimation of energies, single-point calculations on 4-31G-optimized geometries were performed with the d-polarized 6-31G* basis set.[16] The larger proton affinity of **14** as compared with **13** (by 19.1 kcal/mol, 6-31G*//4-31G) also provided another theoretical interpretation for the experimental substituent effects of carbonyl and imino groups in the reactions of cinnamaldehyde and its derivatives in a strong acid (Table II). Furthermore, the larger proton affinities for the allyl–onium dications, as compared with those for the methylium–onium dications (**11** and **12**), provide a basis for assuming that the former dication, stabilized by conjugation of the π electrons, forms more readily.[12e,17]

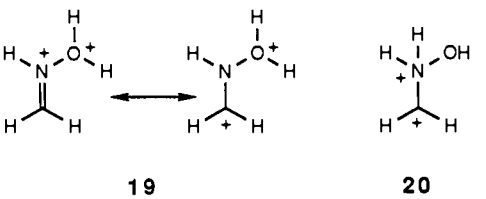
Scheme V



a: R = H, **b**: R = CH_3, **c**: R = Ph

Acid-Catalyzed Reactions of Cinnamaldoxime and Its Derivatives. (*E*)-Cinnamaldoxime (**15a**) and its derivatives (**15b** and **15c**) behaved similarly: **15** reacted readily with benzene to give the corresponding phenylated oxime (**16**) in TFSA in good yields but did not react at all in TFA (Scheme V). This can also be interpreted in terms of involvement of a diprotonated species, **17a–c** or **18a–c**. Molecular orbital calculations (4-31G//4-31G and





6-31G*//4-31G) on a model system, formaldoxime, suggest that the preferred diprotonated species is the N,O-diprotonated dication (**19**), which is 36.3 kcal/mol (6-31G*//4-31G) more stable than the N,N-diprotonated one (**20**) (4-31G-optimized geometries are shown in Chart I).[18] This is reasonable, because the cationic onium center and the carbenium center are separated. Thus, the reactive intermediates are deduced to be N,O-diprotonated cinnamaldoxime derivatives (**17a–c**).[19]

Corresponding (*Z*)-oximes [(*Z*)-**15a** and (*Z*)-**15c**] also give the phenylated products in similar yields under the same reaction conditions.

Acid-Catalyzed Reactions of Nitromethanes Substituted with a Carbonyl Group with Benzenes

Acid-Catalyzed Reactions of Nitronic Acids with Benzene. Nitronic acids (**21**) react with benzene at the ipso position with respect to the nitro group to give the phenylated oximes (**22**) in the presence of TFSA[20,21] and HF.[22] Superficially, the reaction can be understood in terms of Scheme VI. However, the reaction with benzene is not catalyzed by trifluoroacetic acid, which is sufficiently acidic to monoprotonate a nitronic acid **21** to the protonated *aci*-nitro form (**23**).[23,24] The reaction requires a

(15) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

(16) Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *66*, 217.

(17) Total energies of planar O-protonated formaldehyde and planar N-protonated formaldimine, obtained by 4-31G//4-31G are as follows: O-protonated formaldehyde (C_s), −113.98129 au; N-protonated formaldimine (C_{2v}); −94.24964 au. The corresponding proton affinities (4-31G basis set) to methylium-onium dications (**11** and **12**) are −4.7 and −14.2 kcal/mol, respectively.

(18) Total energies of **19** and **20**, obtained by 4-31G//4-31G and 6-31G*//4-31G (in parentheses) are as follows: **19**, −168.96738 au (169.19967 au); **20**, −168.89719 au (−169.14171 au).

(19) This conclusion is consistent with the reported observation of the formation of cyclohexanone oxime *N,O*-dihydrochlorides. Saito, H.; Nukada, K.; Ohno, M. *Tetrahedron Lett.* **1964**, 2124. Saito, H.; Terasawa, I.; Ohno, M.; Nukada, K. *J. Am. Chem. Soc.* **1969**, *91*, 6696.

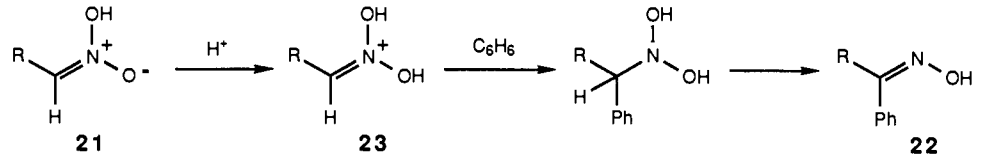
(20) Ohwada, T.; Ohta, T.; Shudo, K. *Tetrahedron* **1987**, *43*, 279.

(21) (a) Ohwada, T.; Itai, A.; Ohta, T.; Shudo, K. *J. Am. Chem. Soc.* **1987**, *109*, 7036. (b) Ohwada, T.; Ohta, T.; Shudo, K. *J. Am. Chem. Soc.* **1986**, *108*, 3029. (c) Okabe, K.; Ohwada, T.; Ohta, T.; Shudo, K. *J. Org. Chem.* **1989**, *54*, 733.

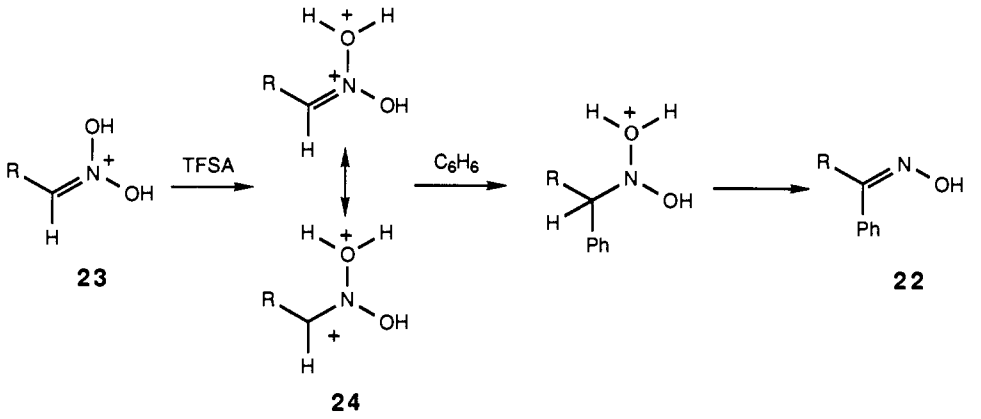
(22) Berrier, C.; Brahmi, R.; Carretre, H.; Coustard, J. M.; Jacquesy, J. C. *Tetrahedron Lett.* **1989**, *30*, 5763.

(23) (a) Hawthorne, M. F. *J. Am. Chem. Soc.* **1957**, *79*, 2510. (b) Kornblum, N.; Brown, R. A. *J. Am. Chem. Soc.* **1965**, *87*, 1742. Kornblum, N.; Brown, R. A. *J. Am. Chem. Soc.* **1964**, *86*, 2681. (c) Edward, J. T.; Tremaine, P. H. *Can. J. Chem.* **1971**, *49*, 3483.

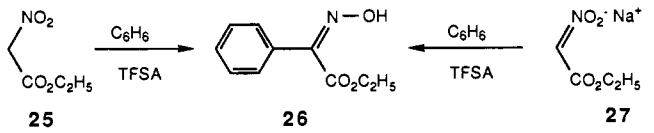
Scheme VI



Scheme VII



Scheme VIII



stronger acid, trifluoromethanesulfonic acid, suggesting intervention of the dication formed by O,O-diprotonation of *aci*-nitroalkanes (**24**) (Scheme VII) rather than the monoprotonated *aci*-nitroalkane. The intermediacy of the dication of the N,O-diprotonated oxime in the phenylation reaction of cinnamaldoximes (vide ante) provided supporting evidence for this postulation. Although phenylation reactions of sodium salts of *aci*-nitroalkanes **21a–d** (R = H, CH_3, C_2H_5, CH_2Ph) were catalyzed by TFSA (Table III), the yields of the phenylated oximes **22a–d** (R = H, CH_3, C_2H_5, CH_2Ph) were increased when the acid was replaced by a slightly weaker acid, TFSA–TFA (10% w/w, acidity H_0 equal to −9.7), which would be sufficiently acidic to diprotonate the *aci*-nitro species.[25]

Acid-Catalyzed Reactions of α-Carbonylnitromethanes with Benzenes. The proposed intermediacy of O,O-diprotonated *aci*-nitroalkanes in the reaction of benzene in TFSA is consistent with the results of previous investigations on the Nef and Meyer reactions;[23] in particular, the intervention of the dication has been proposed in the latter reaction. As a result of further study on the phenylation reactions, we found a facile phenylation reaction of nitromethanes substituted with an electron-withdrawing group, catalyzed by TFSA, to give α-phenylated oximes in high yields.

