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Addition, elimination, exchange, and epimerization in nitro sulfones

Charles A. Kingsbury,* Jon Weinhold and Jeremy Winter

Department of Chemistry, University of Nebraska—Lincoln, Lincoln, NE 68588-0304, USA

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ABSTRACT: Three reactions were studied in the diastereomers of 1-(benzenesulfonyl)-2-nitro-1-phenylpropane (**1A** and **1B**) and briefly in related compounds: *elimination* of the benzenesulfonyl group, *epimerization* of one diastereomer to the other, and *deuterium/hydrogen exchange* at the methine group next to nitro in starting material. The two diastereomers showed quite different reactivity. The high melting diasteromer showed rapid *elimination* and some *exchange*. The low melting diastereomer (at approximately a half-life) showed extensive *epimerization*, and *elimination* to the alkene, but little *exchange*. There is little effect of aromatic substituents on reaction course. The situation is complicated by re-addition of benzenesulfinate to the alkene. The addition reaction was similar to elimination in agreement with the Principle of Microscopic Reversibility expectations. An electron transfer mechanism for addition is calculated to be comparatively favorable. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: deuterium exchange; epimerization; elimination; addition; nitro; sulfone

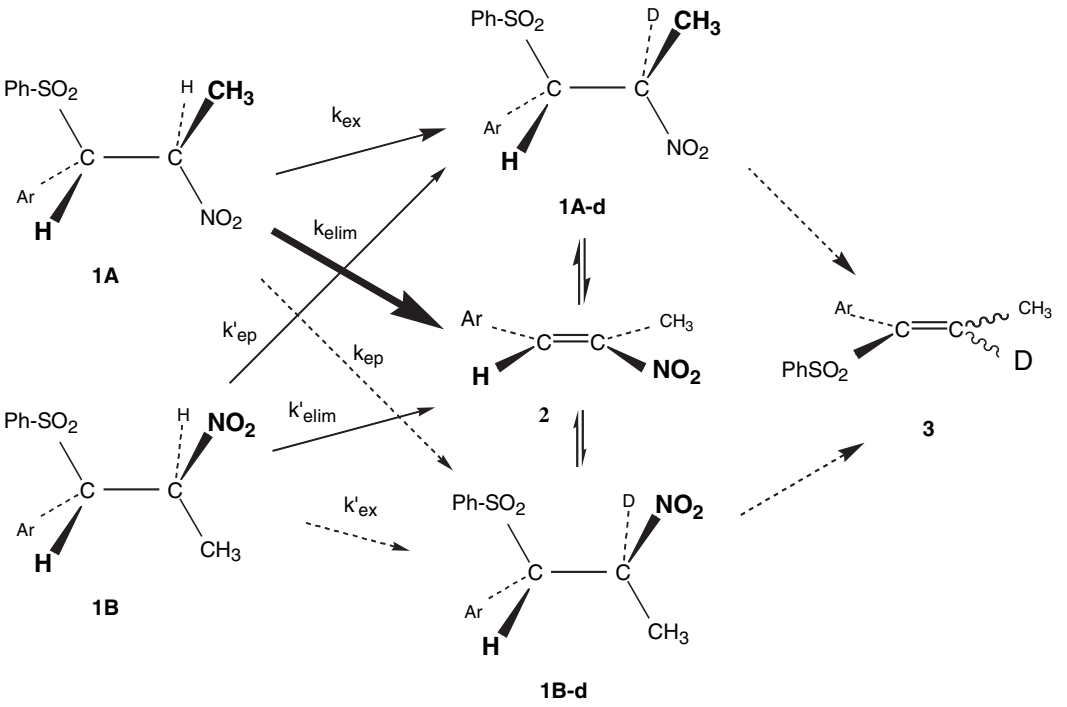
In the 1930s, Wilson, Hsu, Ingold, and Ives carried out some of the first important studies of stabilized carbanions.[1–4] In a ketone with an alpha chiral center, the rate of racemization was equal to the rate of deuterium/hydrogen exchange and to the rate of bromination. The indications were that stabilized long-lived, planar carbanions were of little stereochemical interest. Further work on stabilized anions was not undertaken for many years. In the 1960s, Cram and coworkers revitalized interest in the stereochemical fate carbanions of lesser stability.[5,6] Retention of configuration in D/H exchange often occurred in reactions of sulfones. Streitwieser and co-workers investigated the kinetic acidities of an extensive series of carbon acids and formulated equilibrium constants for acid dissociation.[7,8] Still later, even stabilized carbanions were shown to have non-random stereochemical behavior in specific circumstances of solvent and substituents.[9,10]

The present work concerns the diasteromeric nitrosulfones **1A** and **1B** (Scheme 1). Three reactions of interest: (1) *exchange*, in which deuterium replaces hydrogen, (2) *elimination* of benzenesulfinite, giving the alkene **2**, and (3) *epimerization*, where **1A** forms **1B** and vice versa (always with *exchange*, in the present cases). Substrates **1A** and **1B** show substantially different behavior with sodium benzenesulfinite as base, under the conditions of this study, that is, DMSO*d6*/D_2O solvent (10:1 v/v). This is the standard solvent of the present study, unless otherwise specified. Late in the reaction sequence, two other reactions became apparent: *addition* of benzenesulfinite to the alkene **2** thus re-forming **1A-*d*** and **1B-*d***, and *elimination* of nitrite yielding the sulfone-alkene 3.[11,12]

