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Formation of Stable Meisenheimer Adduct Ion Pairs in Apolar Solvents: Implications for Stereoselective Reactions

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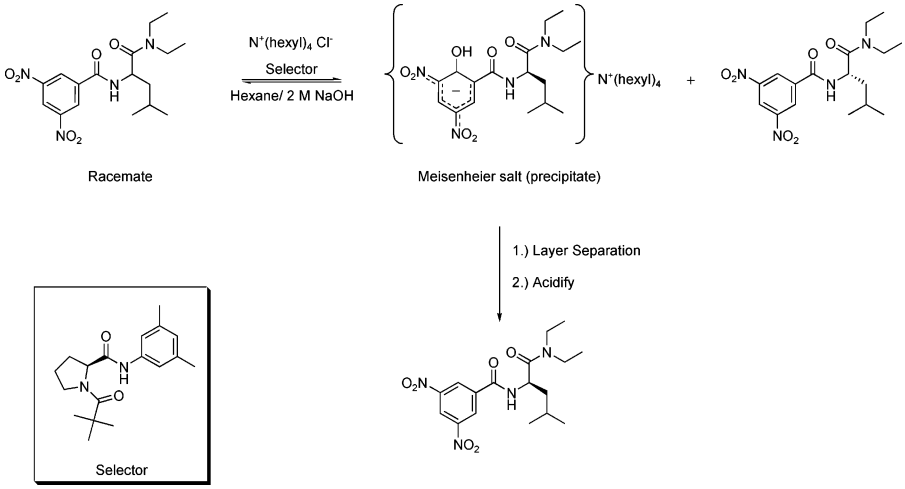

A detailed study concerning the formation of Meisenheimer adducts in biphasic solvent systems is described. The process relies on utilizing a significantly lipophilic quaternary ammonium salt to transfer a nucleophile (e.g., hydroxide ion) between an aqueous and organic layer containing the electron-deficient aromatic substrate. Provided that the organic layer is sufficiently apolar, the resultant Meisenheimer adduct is considerably stable, likely the result of a strong ion-pairing interaction between the large polarizable anionic complex and the diffusively charged tetraalkylammonium cation. Using the diethylamide of 3,5-dinitrobenzoic acid as a model compound, the influence of ion-pairing reagents and solvents on adduct formation was investigated. Dramatically increased equilibrium formation of the Meisenheimer adduct is observed in the biphasic medium (e.g., benzene/2 M NaOH) relative to the same adduct generated in single-phase systems. Spectroscopic studies on this adduct are consistent with those conducted in single-phase polar or dipolar aprotic solvents. The methodology is extended to performing highly enantioselective biphasic kinetic resolutions of several racemic electron-deficient amides.

Introduction

The key intermediate in both the synthetically important nucleophilic aromatic substitution reaction (S_NAr)[1] and the vicarious nucleophilic substitution (VNS) reaction[2] is the negatively charged σ-complex often referred to as a Meisenheimer adduct.[3,4] A significant body of work has been done concerning the rates and equilibrium constants for formation of Meisenheimer adducts in different chemical and biological systems.[5] Stabilities of the adducts increase with increasing electron-withdrawing capacity of the electrophilic aromatic moiety, with increasing basicity of the nucleophile and leaving group,

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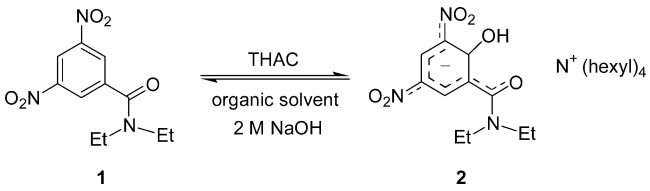
and with decreasing hydrogen bond donating ability of the solvent.[6] The increased stabilities result from either or both an increased rate of formation (k_f) and a decreased rate of decomposition (k_d) of the σ-complex. Importantly, in the case of S_NAr reactions, the transition state is thought to resemble the Meisenheimer adduct intermediate.[7−9] Thus, factors that contribute to adduct stabilization also tend to accelerate the rate of S_NAr reactions. For instance, a large increase in the equilibrium constant for adduct formation as well as the rate of S_NAr reactions is observed in dipolar aprotic solvents relative to protic solvents.[10] Thermodynamic analysis of reactions between nucleophilic alkoxides and electron-poor aromatic substrates indicates that heats of reaction are significantly more exothermic in DMSO than in methanol owing to increased stabilization of the large polarizable Meisenheimer adduct and decreased stabilization of the "hard" alkoxide ion in DMSO.[11] This solvent effect is general over a broad range of electron-poor substrates and nucleophiles.[12]

Electrolyte and micellar effects on σ-complex formation have also been studied extensively.[5] The finding that ion-pairing[13] influences the apparent equilibrium constant for formation of 1,1-dialkoxy adducts in protic solvents is attributed to differences in the stabilities of the Meisenheimer adduct ion pairs relative to that of the nucleophilic alkoxide ion pairs.[14,15] For instance, Crampton and Khan have shown that equilibrium formation of these adducts in methanol increases markedly with increasing sodium methoxide concentration and modestly with increasing tetrabutylammonium hydroxide concentration.[16] In the former case, this nonlinearity is attributed to strong association between sodium cations and the anionic oxygens on the alkoxy substituents of the adduct. On the other hand, the diffusively charged tetraalkylammonium salt stabilizes the anionic σ-complex even in protic solvents where ion pairing is minimal. Bunton and Robinson observed a similar effect while studying S_NAr reactions in water, noting that cations of low charge density (e.g., quaternary ammonium cations) stabilize the Meisenheimer-like transition state.[17] Similarly, cationic micelles[18] and reverse cationic micelles[19] have been used to catalyze S_NAr reactions. The interaction between charged groups on the micelles and the dipolar transition state is one factor contributing to this rate acceleration.