The nitromethane substituted with an ester group, α-ethoxycarbonylnitromethane (**25**), reacted with benzene at 5 °C in the presence of an excess of TFSA (10 equiv with respect to the nitro compound) to afford ethyl benzoylformate oxime (**26**) in 80% yield (Scheme VIII and Table IV). The corresponding sodium salt of the nitroalkane **27** also yielded the oxime (63%) in the reaction with benzene in the presence of TFSA. This similarity of the reactions of the neutral nitro compound **25** and the sodium salt of the *aci*-nitro compound **27** in TFSA suggests the participation

(24) Sodium salt of *aci*-2-phenyl-1-nitroethane yielded a Nef reaction product, 2-phenylethanal (5% yield), together with 2-phenyl-1-nitroethane (53%) in an excess amount of 48% TFSA–H_2O (v/v), where the acidity is equivalent to that of trifluoroacetic acid (H_0 −2.7). The formation of the Nef hydrolysis product can be interpreted in terms of involvement of the O-protonated *aci*-phenylnitroethane.

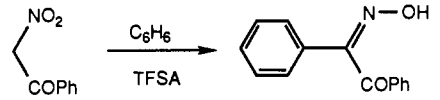
(25) The improvement of the yields is due to the decrease in the formation of polar polymeric products, probably derived from the oxime.

Table IV. Reactions of Nitromethanes Substituted with a Carbonyl Group with Aromatics in the Presence of TFSA

	substituent	aromatic	temp, °C	time, h	oxime
25	$CO_2C_2H_5$	benzene	5	5	**26**, 80%
27	$CO_2C_2H_5$	benzene	5	2.5	**26**, 63%
25	$CO_2C_2H_5$	*p*-xylene	5	2	**28**, 68%
25	$CO_2C_2H_5$	anisole	10	28	**29**, 86%[a]
30	COPh	benzene	5	2	**31**, 71%[b]
30	COPh	*p*-xylene	5	3.5	**34**, 72%[c]
30	COPh	anisole	5	5	**37**, 73%[d]

[a] Para/ortho = 2:1. [b] Accompanied with **32** (6%) and **33** (5%). [c] Accompanied with **35** (21%), **33** (11%), and **36** (4%). [d] Para/ortho = 3:2.

Scheme IX



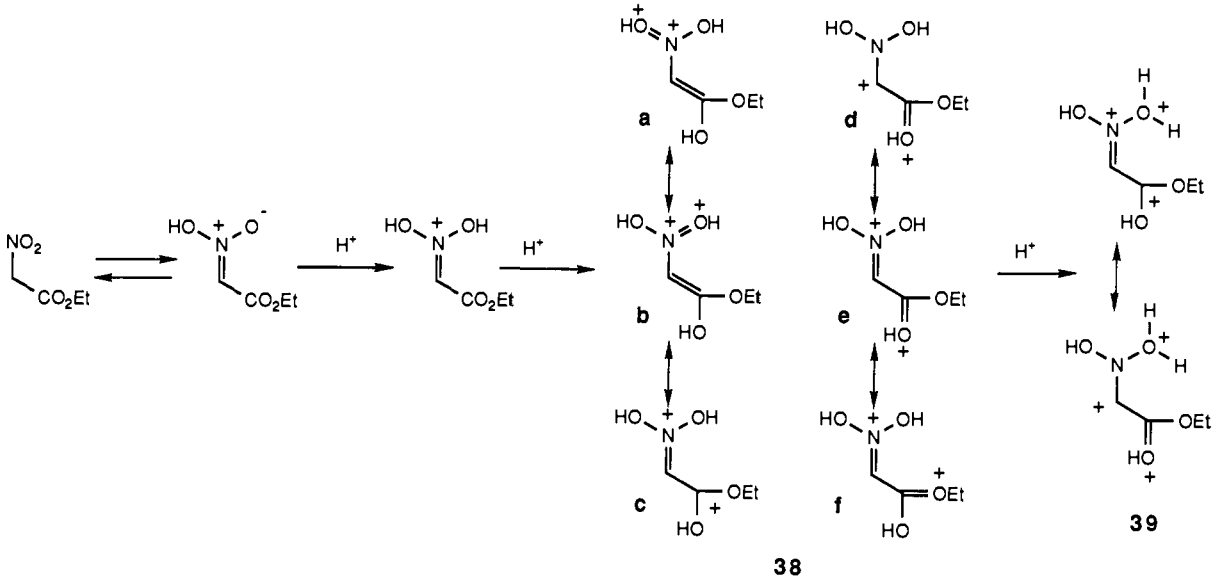
of the equilibrating *aci*-nitro form favored by the substituent effect of the ethoxycarbonyl group. Trifluoroacetic acid did not catalyze the reaction of either the neutral nitromethane **25** or the salt **27** with benzene, resulting in the quantitative recovery of **25** after aqueous workup. The reaction of **25** with substituted benzenes, *p*-xylene and anisole, also gave the corresponding oximes [ethyl (2,5-dimethylbenzoyl)formate oxime (**28**) and ethyl (methoxybenzoyl)formate oxime (**29**), respectively] in high yields (Table IV).

The corresponding reaction occurred in the case of a nitromethane substituted with a ketone, α-benzoylnitromethane (**30**).[26] In TFSA (10 equiv), **30** reacted with benzene to give benzil monooxime **31** in 71% yield (Scheme IX). The reaction was accompanied with the formation of benzaldoxime (**32**) (6%) and benzoic acid (**33**) (5%).[27] The reaction of neutral **30** also proceeded with substituted benzenes, *p*-xylene and anisole, to give the corresponding oximes in high yields (Table IV). In the reaction of **30** with *p*-xylene, the products were 1-phenyl-2-(*p*-xylyl)-ethanedione-2-oxime (**34**) (72%), together with 2,5-dimethyl-

(26) Field, G. F.; Zally, W. J. *Synthesis* **1979**, 275.

(27) The formation of the latter products can be interpreted in terms of the involvement of C–C bond cleavage of the intermediate, phenylated *N*,*N*-dihydroxylamine or its protonated species shown in Scheme XI. The phenylacylium ion would be converted to benzoic acid during aqueous workup.

Scheme X



38 **39**

Table V. ^{1}H NMR Spectroscopic Data for Ions **41** and **42** in TFSA[a]

	temp, °C	H_1	H_o	H_p	H_m	other
41[b]	−30	9.12 (s)	8.73 (d, 7.82)	8.68 (t, 8.31)	8.14 (t, 7.81)	15.28 (bs, OH, 1 H)
42[c]	−20	8.86	8.25	8.11	7.84	3.24 (CH_3)

[a] Chemical shifts are in parts per million from external capillary Me_4Si in acetone-d_6. [b] Coupling modes and ^{1}H–^{1}H coupling constants in hertz are shown in parentheses; s = sharp singlet, bs = broad singlet, d = doublet, t = triplet. [c] Reference 21a.

Table VI. ^{13}C NMR Spectroscopic Data for Ions **41** and **42** in TFSA[a]

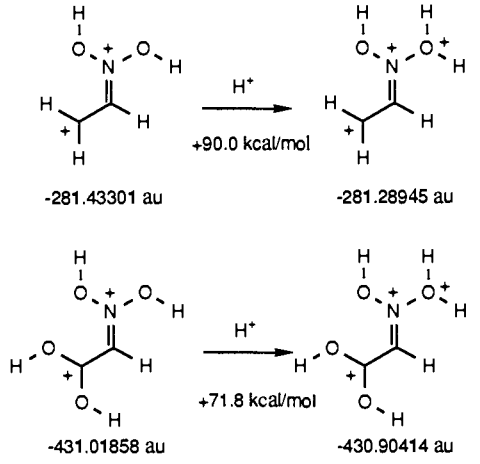
	temp, °C	C_2	C_1	C_o	C_p	C_m	C_{ipso}	other
41[b]	−35	188.0	112.2 (205.5)	132.3 (164.3)	143.1 (164.3)	130.6 (167.3)	127.2	-
42[c]	−20	190.6	130.2	131.2	140.2	130.2	127.5	23.4 (CH_3)

[a] Chemical shifts in parts per million are calibrated from Me_4Si in $CDCl_3$. [b] ^{13}C–^{1}H coupling constants are shown in parentheses in hertz. [c] Reference 21a.

benzaldoxime (**35**) (21%), benzoic acid (**33**) (11%) and 2,5-dimethylbenzophenone (**36**) (4%). The ketone **36** was formed by the reaction of the phenyl acylium ion with *p*-xylene. In the reaction of **30** with anisole, the corresponding oxime, 1-phenyl-2-anisylethanedione-2-oxime (**37**), was obtained in 74% yield (ortho/para ratio 2:3).

Intermediacy of Trications. The facile reaction of the nitroalkane substituted with a carbonyl group provided a striking contrast to the reactions of nitroalkanes (such as nitromethane), which did not yield phenylated products even in a strong acid, suggesting difficulty of enolization to the *aci*-nitro species from the simple nitroalkanes under the conditions used. It is not surprising that the substitution of an electron-withdrawing carbonyl group significantly enhances enolization of the nitro compound **25** to the aci form. The requirement for a strong acid catalyst can also be interpreted in terms of intervention of multiprotonated species as the electrophile, as in the case of the reaction of *aci*-nitromethane. Simple consideration led to a mechanism involving the second protonation on the carbonyl oxygen atom (Scheme X). The electrophilic carbon center (represented by **38d**) of the dication (**38**) seems to be activated.[5] However, this species is considered to be a stable one: a kind of diprotonated nitroethylene (*N,N*-dihydroxyiminium-methylium dication[21]) stabilized by Y-delocalization[28] (**38a–c**), owing to the six delocalized electrons (two π electrons of the olefinic bond and four electrons of lone pairs of two hydroxy groups). This cationic system is also stabilized most efficiently by two hydroxyl groups (represented by **38e,f**), and therefore it would not have a sufficient reactivity toward benzene.[29] Consequently, a triply positively charged cation **39**, an O,O-diprotonated *aci*-nitro species bearing a protonated ethoxycarbonyl group, can be proposed as the intermediate that reacts with nonactivated benzene (Scheme X).[30] Ab initio calculations,

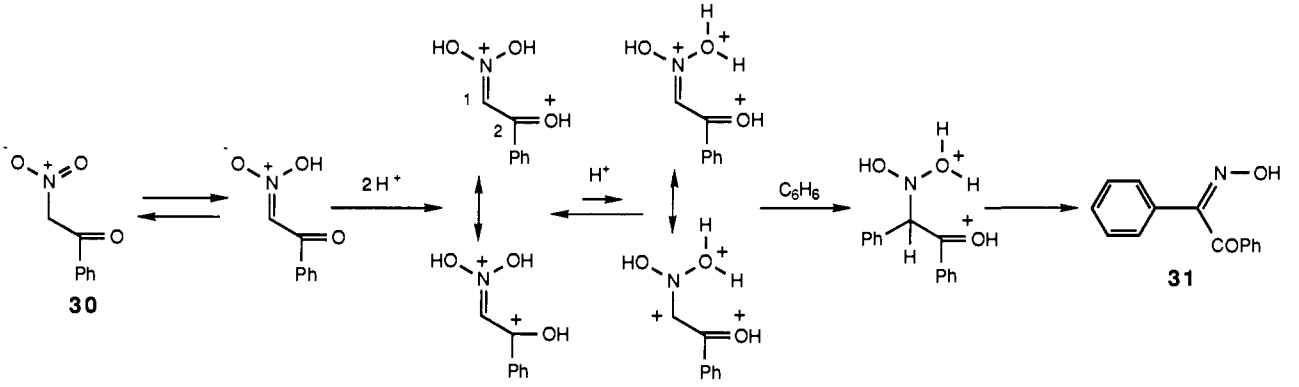
Chart II. 4-31G Calculated Total Energies and Proton Affinities



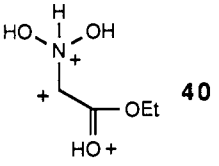
(28) Gund, P. *J. Chem. Educ.* **1972**, *49*, 100. Inagaki, S.; Hirabayashi, Y. *Chem. Lett.* **1982**, 709. Inagaki, S.; Iwase, K.; Goto, N. *J. Org. Chem.* **1986**, *51*, 362.

(29) The *N,N*-dihydroxyiminium–carbenium dication substituted with two electron-donating groups such as methyl groups on the carbenium center, for example, O,O-diprotonated 1-nitro-2-methyl-1-propene, reacted very slowly with benzene, owing to the stability of the dication (ref 21a). Recovery of a large portion of the nitroolefin suggested that the *N,N*-dihydroxyiminium center of the dication does not have a sufficient electrophilicity toward nonactivated benzene, and partial formation of 2-methyl-3-phenyl-1-propen-3-one oxime can be explained in terms of the reaction of more electrophilic species, probably a similar triply positively charged cation, with benzene.

Scheme XI

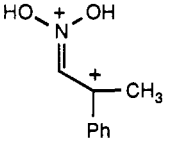


based on the 4-31G basis set, show that the proton affinities (with respect to O-protonation of the iminium moieties) of *N,N*-dihydroxyiminium-methylium dication and *N,N*-dihydroxyiminium-dihydroxymethylium dication are +90.1 and +71.8 kcal/mol, respectively (Chart II). This result suggests that *stabilization* of the carbenium center of the *N,N*-dihydroxyiminium-carbenium dication *facilitates* further O-protonation to give the trication. Participation of the trication **40** could be eliminated for the same reason as in the case of the reactions of cinnamaldoxime discussed above.



40

The ion predominantly formed in TFSA from the nitro ketone **30** can be deduced to be the *N,N*-dihydroxyiminium-phenylhydroxymethylium dication (**41**) on the basis of direct observation by NMR spectroscopy (Tables V and VI). In the ^1H NMR spectrum (in TFSA at −30 °C) a singlet absorption, equivalent to one proton, was observed at 15.28 ppm, which can reasonably be assigned to a C=OH$^+$ group.[28] The chemical shifts of the ^1H and ^{13}C signals of the protonated ion are very close to those observed for the dication **42** (*N,N*-dihydroxyiminium-phenyl-2-

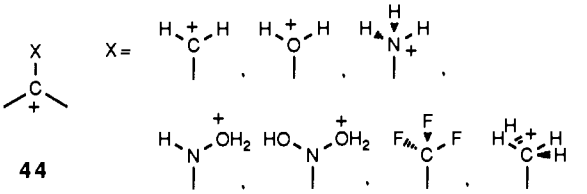


42

ethylium dication) formed from α-methylnitrostyrene.[21a,32] Though the nitro ketone **30** is partially diprotonated in a mixture of TFSA and TFA (1% w/w, H_0 = −7), judging from the UV studies, the reaction with benzene is not promoted in this acid. On the basis of the UV spectroscopic data of the dication **41** in TFSA (λ_{max} = 360 nm, $\epsilon_{\lambda max}$ = 13 500, 0 °C), the absorption (359 nm, ϵ = 4040) of **30** in a mixture of TFSA and TFA (H_0 = −7) indicates approximately 30% formation of the dication **41**. Thus, the facile reaction of **30** with benzene can also be understood in terms of the participation of the more electrophilic trication (**43**), as in the case of the nitroester (Scheme XI). Though we could not detect the triply positively charged ion by NMR spectroscopy, its existence is supported by the fact that the stable guanidinium salt, which is isoelectronic with the dication **41**,[21] can be further protonated to a dication in this acid system.[33] The third protonation site might be the oxygen atom (as in **43**) rather than the nitrogen atom, which would lead to the species corresponding to **40**. This protonation removes the contribution of Y-conjugation, resulted in the activation of the carbenium ion center.