SCHEME 1



1 **2**

In view of the preceding remarks, one may suspect that apolar solvents would provide an ideal environment to stabilize Meisenheimer adducts. Such a system would rely on a lipophilic quaternary ammonium cation or crown ether to transfer the nucleophilic anion from the aqueous into the organic layer. The relatively "unsolvated" anion would than be even more nucleophilic, thus increasing the rate of adduct formation (k_f). The rate of dissociation (k_d) of the resultant adduct should be significantly decreased owing to the tight ion-pairing interaction with the quaternary ammonium cation in the apolar medium since competitive solvation by the medium is reduced. Reported herein is the formation and properties of extremely stable Meisenheimer adduct tetraalkylammonium ion pairs in apolar solvents. Further, a method of performing kinetic resolutions of a series of electron-deficient amides through highly enantioselective formation of stable Meisenheimer adducts will be demonstrated.

Results and Discussion

Spectroscopic Studies. The diethylamide of 3,5-dinitrobenzoic (DNB) acid (**1**) was used as a model compound in this study. Spectroscopic, thermodynamic, and kinetic studies concerning Meisenheimer adduct formation from this substrate or related substrates have been conducted previously using a variety of nucleophiles in either polar solvents or dipolar aprotic solvents.[5,20−22] Nucleophilic addition to 1-X-3,5-dinitrobenzenes (e.g., **1**) will give either of two reversibly formed Meisenheimer adducts owing to the nonequivalence of the 2- and 4-positions. Extensive studies of these types of adducts using visible spectroscopy[21] and flow NMR spectroscopy[23] have shown unambiguously that the 4-complex (para adduct) is kinetically favored while the 2-complex (ortho adduct) is dominant after equilibrium is attained. The proportion of the 4-complex at equilibrium has been estimated at between 5 and 10%.

Upon mixing 1.0 molar equiv of **1** in a benzene-d_6/2 M NaOH (or CCl_4/2 M NaOH) solution containing 1.0 molar equiv of tetrahexylammonium chloride (THAC), the benzene layer immediately turns deep purple and then quickly becomes burgundy colored as the σ-complex **2** is formed (Scheme 1). Interestingly, this adduct ion pair (**2**) shows properties strikingly similar to the adduct generated in water/DMSO or methanol/DMSO mixtures. The

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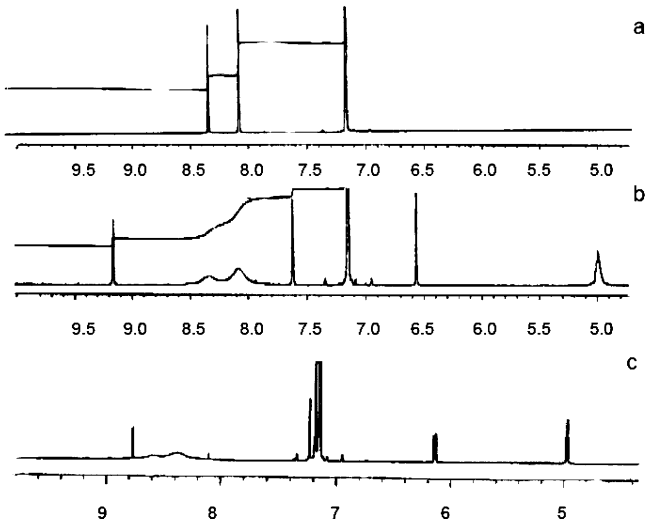


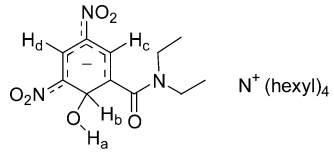
FIGURE 1. (a) 400 MHz ^{1}H NMR of the aromatic region of **1** before the reaction. (b) ^{1}H NMR of the aromatic region of **1** following the biphasic reaction. The spectrum contains both residual starting amide **1** (broad signals) and the Meisenheimer adduct **2** (sharp signals). (c) ^{1}H NMR of the aromatic region of **1** after the reaction and subsequent dilution with DMSO-d_6. Note the resonances corresponding to **2** are shifted upfield, and spin−spin coupling is now apparent.

color change has been observed in DMSO/methanol solutions and has been attributed to rapid equilibration between the 2-complex and the 4-complex.[21] A UV−vis spectrum of **2** closely resembles that reported by Crampton and Khan taken in methanol/DMSO for the ortho-substituted Meisenheimer adduct of **1**.[21] In the present case, a red shift is observed (Supporting Information).

NMR experiments in benzene-d_6/H_2O correspond well with those conducted in DMSO/H_2O on a variety of related DNB containing compounds.[22] ^{1}H NMR spectra of **1** in benzene-d_6 were taken prior to reaction (Figure 1a) with THAC and sodium hydroxide and again after the reaction and subsequent phase separation (Figure 1b). The ^{1}H NMR spectrum of the Meisenheimer adduct formed under biphasic conditions is consistent with the addition of hydroxide ion to the 2-position of the aromatic ring. Three new equal intensity signals are seen for this adduct **2** (at δ = 6.6, 7.6 and 9.2) and arise from hydrogens on the 2, 6, and 4 positions, respectively. One new band is also observed for the hydroxyl proton (δ = 5.0) at the 2-position of the ring. These signals are downfield approximately 0.4 ppm and broader than those of a similar adduct in DMSO.[21] Dilution of the benzene-d_6 with an equal volume of DMSO-d_6 (Figure 1c) sharpens the signals and makes the determination of coupling constants possible (Table 1). This also allows for an upfield shift of the resonances, which approach the previously reported δ values.