Conclusion

Our previous and present studies provide a general formula (**44**) for reactive carbenium ions substituted with a genuine electron-withdrawing group, wherein the substituent X represents carbe-



44

nium,[21] oxonium, ammonium, O-protonated hydroxylamino, O-protonated *N,N*-dihydroxylamino, trifluoromethyl,[5a,6] and the theoretically studied carbonium[34] group.

We also strongly suspect that dicationic or tricationic species may participate in various cationic reactions such as the Gatterman-Koch,[35] Pomeranz-Fritsch,[36] Skraup,[37] and Bischler-Napieralski[38] reactions and other conventional reactions.[39] Reinvestigations of these reactions should have important im-

(30) In the phenylation reaction of the sodium salts of primary *aci*-nitroalkanes, intervention of the nitrile oxide (ref 23) was excluded by the fact that the second phenylation reaction took place with the *N,N*-dihydroxyiminium-carbenium dications of both β-nitrostyrene and β-methyl-β-nitrostyrene in TFSA (ref 20).

(31) Protonation of ketones: Olah, G. A.; O'Brien, D. H.; Calin, M. *J. Am. Chem. Soc.* **1967**, *89*, 3582. Brouwer, D. M. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 879. Brookhart, M.; Levy, G. C.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1735.

(32) α-Methyl-β-nitrostyrene is diprotonated on the nitro group in TFSA as in β-nitrostyrene to yield the dication **42**, which showed UV absorption in TFSA (λ_{max} = 379 nm, $\epsilon_{\lambda max}$ = 13 800) (ref 21a). Furthermore, the dication **42** did not react with benzene at 5 °C (after 40 min) and recovered after aqueous workup.

(33) I.e., ^1H NMR, *N,N,N',N'*-tetramethylguanidinium chloride (in TFSA, −35 °C) 9.24 (NH, 1 H), 8.09 (2 H, NH_2), 3.80 (3 CH_3), 3.68 (1 CH_3); (in TFSA-SbF_5) (2.5:1) at 21 °C 8.35 (NH, 1 H), 7.63 (2 H, NH_2), 3.76 (1 CH_3), 3.74 (1 CH_3), 3.71 (1 CH_3), 3.61 (1 CH_3). The dication of the *N,N*-dimethylammonia-*N',N'*-dimethylcarboxamidium, can also be interpreted in terms of formation of the very stable ammonium-carbenium dication wherein the carbenium center is stabilized by two amino groups. See also: Olah, G. A.; White, A. M. *J. Am. Chem. Soc.* **1968**, *90*, 6087.

(34) Schleyer, P. v. R.; Kos, A. J.; Pople, J. A.; Balaban, A. T. *J. Am. Chem. Soc.* **1982**, *104*, 3771. Lammertsma, K.; Olah, G. A.; Barzaghi, M.; Simonetta, M. *J. Am. Chem. Soc.* **1982**, *104*, 6851.

(35) Adams, R.; Levine, I. *J. Am. Chem. Soc.* **1923**, *45*, 2373. A review: *Organic Reactions*; Wiley: New York, 1949; Vol. 5, p 290. Yato, M.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 691-692.

(36) Sclittler, E.; Muller, J. *Helv. Chim. Acta* **1948**, *31*, 914. A review: *Organic Reactions*; Wiley: New York, 1951; Vol. 6, p 191.

(37) Rapoport, H.; Batcho, A. D. *J. Org. Chem.* **1963**, *28*, 1753. Utermohlen, W. P. *J. Org. Chem.* **1943**, *8*, 544.

(38) A review: *Organic Reactions*; Wiley: New York, 1951; Vol. 6, p 74.

(39) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367, and references cited therein.

plications for the chemistry of Friedel–Crafts and related reactions. The studies described here have also provided versatile synthetic methods for α-phenylation of cinnamaldehyde and its derivatives and for preparation of α-carbonyloximes in high yields.

Experimental Section

General Methods. All the melting points were measured with a Yanagimoto hot-stage melting point apparatus (MP-500) and are uncorrected. Proton NMR spectra were measured on a JEOL GX 400-MHz NMR spectrometer with TMS as an internal reference in $CDCl_3$ as the solvent. ^{13}C NMR spectra were recorded on a JEOL GX-400 (at 100 MHz) in $CDCl_3$, and chemical shifts are reported in parts per million, referenced by assignment of the middle resonance of deuteriochloroform as 77.0 ppm from TMS. Ultraviolet spectra were measured on a Shimadzu UV 200S at 0 °C in acidic media. Flash column chromatography was performed on silica gel (Kieselgel 60, 230–400 mesh, Merck) with the specified solvent.[40] Combustion analyses were carried out in the microanalytical laboratory of this Faculty.

Materials. Trifluoromethanesulfonic acid (TFSA) was purchased from 3M Co. and was purified by distillation under reduced pressure [bp 67 °C (11 mmHg)]. Antimony pentafluoride (SbF_5) was from Aldrich Chemical Co. and was purified by distillation under reduced pressure [bp 81.5 °C (61 mmHg)]. Trifluoroacetic acid (TFA) was purchased from Wako Chemical Co. and used as received.

Cinnamaldehyde (**1a**), 4-phenyl-3-buten-2-one (**1b**), and chalcone (**1c**) were purchased from Wako Chemical Co. and are used after distillation under reduced pressure (in the cases of **1a** and **1b**) or recrystallization from *n*-hexane (in the case of **1c**). 1,5-Diphenyl-1,4-pentadien-3-one (**1d**) was prepared by the condensation reaction of benzaldehyde and acetone in the presence of ethanolic sodium ethoxide at ambient temperature for 2 h.[41] **1d**: mp 109.5–111.5 °C (recrystallized from ethanol, yellow needles); anal. $C_{17}H_{14}O$. *N*-*n*-Butylcinnamaldimine (**4**) was prepared by the condensation reaction of cinnamaldehyde with *n*-butylamine in the presence of anhydrous potassium carbonate (room temperature, 25 h) and purified by distillation under reduced pressure (127 °C/1.2 mmHg) as described previously.[8] *N,N*-Dimethylcinnamaldiminium salt **7** was prepared by the action of *N,N*-dimethylammonium perchlorate on cinnamaldehyde in dry methanol at ambient temperature for 20 h as described previously.[8] *N,N*-Dimethylammonium perchlorate (Caution: *hygroscopic* and *probably explosive*) was obtained by the addition of 70% aqueous perchloric acid into a solution of 50% aqueous dimethylamine, followed by removal of water by distillation under reduced pressure and recrystallization of the residue from ethanol.[42] **7**: mp 133 °C (recrystallized from methanol, yellow needles); anal. $C_{11}H_{14}ClNO_4$. Cinnamaldoxime (**15a**), 4-phenyl-3-buten-2-one oxime (**15b**), and chalcone oxime (**15c**) were obtained in a usual way (NH_2OH·HCl–ethanol–pyridine) from the corresponding carbonyl precursors, and a mixture of the (*E*)- and (*Z*)-oximes was separated by flash column chromatography (AcOEt–*n*-hexane). (*E*)-Cinnamaldoxime [(*E*)-**15a**]: mp 76 °C (recrystallized from CH_2Cl_2–*n*-hexane); anal. C_9H_9NO. (*Z*)-Cinnamaldoxime [(*Z*)-**15a**]: mp 135 °C (recrystallized from CH_2Cl_2–*n*-hexane); anal. C_9H_9NO. (*E*)-4-Phenyl-3-buten-2-one oxime (**15b**): mp 122.5–124.5 °C (recrystallized from CH_2Cl_2–*n*-hexane); anal. $C_{10}H_{11}NO$. (*E*)-Chalcone oxime [(*E*)-**15c**]: mp 114.5–116 °C (recrystallized from benzene–*n*-hexane); anal. $C_{15}H_{13}NO$. (*Z*)-Chalcone oxime [(*Z*)-**15c**]: mp 124–124.5 °C (recrystallized from benzene *n*-hexane); anal. $C_{15}H_{13}NO$.