Extensive line broadening is observed for signals associated with unreacted amide (Figure 1b). A similar observation has been made for spectra taken in DMSO.[23,24] When the reaction is conducted in benzene-d_6/D_2O containing NaOD, the signal of the Meisenheimer adduct at δ = 9.2, attributed to the hydrogen on the 4-position of the aromatic ring, almost completely disappears through deuterium exchange within 20 min. Bacaloglu and co-workers have performed a series of elegant studies concerning both the origin of ^{1}H NMR line broadening of the unreacted substrate and the exchange of arene hydrogens in D_2O which accompanies hydroxide attack on electron-deficient arenes.[22,24−26] Their data provide compelling evidence that adduct formation proceeds through several intermediates, one being a charge-transfer complex of a radical anion and $^{\bullet}$OH. This complex readily exchanges hydrogens with D_2O or exchanges electrons with the substrate, hence resulting in the observed line broadening. We also note that exchange is markedly faster at the 4-position than at the 2- or 6-position. In apolar media, the charge-transfer complex is capable of dissociating, giving a free radical anion.[22] Indeed, preliminary EPR analysis confirms the existence of radicals in a benzene-d_6 solution of adduct **2**.[27]

TABLE 1. ^{1}H NMR Data of Ortho-Substituted Meisenheimer Adduct



protons	δ value	pattern	J_1	J_2	integration
H_a	4.97	d	6.6		1
H_b	6.14	dd	6.6	1.2	1
H_c	7.24	d	2.0		1
H_d	8.77	dd	2.0	1.2	1

Nucleophilic addition to the 2-position of **1** results in the creation of a stereocenter at the newly formed sp^3-hybridized stereocenter of **2** (Scheme 1). We reasoned that if the interconverting enantiomers of **2** were sufficiently long-lived, a chiral solvating agent might differentiate the enantiomers since the arene hydrogens become diastereotopic and are capable of showing different ^{1}H NMR chemical shifts. When 1 molar equiv of a chiral proline selector, (*S*)-**8** (see Figure 3), was added to the δ_6-benzene layer of preformed **2**, the signal at δ = 6.6 ppm of the adduct (Figure 2), a broad doublet in the absence of DMSO-d_6, is doubled with a $\Delta\delta$ exceeding 0.12 ppm (ca. 50 Hz at 400 MHz, a value too great to be a spin−spin coupling). An identical ^{1}H NMR pattern is generated if starting amide and the proline selector (*S*)-**8** are premixed prior to the reaction with THAC and sodium hydroxide. To the best of our knowledge, this is the first direct observation of enantiomeric Meisenheimer adducts.

Oxidation of Meisenheimer Adducts. Acidic work-up of the organic layer results in regeneration of the starting amide **1**. Typically, decomposition of Meisenheimer adducts is extremely rapid in acidic media, even for adducts considerably more stable than **2**.[5] In this case, treatment with fairly concentrated acidic solutions (greater

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(27) The EPR spectrum is provided in Supporting Information. It should be noted that radicals are often observed in solutions of aromatic compounds with bases and may not be associated with the formation of an adduct.

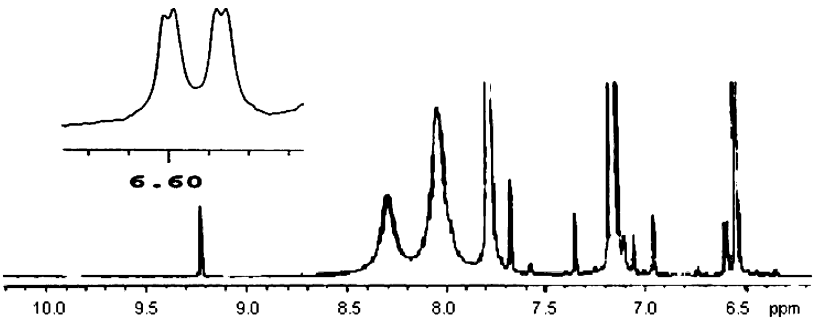
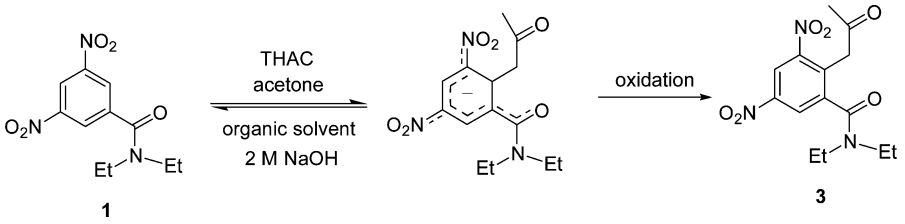


FIGURE 2. Nonequivalence of hydrogen atoms bound to the sp^3-hybridized C2 atom of the racemic Meisenheimer adduct **2** in the presence of chiral selector (*S*)-**8**. The additional bands observed in the spectrum (relative to Figure 1b) are from the chiral selector. The inset shows the splitting of the hydrogen C-2 band induced by the chiral selector.

SCHEME 2



than 2 M HCl) is required to cause rapid disappearance of the burgundy color and reversion of the Meisenheimer adduct to the starting amide.[28] If reaction mixtures are allowed to stand, substitution products are gradually formed and can be isolated after acidic workup. The extent of recovery of **1** depends on the organic solvent, reaction time, temperature, and whether oxygen has been excluded from the reaction vessel. Oxidation of the C-adduct can result in hydrogen-atom replacement. However, with hydroxide as a nucleophile (Scheme 1), the phenol resulting from oxidation of **2** could not be recovered, the ipso-substituted phenol resulting from nucleophilic substitution of a nitro group with a hydroxyl group accounting for the majority of recovered byproducts.[29]

If a small quantity of acetone is present in the reaction flask under otherwise identical conditions, the organic layer turns blue as a C-adduct is formed from acetonate attack of the DNB ring of **1**. Oxidation of the C-adduct affords the Janovsky product (**3**), which is the major byproduct (Scheme 2).[30] The ortho-substituted and para-substituted (not shown) Janovsky products are formed in approximately a 1:1 ratio. In all cases, reactions carried out under oxygen-free conditions give increased levels of amide regeneration upon acidification. The small quantity of **3** obtained from oxygen-free runs is thought to result from an intermolecular self-oxidation process known as "spontaneous" aromatization.[31]

Influence of PTC and Solvent on Meisenheimer Adduct Formation. The thermodynamic equilibrium constant for formation of the 2-substituted methoxide adduct of **1** in methanol has previously been determined to be $K = 1 \times 10^{-4}$ L/mol.[21] Hydroxide addition to **1**, which affords adduct **2**, is expected to give a slightly lower equilibrium constant.[5] The overall equilibrium formation of Meisenheimer adduct **2** in the biphasic processes described depends on the extent of partitioning of the nucleophile (hydroxide) into the organic solvent (or to the biphasic interface) as well as the intrinsic equilibrium constant governing adduct formation. To determine the factors that contribute to Meisenheimer adduct formation in biphasic solvent systems, the influence of different PTCs and organic solvents was investigated.

To standardize reaction conditions, biphasic mixtures containing substrate **1** and an ion-pairing reagent were stirred for three minutes and the layers were separated.[32] Immediately following phase separation, the organic layer was analyzed by ^{1}H NMR using 1,3,5-*tert*-butylbenzene as an internal standard.[33] Results concerning the influence of different quaternary ammonium salts and organic solvents on the extent of adduct formation are given in Table 2. Clearly, the lipophilicity of the quaternary ammonium salt has a dramatic impact on Meisenheimer adduct formation as it effects both the solubility of the adduct in the nonpolar phase and the distribution of hydroxide into the organic solvent.[34] PTCs with smaller quaternary alkyl groups (e.g., tetrabutyl) are incapable of transferring hydroxide ion from NaOH into benzene or CCl_4 and no Meisenheimer adduct is generated (entry 7). With larger quaternary ammonium alkyl groups, such as tetrahexyl or tetraoctyl, a considerable quantity of adduct is formed. Increasing the molar

(28) Addition of concentrated HCl may potentially give rise to a nitronic acid, which could compromise some of the substrate.

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(32) Phase separation may perturb the overall equilibrium established in the biphasic mixture. However, control experiments conducted on the biphasic solution show almost identical results (by ^{1}H NMR) to those obtained after phase separation.

(33) As transfer of hydroxide ion between the aqueous layer and organic layer may be rate limiting, the extent of adduct formation could increase over time until equilibrium is achieved. In the case of substrate **1**, however, there is no increase in adduct formation when reactions mixtures were allowed to stir for longer periods of time.

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TABLE 2. Influence of Different Quaternary Ammonium Salts on the Formation of Meisenheimer Adducts Formed from 1[a]

entry	quaternary alkyl group[b]	anion	NaOH (M)	solvent	PTC (equiv)	adduct[d] (%)
1	hexyl	Cl	2	benzene-d_6	1.0	20
2	hexyl	Cl	6	benzene-d_6	1.0	50
3	hexyl	Br	2	benzene-d_6	1.0	6.4
4	hexyl	I	2	benzene-d_6	1.0	not formed
5	hexyl	Cl	2	benzene-d_6	3.0	41
6	pentyl	Cl	2	benzene-d_6	1.0	<1.0
7	butyl	Cl	2	benzene-d_6	1.0	not formed
8	octyl	Br	2	benzene-d_6	1.0	6.1
9	hexyl	Cl	2	CCl_4[c]	1.0	21
10	hexyl	Cl	2	CD_2Cl_2	1.0	4.4

[a] Biphasic mixtures were stirred for 3 min, and ^{1}H NMR spectra were acquired after phase separation. Total acquisition time was 10 min except for the octyl bromide case (30 min). [b] Symmetrical tetraalkylammonium halide used in all examples. [c] Contained 10 mol % of benzene-d_6 by volume. [d] Based on ^{1}H NMR internal standard analysis using 1,3,5-*tert*-butylbenzene as an internal standard. Separate analyses were conducted immediately following phase separation and 30 min after phase separation, and results were similar.

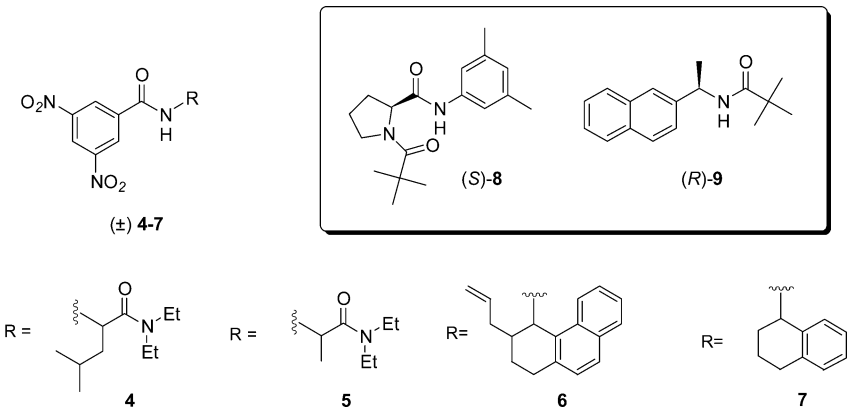


FIGURE 3. Structures of racemic DNB amides and chiral selectors used in kinetic resolutions.

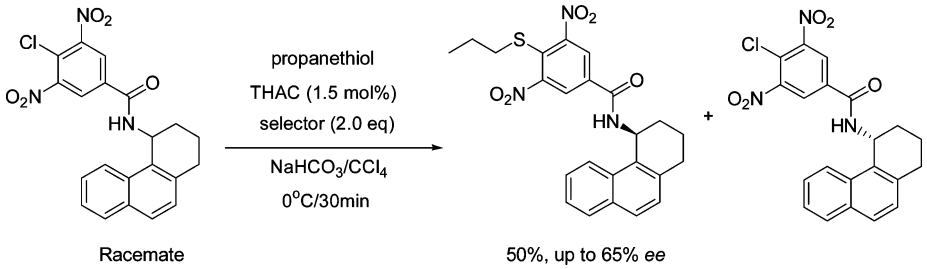
quantity of the PTC or the molarity of NaOH results in additional generation of the Meisenheimer adduct (entry 2). There is also a significant counterion effect. Reactions with tetrahexylammonium chloride (entry 1) give three times more adduct generation than those with tetrahexylammonium bromide (entry 3). Tetrahexylammonium iodide fails to give any adduct formation. These results are typical of PTC processes and are indicative of the "poisoning" effect caused by polarizable counterions.[34] Taken together, the influence on size of both the quaternary ammonium cation and its counterion reflect the importance of hydroxide partitioning and adduct solubility on the equilibrium process.