Nitroalkanes (nitromethane, nitroethane, and 1-nitropropane) were available from Wako and were used after distillation under reduced pressure. 2-Phenyl-1-nitroethane was prepared by the action of sodium borohydride in 2-propanol on β-nitrostyrene, as described previously:[43] pale yellow oil (82–88 °C/0.5 mmHg). Sodium salts of *aci*-nitroalkanes (**21a–d**), α-ethoxycarbonylnitromethane (**25**), and α-benzoylnitromethane (**30**) were prepared as previously described.[23b] The salt was dried well under vacuum and then ground to a fine powder. Prolonged storage of the salt should be avoided.

α-Ethoxycarbonylnitromethane (**25**) was purchased from Aldrich and was used after distillation under reduced pressure. α-Benzoylnitromethane (**30**) was prepared by condensation reaction of phenyl benzonate with nitromethane in the presence of potassium *tert*-butoxide in dimethyl sulfoxide.[26] **30**: mp 107–107.5 °C (recrystallized from *n*-hexane); anal. $C_8H_7NO_3$.

Reaction of Cinnamaldehyde with Benzene in the Presence of TFSA. A solution of cinnamaldehyde (**1a**) (256 mg) in benzene (4 mL, total benzene 30 equiv) was added in portions to an ice-cooled mixture of TFSA (17.7 mL, 100 equiv) and benzene (1.15 mL), with vigorous stirring. After the addition of the reagents, the cooling bath was removed. The reaction mixture was stirred at 23 °C for 24 h. The resultant reaction mixture was poured into a large excess of ice and water (400 mL) and extracted with methylene chloride (500 mL). The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue (277 mg) was flash-chromatographed (the eluent was *n*-hexane, subsequently AcOEt–*n*-hexane 1:50, and finally AcOEt–*n*-hexane 1:5) to give 23 mg (6%) of 3-phenylindene and 223 mg (87%) of recovered aldehyde. 3-Phenylindene:[44] ^1H NMR 7.62–7.16 (9 H, m), 6.58 (1 H, t, 2.2 Hz), 3.51 (2 H, d, 2.2 Hz).

Acid-Catalyzed Reactions of 4-Phenyl-3-buten-2-one with Benzene. (A) Catalysis by TFSA. A similar reaction of 4-phenyl-3-buten-2-one (**1b**) with benzene in the presence of TFSA (100 equiv) at 23 °C for 24 h gave a mixture of methylphenylindenes[45] (the ratio of 1-methyl-3-phenylindene and 3-methyl-1-phenylindene was 2:1, estimated from the ^1H NMR) in 60% yield, with 18% recovery of **1b**. 1-Methyl-3-phenylindene: ^1H NMR 7.62–7.23 (10 H, m), 6.52 (1 H, d, 2.2 Hz), 3.60 (1 H, d, q, 7.3 Hz, 2.2 Hz), 1.40 (3 H, d, 7.3 Hz). 3-Methyl-1-phenylindene: ^1H NMR 7.33–7.09 (10 H, m), 6.26 (1 H, s), 4.54 (1 H, s), 2.21 (3 H, s).

(B) Catalysis by TFSA–SbF_5. 4-Phenyl-3-buten-2-one (**1b**) (248 mg, 1.70 mmol) was allowed to react with benzene (30 equiv) in the presence of TFSA–SbF_5 (mole ratio 95:5, 100 equiv with respect to the ketone) at 23 °C for 8 h. The reaction mixture was poured into a large excess of ethanolic potassium ethoxide (1.03 equiv with respect to the acid, 9.41 g of KOH in 228 mL of EtOH) cooled to −60 °C, with vigorous stirring. After being warmed to ambient temperature (30 min), the resultant solution was diluted with water (200 mL), extracted with CH_2Cl_2 (700 mL), dried over Na_2SO_4, and concentrated. The residue was flash-chromatographed (*n*-hexane, subsequently *n*-hexane–AcOEt) to give 162 mg (46%) of a mixture of methylphenylindenes and 72 mg (29%) of the recovered ketone. The methylphenylindenes were identical with those obtained above.

Acid-Catalyzed Reactions of Chalcone with Benzene. (A) Catalysis by TFSA. A similar reaction of chalcone (**1c**) with benzene in the presence of TFSA (100 equiv) at 23 °C for 24 h gave the phenylated ketone **2c** (76% yield) and 1,3-diphenylindene (7% yield). **2c**: mp 94 °C (recrystallized from *n*-hexane); ^1H NMR 7.95–7.92 (2 H, m), 7.55 (1 H, m), 7.44 (2 H, m), 7.28–7.25 (8 H, m), 7.17 (2 H, m), 4.83 (1 H, t, 7.3 Hz), 3.74 (2 H, d, 7.3 Hz); anal. $C_{21}H_{18}O$. 1,3-Diphenylindene: ^1H NMR 7.65 (2 H, m), 7.61–7.58 (1 H, m), 7.49–7.44 (2 H, m), 7.41–7.36 (1 H, m), 7.33–7.16 (8 H, m), 6.64 (1 H, d, 2.2 Hz), 4.70 (1 H, d, 2.2 Hz). The cyclized product was identified on the basis of the ^1H NMR spectrum.[46]

(B) Catalyst of TFSA–SbF_5. A similar reaction of chalcone (**1c**) with benzene in the presence of TFSA–SbF_5 (mole ratio 95:5, 100 equiv with respect to the ketone) at 23 °C for 8 h followed by a similar base workup gave the phenylated ketone **2c** in 89% yield, with 9% recovery of the ketone. **2c** was identical with the product obtained in (A).

Reaction of 1,5-Diphenyl-1,4-pentadien-3-one with Benzene in the Presence of TFSA. A similar reaction of 1,5-diphenyl-1,4-pentadien-3-one (**1d**) with benzene in the presence of TFSA (100 equiv) at 23 °C for 1.5 h gave the monophenylated ketone **2d** in 98% yield. **2d**: mp 131.5–133 °C (recrystallized from *n*-hexane–CH_2Cl_2); anal. $C_{23}H_{20}O$; ^1H NMR 7.52–7.48 (2 H, m), 7.40–7.37 (3 H, m), 7.31–7.25 (8 H, m), 7.20–7.16 (2 H, m), 7.52 (1 H, d, 16.0 Hz), 6.70 (1 H, d, 16.0 Hz), 4.74 (1 H, t, 7.5 Hz), 3.43 (2 H, d, 7.5 Hz).

Reaction of *N*-*n*-Butylcinnamaldimine with Benzene in the Presence of TFSA. A mixture of TFSA (1.27 mL, 10 equiv with respect to the substrate) and benzene (3.82 mL) was stirred well, and 269 mg (1.43 mmol) of *N*-*n*-butylcinnamaldimine was added all at once together with 2 mL of benzene (total amount used was 30 equiv) at 0 °C in an ice–water bath. Then the cooling bath was removed and the mixture was stirred at 23 °C for 24 h. The resultant reaction mixture was poured into 500 mL of ice and water, and the whole was extracted with three portions of 200 mL of methylene chloride. The organic layer was dried over Na_2SO_4, filtered, and evaporated to afford 379 mg of crude products. The residue was flash-chromatographed (eluted with AcOEt–*n*-hexane 1:9) to give 118 mg (39% yield) of 3,3-diphenylpropanal (**2a**) and 4.0 mg (2% yield) of cinnamaldehyde. The yields were estimated from the ^1H NMR signal integrals, using nitromethane as an internal standard. **2a**: ^1H NMR ($CDCl_3$) 9.71 (1 H, d, 1.6), 7.30–7.16 (10 H, m, aromatic), 4.61 (1 H, t, 8.7), 3.15 (2 H, d, d, 9.1, 1.8). The assignment of **2a** was

(40) Still, W. C.; Kanh, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(41) Varma, R. S.; Kabalka, G. W.; Evans, L. T.; Pagni, R. M. *Synth. Commun.* **1985**, *15*, 279.
(42) Leonard, N. J.; Paukstelis, J. V. *J. Org. Chem.* **1963**, *28*, 3021.
(43) Sinhababu, A. K.; Borchardt, R. T. *Tetrahedron Lett.* **1983**, 227.
(44) Friedrich, E. C.; Taggart, D. B. *J. Org. Chem.* **1975**, *40*, 720.
(45) Taylor, A. R.; Keen, G. W.; Eisenbraun, E. J. *J. Org. Chem.* **1977**, *42*, 3477.
(46) Miller, L. L.; Boyer, R. F. *J. Am. Chem. Soc.* **1971**, *93*, 650.

also confirmed after oximation (vide post).