To get an accurate picture of the stabilizing effect of quaternary ammonium cations on Meisenheimer adducts, one would have to uncouple the partitioning of the various species between the immiscible liquid phases and the association constants of the various ion pairs from the equilibrium constant for formation of the Meisenheimer adduct(s). In a biphasic medium, these processes are quite dependent on the organic solvent. For instance, as the organic solvent is changed from benzene-d_6 or CCl_4 (entries 1 and 9 in Table 2) to CD_2Cl_2 (entry 10) under otherwise identical conditions, a 5-fold reduction in adduct generation is observed despite the fact that hydroxide ions are more readily transferred into CD_2Cl_2 than into CCl_4 or benzene. In either case, the thermodynamic equilibrium constant is dramatically higher than previously reported data for compound **1**.[21] These results support the supposition that quaternary ammonium cations stabilize Meisenheimer adducts in solvents of low polarity that do not provide competing solvation effects. In hydrocarbon solvents such as hexane, Meisenheimer adduct **2** separates as a highly viscous, burgundy colored salt which contains excess THAC, making quantitative evaluation difficult.

Substrate and Nucleophile Effects. In both polar protic and dipolar aprotic solvents, stabilities of Meisenheimer adducts are directly related to the electron-deficiency of the aromatic moiety. Not surprisingly, similar results are observed in these biphasic systems. For instance, 1,3-dinitrobenzene fails to give discernible ^{1}H NMR signals indicative of adduct formation under standard reaction conditions as described in Table 2, although the organic layer turns red following hydroxide addition. On the other hand, 1-trifluoromethyl-3,5-dinitrobenzene gives 24% adduct formation after stirring for 3 min in benzene-d_6/2 M NaOH in the presence of one molar equivalent of THAC, a value similar to that from substrate **1** under identical conditions (see entry 1 in Table 1). In contrast, in single phase systems, the equilibrium constant for adduct formation of **1** is several orders of magnitude lower than that of 1-trifluoromethyl-3,5-dinitrobenzene.[5] We suspect that polar solvents will solvate the amide to a greater extent than the trifluoromethyl group and thus, in the former case, adduct formation will be impeded. This solvation effect will be abrogated in nonpolar solvent systems described here.

Racemic DNB amides **4**−**6** (Figure 3) readily form Meisenheimer adducts under biphasic PTC conditions. These compounds generally give a 4-fold reduction in adduct formation relative to substrate **1**. This result is

SCHEME 3



surprising being that the electron-withdrawing capacities of the aromatic rings are similar. Steric hindrance between the bulky quaternary ammonium cation and the groups emanating from the stereocenter of molecules **4**−**6** may preclude an optimized ion-pairing interaction with the negatively charged adduct, thus destabilizing the complex. Furthermore, the relatively bulky substrates **4**−**6** may not be present at high concentrations at the biphasic interface where the reaction likely takes place. Such interfacial effects have been observed with similar substrates in biphasic PTC hydrolysis reactions.[35]

The quantity of Meisenheimer adduct generated is also highly dependent on the nucleophile. With acetonate as a nucleophile (Scheme 2), the amount of Meisenheimer adduct (C-adduct) that is formed greatly exceeds that of the O-adduct resulting from simple hydroxide attack. This result is consistent with data from single-phase systems and is attributed to the C-adduct being more thermodynamically stable then the corresponding O-adduct.[5] Also, partitioning of acetonate ions into a nonpolar solvent occurs much more readily than extraction of hydroxide ions. The combination of these factors likely contribute to the greater extent of adduct formation.

Biphasic Kinetic Resolutions. The rational design and evaluation of small-molecule chiral selectors and chiral stationary phases has been studied extensively in our laboratories.[36] When a chiral selector preferentially undergoes multiple simultaneous intermolecular interactions with one enantiomer of a racemate, the resulting diastereomeric complexes are energetically nondegenerate. The more strongly complexed enantiomer may be stabilized and sequestered from reaction with a third component. For example, we have demonstrated that a two-component PTC methodology using an achiral quaternary ammonium salt in conjunction with a chiral selector can effect enantioselective hydrolysis[35] and S_NAr reactions.[37] A kinetic resolution involving an S_NAr reaction is shown in Scheme 3. Notably, the reaction proceeds through the intermediacy of a Meiseheimer adduct.

The remarkable stability of Meisenheimer adducts described above prompted us to explore the possibility of direct kinetic resolution of racemic DNB amides in the presence of a suitable chiral complexing agent. Biphasic kinetic resolutions of racemic DNB amides were carried out using chiral selectors developed for chromatographic purposes and THAC as an achiral ion-pairing reagent. Structures of the racemic amides and chiral selectors are shown in Figure 3. The results of several kinetic resolutions are displayed in Table 3. In all cases, an organic solution (CCl_4 or hexane) containing 1.0 molar equiv of racemic amide, 2.0 molar equiv of selector, and 0.5 molar equiv of THAC was added to an equal volume of 2 M NaOH and stirred at room temperature (or at 0 °C). The composition of the residual amide enantiomers in the resultant burgundy colored organic layer was monitored over time by chiral HPLC. In CCl_4, approximately 5% of each of the racemic amides **4**−**7** had been consumed after five minutes. Additional amide is consumed by oxidative degradation of the Meisenheimer adducts as the reaction is allowed to proceed in an open vessel. The extent of reaction ultimately approaches 50%, corresponding to the amount of THAC added. If 1 molar equiv of acetone is initially present in the CCl_4, 50% conversion is achieved within 10 min through formation of the more stable C-adduct. Enantioselectivities of C-adduct formation are nearly identical to those of O-adduct formation. When the reaction mixture is allowed to stand open for 24 h, the biphasic reaction of (±)-**6** in the presence of THAC, acetone, and selector (*S*)-**8** afford the enantioenriched Janovsky product resulting from oxidation of the C-adduct.[37]

Meisenheimer adduct ion pairs generated in hexane under acetone-free conditions precipitate as viscous salts, similar to that observed with achiral amide **1**. After being stirred for several minutes, the hexane layer can be carefully separated from the salt (see experimental).

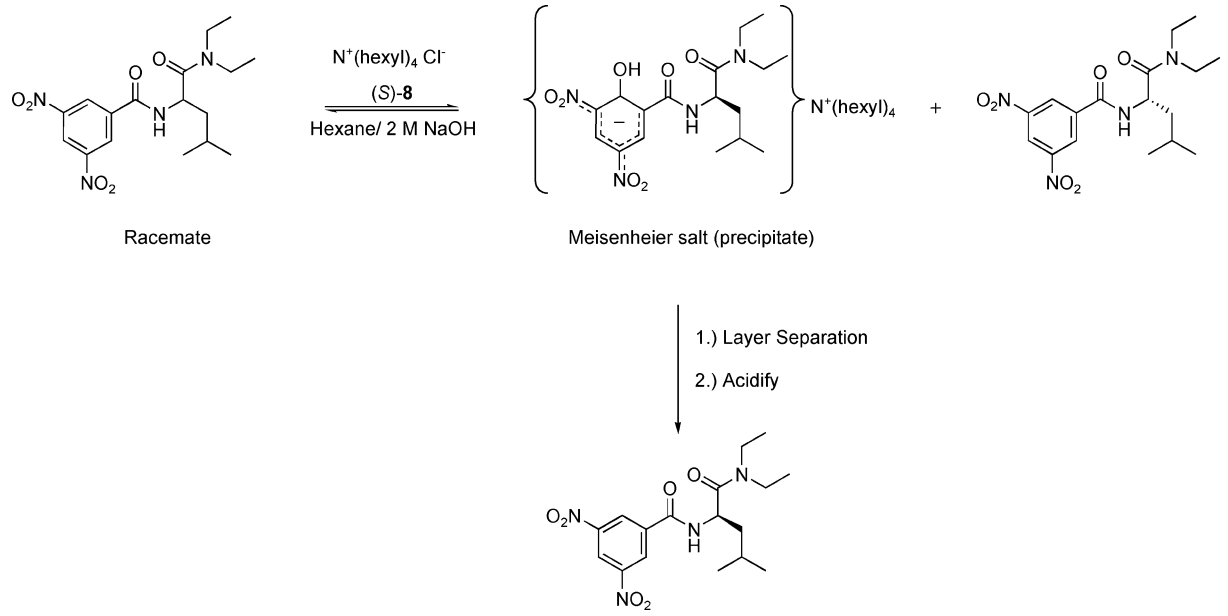
TABLE 3. Stereoselective Generation of Meisenheimer Complexes[a]

entry	amide	selector	solvent	*T* (°C)	% conv[b]	% ee[c]	**s**[d]
1	(±)-**4**	(*S*)-**8**	CCl_4	22	50	85 (*S*)	33
2	(±)-**4**	(*S*)-**8**	hexane	22	30	42 (*S*)	150
3	(±)-**5**	(*S*)-**8**	CCl_4	22	50	65 (*S*)	9
4	(±)-**5**	(*S*)-**8**	hexane	22	41	50 (*S*)	10
5	(±)-**5**	(*S*)-**8**	hexane	0	40	58 (*S*)	26
6	(±)-**6**	(*S*)-**8**	CCl_4	22	46	53 (*S*)	7
7	(±)-**6**	(*S*)-**8**	hexane	22	43	51 (*S*)	8
8	(±)-**6**	(*S*)-**8**	hexane	0	39	50 (*S*)	14
9	(±)-**6**	(*R*)-**9**	CCl_4	22	50	70 (*R*)	12
10	(±)-**6**	(*R*)-**9**	CCl_4	0	41	58 (*R*)	18
11	(±)-**7**	(*R*)-**9**	hexane	0	44	20 (*R*)	2

[a] Standard conditions entailed use of 0.01 mmol (1 molar equiv) of racemic amide, 0.02 mmol (2 molar equiv) of selector, and 0.005 mmol (0.5 molar equiv) of THAC added to 2.0 mL of the indicated solvent, 0.1 mL of methylene chloride, and 2 mL of 2 M NaOH. The reaction was rapidly stirred magnetically. Aliquots were assayed periodically by chiral HPLC. [b] Total quantity of starting amide consumed prior to workup, based on HPLC internal standard analysis (see the Experimental Section). [c] Enantiomeric excess of the unreacted substrate. [d] Stereoselectivity factor.

(35) Snyder, S. E.; Pirkle, W. H. *Org. Lett.* **2002**, *4*, 3283−3286.
(36) For a comprehensive review on the design of chiral selectors, see: Welch, C. *J. Chromatogr. A*, **1994**, *666*, 3−26.
(37) Snyder, S. E.; Shvets, A. B.; Pirkle, W. H. *Helv. Chim. Acta* **2002**, *85*, 3605−3615.

SCHEME 4



Dissolution of this salt in methylene chloride followed by acidification results in regeneration of the amide enantiomer having the opposite configuration of the enantiomer that remains in the hexane. An example of the biphasic (hexane/2 M NaOH) kinetic resolution of (±)-**4** in the presence of (*S*)-**8** is shown in Scheme 4. Unlike reactions conducted in CCl_4, only a small amount of amide is lost through oxidative degradation since the adduct is removed from solution by precipitation. Hence, significant quantities of both enantiomers can be recovered. In the salt, the ratio of the quaternary ammonium cation of THAC to the anionic Meisenheimer adduct is generally greater than one, although the exact ratio is case dependent. Consequently, loss of THAC through its incorporation into the salt results in conversions lower than 50% unless more than 0.5 molar equiv of THAC is used.