Reaction of *N,N*-Dimethylcinnamaldiminium Salt with Benzene in the Presence of TFSA. A mixture of TFSA (0.43 mL, 10 equiv) and benzene was stirred well, and 103 mg of *N,N*-dimethylcinnamaldiminium salt **7** was added all at once together with 2 mL of benzene (total amount used was 30 equiv) at 0 °C in an ice–water bath. The mixture was stirred at 23 °C for 24 h. The resultant reaction mixture was poured into 500 mL of ice and water, and the whole was extracted with methylene chloride. The organic layer was dried over Na_2SO_4, filtered, and evaporated to afford 96 mg of an inseparable mixture of 3,3-diphenylpropanal (**2a**) (83% yield) and cinnamaldehyde (16% yield). The yields were estimated from the ^1H NMR signal integrals.

Reaction of Cinnamaldoxime with Benzene in the Presence of TFSA. (*E*)-Cinnamaldoxime (**15a**) (150 mg) was allowed to react with benzene (2.7 mL, 30 equiv) in the presence of TFSA (0.90 mL, 10 equiv) at 23 °C for 20 h. The mixture was poured into a large excess of ice and water (500 mL), followed by extraction with methylene chloride. The resultant residue was flash-chromatographed (AcOEt–*n*-hexane 1:5) to give 211 mg (92%) of the phenylated oxime **16a** and 2 mg (2%) of recovered oxime **15a**. **16a**: mp 101–102 °C (recrystallized from CH_2Cl_2–*n*-hexane, colorless cubes). The oxime was identical with an authentic sample (prepared from α-phenylcinnamaldehyde by hydrogenation over Pd on C after usual oximation) in terms of the IR and ^1H NMR spectra.

(*Z*)-Cinnamaldoxime was also allowed to react with benzene (30 equiv) in the presence of TFSA (10 equiv) at 23 °C for 24 h to give 77% yield of the phenylated oxime. The product oxime was identical with the oxime obtained from the reaction of (*E*)-cinnamaldoxime in terms of the IR and ^1H NMR spectra.

Acid-Catalyzed Reactions of 4-Phenyl-3-buten-2-one Oxime with Benzene. (A) Catalysis by TFSA. A similar reaction of (*E*)-4-phenyl-3-buten-2-one oxime (**15b**) with benzene in the presence of TFSA (10 equiv) at 23 °C for 6 h gave the phenylated oxime **16b** in 90% yield, with 2% recovery of the oxime **15b**. **16b**: ^1H NMR a mixture of isomers of the oxime, 7.30–7.16 (10 H, m), 4.30 (1 H, t, 8.1 Hz), 2.95 (2 H, d, 8.1 Hz), 1.80 (3 H, s), 7.30–7.16 (10 H, m), 4.43 (1 H, t, 8.1 Hz), 3.10 (2 H, d, 8.1 Hz), 1.56 (3 H, S).

(B) Catalysis by TFSA–SbF_5. A similar reaction of (*E*)-4-phenyl-3-buten-2-one oxime (**15b**) with benzene in the presence of TFSA-SbF_5 (mole ratio 2.5:1, 10 equiv with respect to the oxime) at 23 °C for 3 h and workup as above gave the phenylated ketone **16b** in 91% yield, with 3% recovery of the ketone.

Acid-Catalyzed Reactions of Chalcone Oxime with Benzene. (A) Catalysis by TFSA. A similar reaction of (*E*)-chalcone oxime (**15c**) with benzene in the presence of TFSA (100 equiv) at 23 °C for 1.5 h gave the phenylated oxime **16c** in 99% yield. **16c**: mp 131.5 °C (recrystallized from benzene–*n*-hexane); ^1H NMR 7.57 (1 H, bs), 7.33–7.12 (15 H, m), 4.38 (1 H, t, 8.1 Hz), 3.57 (2 H, d, 8.1 Hz); anal. $C_{21}H_{19}NO$.

(*Z*)-Chalcone oxime also reacted with benzene (30 equiv) in the presence of TFSA (10 equiv) at 23 °C for 24 h to give the phenylated oxime in 100% yield: mp 129 °C (recrystallized from CH_2Cl_2–*n*-hexane); anal. $C_{21}H_{19}NO$. The product oxime was identical with the oxime obtained from the reaction of (*E*)-cinnamaldoxime in terms of the IR and ^1H NMR spectra.

(B) Catalysis by TFSA–SbF_5. A similar reaction of (*E*)-chalcone oxime (**15c**) with benzene in the presence of TFSA–SbF_5 (mole ratio 95:5, 100 equiv with respect to the oxime) at 23 °C for 15 min gave the phenylated ketone **16c** in 65% yield.

Acid-Catalyzed Reaction of the Sodium Salt of Nitromethane with Benzene. (A) Catalysis by TFSA. A mixture of TFSA (13.2 mL, 500 equiv with respect to the salt) and benzene (13.2 mL, 500 equiv) cooled to 4 °C (in ice and water) was stirred well, and the powdered sodium salt of nitromethane **21a** (24 mg) was added all at once (*Caution*).[47] The mixture was stirred at 4 °C for 30 min, and the whole was poured into a large excess of ice and water (400 mL) and extracted with methylene chloride (200 mL). The extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was flash-chromatographed (AcOEt–*n*-hexane 1:6) to give 12 mg (33% yield) of benzaldoxime **22a** as a colorless oil. **22a** was identical with an authentic sample, prepared by usual oximation from benzaldehyde, in terms of the IR and ^1H NMR spectra.

(B) Catalysis by TFSA–TFA. A mixture of 10% (w/w) of TFSA (1.34 g) in TFA (13.7 g) (the acid is 30 equiv with respect to the salt) and benzene (10.6 mL, 30 equiv) cooled to 2 °C (in ice and water) and stirred well, and the powdered sodium salt of nitromethane **21a** (329 mg) was added over 8 min (*Caution*).[47] The mixture was stirred at 2 °C for 1 h, and the whole was poured into a large excess of ice and water (400 mL) and extracted with methylene chloride (500 mL). The extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was flash-chromatographed (AcOEt–*n*-hexane 1:5) to give 161 mg (35% yield) of benzaldoxime **22a**.

Acid-Catalyzed Reaction of the Sodium Salt of Nitroethane with Benzene. (A) Catalysis by TFSA. A similar reaction of the sodium salt of nitroethane **21b** at 5 °C for 2 h gave the acetophenone oxime (**22b**) in 40% yield, together with acetophenone in 3% yield. **22b**: mp 58 °C (recrystallized from *n*-hexane, colorless needles); anal. C_8H_9NO; ^1H NMR 7.60 (2 H, m), 7.36 (3 H, m), 6.76 (1 H, bs, OH), 2.30 (3 H, s). **22b** and acetophenone obtained in the reaction were identical with the authentic samples in terms of the IR and ^1H NMR spectra.

(B) Catalysis by TFSA–TFA. Reaction of the sodium salt of nitroethane **21b** with benzene in the presence of 10% (w/w) of TSFA in TFA gave the acetophenone oxime (**22b**) in 63% yield, together with acetophenone in 2% yield.