The results of kinetic resolutions displayed in Table 3 are consistent with previously reported enantioselective S_NAr and hydrolysis reactions.[35,37] The enantiomer forming the more stable complex with the chiral selector (based on chiral HPLC analysis) is sequestered from adduct formation. The inhibitory effect of the selector is supported by the observation that increasing the concentration of selector results in an increase in enantioselectivity. Conversely, increasing the amount of THAC has little impact on stereoselectivity factors (*s*) of kinetic resolution, despite having a dramatic influence on the extent of adduct formation. We propose that the inhibitory effect of the selector can be rationalized through invoking transition state theory.[38] Namely, the selector stabilizes the ground state of the sequestered enantiomer to a greater extent than the Meisenheimer-like transition state. An essential element of chiral recognition involves a face-to-face $\pi-\pi$ interaction between the electron-poor DNB rings of compounds **4**−**7** with the electron-rich aromatic ring of either (*S*)-**8** or (*R*)-**9**. For the more stable diastereomeric complex, this $\pi-\pi$ interaction is strengthened by complementary hydrogen bonding interactions. This $\pi-\pi$ interaction sterically protects one face of the DNB ring from reaction while simultaneously reducing the electron affinity and hence susceptibility to nucleophilic attack. On the other hand, the electron-rich aromatic moiety of the Meisenheimer-like transition state will not be able to engage in this stabilizing $\pi-\pi$ interaction with the aromatic ring of the selector.

Under the stated reaction conditions in Table 3, substantial enantioselectivities are often achieved, even at room temperature. Kinetic resolution of (±)-**4**, utilizing selector (*S*)-**8** in hexane, gives stereoselectivity factors approaching the maximum that can experimentally be determined for a kinetic resolution (entry 2). Importantly, this method provides a means of resolving racemic precursors of several widely used chiral stationary phases.

Conclusions

A novel method for generating Meisenheimer adducts in a biphasic media using phase transfer catalysts (PTC) is described in detail. Characterization of the Meisenheimer adducts was conducted using a variety of spectroscopic techniques. In general, the properties of these adducts are remarkably similar to adducts generated in polar solvents. However, the quaternary ammonium cation has a profound stabilizing effect on Meisenheimer adducts generated in apolar solvents, the result of a tight electrostatic interaction. In biphasic systems, the overall equilibrium governing formation of Meisenheimer adducts is a function of several factors including bulk of the quaternary ammonium cation of the PTC, polarizability of the counterion of the PTC, mol % of the PTC, polarity of the organic solvent and nature of the nucleophile. These factors contribute to both the distribution of nucleophile in the organic layer as well as the intrinsic equilibrium constant for adduct formation.

The approach has also been applied to highly enantioselective biphasic kinetic resolution mediated by ratio-

(38) For a discussion of transition-state-theory, see: Klumpp, G. W. *Reactivity in Organic Chemistry*; Wiley: New York, 1982; pp 227–378.

nally designed chiral selectors. The selector effectively inhibits one enantiomer from nucleophilic attack. Serendipitously, the enantioenriched Meisenheimer adducts precipitate from hexane and can be effectively separated from the solution, which is enriched in the other (sequestered) enantiomer. This strategy can be used to resolve a variety of electron-deficient aromatic compounds, some of which are used as selectors in commercial HPLC columns.

The inhibitory influence of chiral selectors on solution-state processes appears to be quite general. A logical next step would involve the design of selectors that can accelerate reactions. In principle, the design criteria will be the same but will take into account interactions of the selector with the transition state of the reaction rather than the reactant itself. Reactions which proceed through well-understood Meisenheimer-like transition states might provide a model to study enzyme-like small-molecule organocatalytic systems. The stabilizing effect of quaternary ammonium cations on Meisenheimer adducts should be an essential feature of selector design. Future research will be geared toward rationally designing chiral quaternary ammonium salts capable of stabilizing Meisenheimer-like transition states and catalyzing enantioselective S_NAr and related reactions.

Experimental

Biphasic Reaction of *N*,*N*-Diethyl-3,5-dinitrobenzamide (1) with Sodium Hydroxide under PTC Conditions. *N*,*N*-Diethyl-3,5-dinitrobenzamide (134 mg, 0.5 mmol) and THAC (98 mg, 0.25 mmol) were placed in an oven-dried (*acetone free!*) round-bottom flask equipped with a stir bar. The mixture was dissolved in 10 mL of benzene followed by addition of 10 mL of 2 M NaOH via glass pipet. Immediately, the benzene layer turned purple and then burgundy red. An open-ended short glass column was attached to the flask in order to prevent splattering of the solution. The reaction mixture was stirred rapidly with the round-bottom flask open to air. The benzene layer gradually turned to a dark purple color as the reaction proceeded. The aqueous layer turned a pale yellow color. After 28 h, the layers were separated.

Treatment of the Aqueous Layer. The aqueous layer was washed with 5 mL of CH_2Cl_2 and then acidified with 5 mL of 6 M HCl. After the yellow color disappeared, the aqueous layer was washed with 30 mL of CH_2Cl_2, dried over sodium sulfate, and concentrated under reduced pressure to yield 4 mg of solid. ^{1}H NMR indicates that the solid is primarily THAC with a trace of 3,5-dinitrobenzoic acid.

Treatment of the Organic Layer. The benzene was removed and washed with 5 mL of distilled water (water wash was discarded). The benzene layer was than mixed with 5 mL of 6 M HCl. The purple color transformed immediately to red, orange, and then finally to yellow. The mixture was allowed to stir for an additional 10 min. The organic layer was separated from the 6 M HCl and then rinsed with distilled water, dried over sodium sulfate, and concentrated. Approximately 100 mg (75%) of **1** was recovered after flash column chromatography on silica gel in 10−20% ethyl acetate in CH_2Cl_2. The ipso-substituted phenol (*N*,*N*-diethyl-3-hydroxy-5-nitrobenzamide) (13 mg) was isolated from the column (see characterization below). Silica was removed from the column in sections, and the organic material was eluted from each section with pure methanol. Two major fractions were identified by ^{1}H NMR: the tetrahexylammonium salt of the ipso-substituted phenolate (19 mg) and a trace of 3,5-dinitobenzoate.