Acid-Catalyzed Reaction of the Sodium Salt of *aci*-1-Nitropropane with Benzene. (A) Catalysis by TFSA. Reaction of the sodium salt of *aci*-1-nitropropane **21c** (1.117 g, 10 mmol) with benzene in the presence of TFSA (30 equiv) at 5 °C for 2 h gave propiophenone oxime (**22c**) in 54% yield, together with propiophenone **22c** in 2% yield: mp 50–51 °C (recrystallized from *n*-hexane, colorless needles); anal. $C_9H_{11}NO$; ^1H NMR 7.60 (2 H, m), 7.40 (3 H, m), 6.10 (1 H, bs, OH), 2.84 (2 H, q, 10.0 Hz), 1.20 (3 H, t, 10.0 Hz). **22c** and propiophenone obtained in the reaction were identical with the authentic samples in terms of the IR and ^1H NMR spectra.

(B) Catalysis by TFSA–TFA. Reaction of the sodium salt of nitropropane **21c** with benzene in the presence of 10% (w/w) of TFSA in TFA (the acid is 30 equiv with respect to the salt) at 5 °C for 1.5 h gave propiophenone oxime (**22c**) in 68% yield, together with propiophenone in 4% yield.

Acid-Catalyzed Reaction of the Sodium Salt of *aci*-2-Phenyl-1-Nitroethane with Benzene. (A) Catalysis by TFSA. Reaction of the sodium salt of *aci*-2-phenyl-1-nitroethane **21d** with benzene in the presence of TFSA (30 equiv) at 4 °C for 1 h gave deoxybenzoin oxime (**22d**) in 33% yield and 2-phenyl-1-nitroethane in 22% yield. **22d** was identical with an authentic sample, prepared by the TFSA-catalyzed reaction of 1-nitroethylene with benzene,[21a] in terms of the IR and ^1H NMR spectra.

(B) Catalysis by TFSA–TFA. Reaction of the sodium salt of *aci*-2-phenyl-1-nitroethane **21d** with benzene in a mixture of 10% (w/w) of TFSA in TFA (the acid is 30 equiv with respect to the salt) at 4 °C for 1 h gave deoxybenzoin oxime (**22d**) in 74% yield and 2-phenyl-1-nitroethane in 12% yield.

Acid-Catalyzed Reaction of α-Ethoxycarbonylnitromethane with Benzene. A solution of α-ethoxycarbonylnitromethane (**25**) (265 mg) in 1 mL of methylene chloride was added to a well-stirred heterogeneous mixture of TFSA (1.77 mL, 10 equiv with respect to **25**) and benzene (1.77 mL, 10 equiv with respect to **25**) with methylene chloride as a cosolvent (1 mL) cooled to 0 °C in an ice–water bath. After 2 h 0 °C, the reaction mixture was poured into a large excess of ice and water (400 mL) and extracted with methylene chloride (600 mL). The extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was flash-chromatographed (AcOEt–*n*-hexane 1:4) to give 306 mg (80% yield) of ethyl benzoylformate oxime (**26**): mp 109–112 °C (recrystallized from *n*-hexane, colorless plates); anal. $C_{12}H_{15}NO_3$; ^1H NMR 7.53–7.51 (2 H, m), 7.47–7.44 (3 H, m), 4.35 (2 H, q, 7.3 Hz), 1.35 (3 H, t, 7.3 Hz).

Acid-Catalyzed Reaction of the Sodium Salt of α-Ethoxycarbonylnitromethane with Benzene. The sodium salt of α-ethoxycarbonylnitromethane (**27**) (312 mg) was added in portions to an ice-cooled mixture of TFSA (1.77 mL, 10 equiv) and benzene (1.76 mL, 10 equiv) with methylene chloride as a cosolvent (2 mL). The mixture was vigorously stirred at 0 °C for 2.5 h, followed by aqueous workup similar to the above. The residue obtained was flash-chromatographed with AcOEt–*n*-hexane (1:5) as the eluent to give 245 mg (63%) of the phenylated oxime **26** and 58 mg (25%) of diethoxycarbonylfuroxane. The former product was identical with an authentic sample (obtained above) in terms of the IR and ^1H NMR spectra. Diethoxycarbonylfuroxane: colorless oil [purified by molecular distillation at 35 °C (external temp)/0.1 mmHg]; anal. $C_8H_{10}N_2O_6$; ^1H NMR 4.50 (2 H, q, 7.3 Hz), 4.45 (2 H, q, 7.3 Hz), 1.44 (3 H, t, 7.3 Hz), 1.39 (3 H, t, 7.3 Hz); ^{13}C NMR 156.7 (s), 155.1 (s), 148.3 (s), 106.7 (s), 63.6 (t, 146.7 Hz), 13.9 (q, 129.1).

Acid-Catalyzed Reaction of the Sodium Salt of α-Ethoxycarbonylnitromethane with Benzene in TFA. The sodium salt of α-ethoxycarbonylnitromethane (**27**) (466 mg) was added in portions to an ice-cooled mixture of TFA (2.3 mL, 10 equiv) and benzene (8.0 mL, 30 equiv) over 5 min. The resultant solution was vigorously stirred at 5 °C for 2 h, poured into 300 mL of ice and water, and extracted with methylene chloride (400 mL). Evaporation of the solvent gave 388 mg (97%)

(47) A safety shield and safety spectacles are recommended during this process, because reaction of the sodium salt of *nitromethane* sometimes takes place violently in the acid.

of recovered nitro ester **25**.

Acid-Catalyzed Reaction of α-Ethoxycarbonylnitromethane with Substituted Benzenes. (A) ***p*-Xylene.** A similar reaction of α-ethoxycarbonylnitromethane (**25**) with xylene (10 equiv, 140 °C/760 mmHg) in the presence of TFSA (10 equiv) with methylene chloride as a cosolvent at 5 °C for 2 h gave the oxime **28** in 68% yield: mp 106-106.5 °C (recrystallized from *n*-hexane, colorless needles); anal. $C_{10}H_{11}NO_3$; ^{1}H NMR 7.16 (2 H, s), 6.97 (1 H, s), 4.33 (2 H, q, 7.3 Hz), 2.34 (3 H, s), 2.19 (3 H, s), 1.33 (3 H, t, 7.3 Hz); ^{13}C NMR 156.7 (s), 155.1 (s), 148.3 (s), 110.7 (s), 63.6 (t, 146.7 Hz), 13.9 (q, 129.1 Hz).

The corresponding sodium salt of α-ethoxycarbonylnitromethane (**27**) also reacted with *p*-xylene in the presence of TFSA (10 equiv) at 5 °C for 4 h to give the oxime **28** (62% yield) and diethoxycarbonylfuroxane (22% yield).

(B) Anisole. A similar reaction of α-ethoxycarbonylnitromethane (**25**) with anisole (10 equiv, 85 °C/70 mmHg) in the presence of TFSA (10 equiv) at 10 °C for 28 h gave a mixture of the oximes **29** in 86% yield (*o*/*p* ratio 1:2, estimated from the ^{1}H NMR spectra). ***p*-29**: mp 124-125.5 °C (recrystallized from *n*-hexane, colorless needles); anal. $C_{11}H_{13}NO_4$; ^{1}H NMR 7.54 (2 H, d, 8.4 Hz), 6.96 (2 H, d, 8.8 Hz), 4.36 (2 H, q, 7.3 Hz), 3.85 (3 H, s), 1.37 (3 H, t, 7.3 Hz). ***o*-29**: 7.40 (1 H, t, d, 7.9 Hz, 1.8 Hz), 7.36 (1 H, d, d, 7.7 Hz, 1.83 Hz), 7.02 (1 H, t, 7.7 Hz), 6.96 (1 H, d, 8.4 Hz), 4.30 and 4.12 (2 H, q, 7.3 Hz), 3.78 (3 H, s), 1.29 and 1.25 (3 H, t, 7.3 Hz).

The corresponding sodium salt of α-ethoxycarbonylnitromethane (**27**) also reacted with *p*-xylene in the presence of TFSA (10 equiv) at 5 °C for 4.5 h to give a mixture of the oximes **29** (51% yield, *o*/*p* ratio 1:3.3) and diethoxycarbonylfuroxane (15% yield).

Acid-Catalyzed Reaction of α-Benzoylnitromethane with Benzene. The acid-catalyzed reaction of α-benzoylnitromethane (**30**) with benzene was performed as described in the case of α-ethoxycarbonylnitromethane (**25**). α-Benzoylnitromethane (**30**) was allowed to react in a mixture of TFSA (3.5 mL, 10 equiv) and benzene (3.5 mL, 10 equiv) with methylene chloride (4 mL) as a cosolvent at 5 °C for 2 h. The residue, obtained by aqueous workup, was purified by flash column chromatography with (CH_2CL_2-*n*-hexane 2:1) to give 639 mg (71%) of benzil monooxime (**31**), together with 28.6 mg (6%) of benzaldoxime (**32**) and 26.6 mg (5%) of benzoic acid (**33**). **31**: mp 134-138.5 °C (recrystallized from *n*-hexane); anal. $C_{14}H_{11}NO_2$; ^{1}H NMR 8.02 (2 H, d, d, 8.6 Hz, 1.5 Hz), 7.62-7.58 (3 H, m), 7.48 (2 H, t, 7.7 Hz), 7.45-7.26 (3 H, m). The two byproducts **32** and **33** were identical with the authentic samples in terms of the IR and ^{1}H NMR spectra.

Acid-Catalyzed Reaction of α-Benzoylnitromethane with Substituted Benzenes. (A) ***p*-Xylene.** A similar reaction of α-benzoylnitromethane (**30**) with *p*-xylene (10 equiv) in the presence of TFSA (10 equiv) at 0 °C for 1.5 h gave **34** in 72% yield, (2,5-dimethylphenyl)carboaldoxime (**35**) in 21% yield, benzoic acid (**33**) in 11% yield, and 2,5-dimethylbenzophenone (**36**) in 4% yield. **34**: mp 132-133 °C (recrystallized from *n*-hexane, colorless needles); anal. $C_{16}H_{15}NO_2$; ^{1}H NMR 8.07 (2 H, d, d, 8.3 Hz, 1.5 Hz), 7.96 (1 H, bs, OH), 7.61 (2 H, t, t, 7.3 Hz, 1.5 Hz), 7.49 (2 H, t, 7.33 Hz), 7.19 (1 H, d, 7.69 Hz), 7.15 (1 H, d, d, 8.43 Hz, 1.5 Hz), 7.03 (1 H, s), 2.35 (3 H, s), 2.24 (3 H, s). **35**: mp 64-64.5 °C (recrystallized from *n*-hexane, colorless cubes); anal. $C_9H_{11}NO$; ^{1}H NMR 8.64 (1 H, bs, OH), 8.40 (1 H, s), 7.48 (1 H, s), 7.10 (1 H, d, 8.1 Hz), 7.07 (1 H, d, 7.7 Hz), 2.38 (3 H, s), 2.32 (3 H, s); mass spectrum (*m*/*e*) 149. **33** was identical with an authentic sample in terms of IR and ^{1}H NMR spectra. **36** was identical with an authentic sample, prepared from the acid-catalyzed reaction of benzoic acid with *p*-xylene in the presence of TFSA at room temperature for 5 h (68% yield), in terms of the IR and ^{1}H NMR spectra: ^{1}H NMR 7.81 (2 H, d, 8.1 Hz), 7.58 (1 H, t, 7.3 Hz), 7.49 (2 H, t, 7.7 Hz), 7.20 (1 H, d, 7.7 Hz), 7.17 (1 H, d, 7.7 Hz), 7.12 (1 H, s), 2.33 (3 H, s), 2.27 (3 H, s).

(B) Anisole. A similar reaction of α-benzoylnitromethane (**30**) with anisole (10 equiv) in the presence of TFSA (10 equiv) at 5 °C for 2.5 h gave the phenylated oximes **37** in 73% yield (*o*/*p* ratio 2:3, estimated from the ^{1}H NMR spectra). ***o*-37**: ^{1}H NMR 8.02 (2 H, d, d, 7.9 Hz, 1.83 Hz), 7.57 (2 H, m), 7.46 (2 H, t, 7.7 Hz), 7.41 (1 H, t, 7.32 Hz), 7.06 (1 H, t, 7.3 Hz), 6.94 (2 H, d, 8.8 Hz), 3.80 (3 H, s). ***p*-37**: 7.99 (2 H, d, d, 8.1 Hz, 1.5 Hz), 7.64 (2 H, d, 8.8 Hz), 7.58 (1 H, t, 7.3 Hz), 7.46 (2 H, t, 7.7 Hz), 6.94 (2 H, d, 8.8 Hz), 3.83 (3 H, s).

Calculation Methods. The calculations were performed at the Computer Center of the University of Tokyo. The ab initio calculations were carried by using a modified version of the Gaussian 80 computer programs (Gaussian 80H).[48] Structures of neutral molecules and cations were optimized by using Martaugh-Sargent gradient optimization techniques and the standard 4-31G basis set.[13] The optimizations were done with the assumed restriction of C_s symmetry for all species, except for H_2O (C_{2v}), NH_3 (C_{3v}), and **11** (C_{2v}). To estimate the energetics accurately, single-point calculations on 4-31G-optimized geometries were also performed with d-polarized 6-31G*.[16]

Preparation and NMR Studies of Ions in Acids. All samples of ions in TFSA and TFSA-SbF_5 (2.5:1, mole ratio) were prepared below -45 °C in a dry ice-ethanol bath. The digital resolutions in the observed NMR spectra are as follows: ±0.49 Hz in ^{1}H NMR and ±2.9 Hz in ^{13}C NMR spectra. Other experimental details have been described previously.[5a]

(48) Binkley, J. S.; Whiteside, R. A.; Krishnam, R.; Seeger, R.; De Frees, D. J.; Schlegel, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. *QCPE* **1981**, *No. 13*, 406.

An Entry to the Ring B:Ring C Bishydroquinone Leucodaunomycin Series Containing an Intact Carbohydrate

Gary A. Sulikowski,[†] Edward Turos,[†] Samuel J. Danishefsky,*[,†] and Gayle M. Shulte[‡]

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511-8118, and Yale University Center for Chemical Instrumentation, New Haven, Connecticut 06511. *Received July 30, 1990*

Abstract: It has been found that diacetylation of the phenolic hydroxyl groups at C-6 and C-11 of daunomycin provides a product (see compound **12**) that undergoes reduction of the ring C quinone to a hydroquinone without loss of the glycosyloxy function at C-7. Access to a stable heptaacetate (see compound **14**) incorporating the nuclear bishydroquinone ensemble is thus provided. Basic hydrolysis of **14** accompanied by oxidation restores *N*-acetyldaunomycin. The success of this reaction reveals a surprising resistance to quinone methide formation via such leuco intermediates.

Introduction and Scope of the Investigation

It has been claimed[1] that the spectrum of applications of the anthracycline antibiotics[2] (see daunomycin (**1a**) and adriamycin (**1b**)) in cancer chemotherapy is second only to that of the classical alkylating agents. Of the naturally occurring antitumor compounds, the anthracyclines are the most widely used. The considerable efforts that have been expended in understanding the chemistry of the anthracyclines and their interactions with other biomolecules have identified a variety of possibilities for their mechanism(s) of action.[3,4] Among the pathways that have been

[†] Yale University.
[‡] Yale University Center for Chemical Instrumentation.

(1) Myers, C. E., Jr.; Chabner, B. A. In *Cancer Chemotherapy*; Chabner, B. A., Collins, J. M., Eds; J. B. Lippincott: Philadelphia, 1990; Chapter 14, p 356.

(2) (a) Lown, J. W., Ed. *Anthracycline and Anthracenedione-Based Anticancer Agents*; Elsevier: Amsterdam, 1988. (b) Suarato, A.; Angelucci, F.; Bargiotti, A. *Chim. Oggi* **1990**, *8*, 9. (c) Arcamone, F. *Med. Res. Rev.* **1984**, *4*, 153.

0002-7863/91/1513-1373$02.50/0