Major recovered byproduct *N*,*N*-diethyl-3-hydroxy-5-nitrobenzamide: mp = 182−184 °C; ^{1}H NMR ($CDCl_3$/benzene-d_6, 4:1) δ 1.16 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 3.29 (q, J = 7.1 Hz, 2H), 3.59 (q, J = 7.1 Hz, 2H), 7.17 (dd, J = 2.2 Hz, 1.3 Hz, 1H), 7.59 (t, J = 2.2 Hz, 1H), 7.64 (dd, J = 2.0 Hz, 1.3 Hz, 1H), 9.45 (s, broad, 1H); ^{13}C NMR ($CDCl_3$/benzene-d_6, 4:1) δ 12.7, 14.1, 39.6, 43.5, 111.0, 112.4, 119.7, 139.6, 149.2, 158.4, 169.8; IR (KBr pellet) 3435, 3078, 2987, 2698, 1903, 1610, 1574, 1448, 1223, 889, 827, 754 cm^{-1}; HRMS-FAB (m/z) [M + H]$^+$ calcd for $C_{11}H_{14}N_2O_4$ 238.0954, found 238.0953

Biphasic Reaction of *N*,*N*-Diethyl-3,5-dinitrobenzamide (1) with Acetone under PTC Conditions (Scheme 2). *N*,*N*-Diethyl-3,5-dinitrobenzamide (134 mg, 0.5 mmol) and THAC (196 mg, 0.5 mmol) were placed in a scintillation vial equipped with a stir bar. The aluminum foil lining of the cap was replaced with a Teflon lining. The solid was dissolved in 10 mL of CCl_4, and 50 μL of acetone was added via syringe, followed by 5 mL of 2 M NaOH. The organic layer turned dark blue immediately upon addition of aqueous base. The reaction was stirred vigorously for 4 h in the capped vial. Stirring was stopped to allow for phase separation. The organic layer was diluted with 10 mL of CH_2Cl_2 and separated from the aqueous layer. The organic phase was combined with 10 mL of 6 M HCl and stirred for an additional 10 min. The color of the organic phase changed from dark blue to yellow-orange. The organic phase was extracted sequentially with saturated solutions of $NaHCO_3$ and NaCl, dried over sodium sulfate, and concentrated under reduced pressure. Starting substrate **1**, 53 mg (40%), was recovered after flash column chromatography using 10% diethyl ether in CH_2Cl_2. An oily mixture of the *o*- and *p*-acetonate adducts (Janovsky products), 14 mg (9%), was isolated in a 1.2: 1.0 (ortho/para) ratio. A fraction enriched in the ortho isomer (**3**) was obtained after flash column chromatography (10% acetone in CH_2Cl_2): ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 2.34 (s, 3H), 3.15 (broad, 1H), 3.19 (broad, 1H), 3.42 (broad, 1H), 3.76 (broad, 1H), 4.20 (broad, 1H), 4.40 (broad, 1H), 8.30 (d, J = 2.4 Hz, 1H), 8.89 (d, J = 2.4 Hz, 1H); HRMS-FAB (m/z) [M + H]$^+$ calcd for $C_{14}H_{18}N_3O_6$ 324.1196, found 324.1195.

General Procedure for Enantioselective Meisenheimer Adduct Formation in Hexane (Table 3). To a solution of racemic **4** (0.01 mmol) and (*S*)-**8** (0.02 mmol) in 2 mL of hexane and 0.1 mL of CH_2Cl_2 was added 2 mL of 2 M NaOH and THAC (0.05 mmol). Immediately following THAC addition, a burgundy colored, highly viscous, sludge-like salt formed at the biphasic interface. The solution was stirred for 10 min in a screw-capped scintillation vial. The contents were than diluted with 5 mL of hexane. The hexane layer was removed carefully with a pipet, so not to mix with the precipitate at the organic/aqueous interface. The mixture was than diluted twice more with hexane, and the hexane layer was removed carefully each time. All hexane layers were combined and washed with 2 M HCl and water. The hexane was dried over sodium sulfate and concentrated under reduced pressure. The contents from the original scintillation vial, now containing the viscous salt and 2 M NaOH, were diluted with CH_2Cl_2. The salt immediately dissolved in the CH_2Cl_2, generating a burgundy colored organic layer. The mixture was added to a separatory funnel and diluted with water. The layers were separated and the organic layer was stirred with an equal volume of 3 M HCl until the color completely disappeared. The layers were separated and the CH_2Cl_2 was washed with water, dried over sodium sulfate, and concentrated under reduced pressure. Enantiomeric excess of the hexane layer and the salt were determined by chiral HPLC (see below). To determine the amount of **4** lost to oxidation, the contents from the hexane layer (including washings) and the solid (salt) layer were taken up in CH_2Cl_2 and combined. HPLC internal standard analysis indicated that approximately 92% of **4** was recovered.

Monitoring of Kinetic Resolutions by Chiral HPLC (Table 3). Chromatographic runs were recorded at ambient temperature with the flow rate 2 mL/min. Percent conversions

were monitored by HPLC using internal standard analysis. The chiral selector was used as an internal standard. Stock solutions of the chiral selector with variable concentrations of the racemic amide were prepared and analyzed by HPLC. By comparing total areas under the peaks, calibration curves were generated. An excellent linear plot was obtained for each selector/racemate combination. For the reactions described in Table 3, aliquots were taken at various times. For each aliquot, the relative area between the racemate and internal standard (selector) was compared to the calibration curve to determine extent of conversion. Conversion data obtained from assaying the final aliquot (right before layer separation), matched well with isolated yields achieved after workup and flash column chromatography. Enantiomeric purity was determined by chiral HPLC (see the Supporting Information for chromatography columns and conditions). Absolute configurations were assigned by comparing to authentic samples of each enantiomer of the racemic mixture.

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Supporting Information Available: Detailed procedures and spectral data for new compounds including EPR data and UV−vis spectra of the Meisenheimer adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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