Studies by Bordwell and coworkers showed that methyl phenyl sulfone was approximately 10^{12} times weaker as a carbon acid than nitromethane in DMSO.[13,14] In the present study, exchange α to nitro was indeed faster than exchange α to the sulfone group in the early stages of reaction. However, elimination of hydrogen α to the sulfone and nitrite to form **3** occurred late in the reaction. For **1b** (Ar = 3-NO_2Ph), **3** was the major product.[15,16–18] The reactivity difference in the present case was hardly as high as 10^{12}, even allowing for the enhancement of the aromatic group. Kinetic and equilibrium effects, of course, need not be the same.[7]

For the high melting diastereomer **1A**, *elimination* to form the alkene **2** was extremely rapid at first. As the reaction progresses, *elimination* appears to slow, and the reaction does not proceed to completion. *Exchange* occurs on **1A** to form **1A-*d***, with very little **1B-*d*** in

**Correspondence to:* C. A. Kingsbury, Department of Chemistry, University of Nebraska—Lincoln, Lincoln, NE 68588-0304, USA.
E-mail: ckingsbu@unlunix.unl.edu



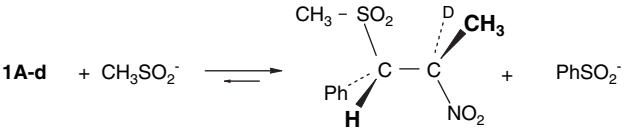
Scheme 1

evidence. E*pimerization* is the least significant process: ($k_{elim} > k_{ex} \gg k_{ep}$). In a typical case, after 62% of the original **1A** had disappeared, an almost equal quantity of alkene **2** was formed. Of the remaining **1A**, 39% deuterium for hydrogen exchange had occurred giving **1A-*d***. At this point, only 3% of the second diastereomer, **1B-*d***, was in evidence (all exchanged).

The isomers **1A** and **1B** are not far different in stability, and stability differences are not likely to weigh heavily on the reaction results. Experimentally, **1B** dominated at equilibrium by about a factor of two. Molecular mechanics (MMX force field)[19] indicates a lower energy for **1B** over **1A** by 0.07 kcal. PM3 calculations also indicated similar stability of **1A** (−27.46 kcal) and **1B** (−26.54 kcal) under 'solvation model' conditions, that is, close to aqueous dielectric constant.[20,21] For **4**, isomer **4B** was favored over **4A** by 1.2 kcal at the pBP/DN* level under solvation conditions.

As the reaction progresses, the reaction mixture becomes buffered due to formation of $PhSO_2H(D)$ as *elimination* occurs, and k_{elim} appears to slow. In fact, the concentration of the alkene **2** declines after an initial surge. The following plot shows a time study of the reaction of **1A**.

Under the buffered conditions, *addition* of $PhSO_2D$ to **2** occurs reforming **1A-*d*** and **1B-*d***. This was shown by using methanesulfinite and also 4-toluensulfinite as base. With methanesulfinite ($CH_3SO_2^-$) present, **1A** was almost completely converted to the methanesulfonyl analog, **4** (plus alkene **2**). The equilibrium ratio of **4B-*d*** to **4A-*d*** was again about 2:1. Treatment of **4A** with benzenesulfinite gave only small amounts of **1A-*d*** and **1B-*d***.



4A-d (also **4B-d**)

The low melting diastereomer **1B** is less reactive than **1A** and shows more complex behavior. *Epimerization* of **1B** to form **1A-*d*** is quite rapid, as is *elimination* to form the alkene **2**. *Exchange* (**1B** → **1B-*d***) is very slow, that is, $k'_{ep} \sim k'_{elim} \gg k'_{ex}$. In a typical case, at a point where 41% of the original **1B** had disappeared, 23% of alkene **2** and 18% of **1A-d** appeared. However, of the remaining **1B**, *exchange* to form **1B-*d*** had occurred only to a few percent. After 2 weeks, some unexchanged **1B** was still in evidence. Thus, **1B** forms the intermediate carbanion somewhat slowly, and carbanion does not return to form **1B-*d***. Thus, the *elimination* reaction is reversible ($E1_{cb}r$) in the case of **1A**, but irreversible ($E1_{cb}ir$) in the case of **1B**.[22]

OTHER REACTIONS

The reactions shown in Scheme 1 were remarkably similar in cases where the aromatic group, Ar, ranged

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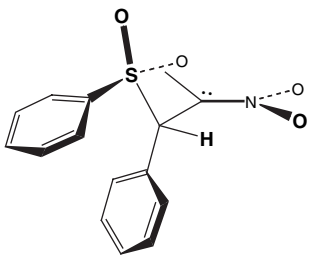
from 4-anisyl, 4-CH_3Ph, Ph, 4-ClPh, to 3-NO_2Ph. Diastereomers **1A** with various aromatic substituents showed $k_{elim} > k_{ex} \gg k_{ep}$ and **1B** (various substituents) showed $k'_{ep} \sim k'_{elim} \gg k'_{ex}$. As noted above, the 4-ClPh and especially the 3-NO_2Ph cases tended to form **3**. Reactions with more limited D_2O present or limited benzenesulfinite as base were unremarkable. Other bases, such as acetate, triethyl amine, or even benzeneselenite (a stronger base[23]) gave rapid *elimination* forming alkene **2**.[19] 'Proton sponge', ***N,N,N′N′***-tetramethylnaphthalen-1,8-diamine, initially showed results similar to benzenesulfinite as base.[9] After the reaction has proceeded to a few per cent, benzenesulfinite is generated, and this may be the actual agent producing the chemical changes. The ultimate product mixture was rich in **3**. The sulfide analogous to **1A** underwent *epimerization* and *exchange*, but *elimination* to form **2** was of little importance. Studies of the sulfoxide corresponding to **1A** were unsatisfactory due to solubility problems.

CONCLUSIONS

The stereochemical outcome is that both **1A** and **1B** form **1A-*d***, although **1B-*d*** dominates at equilibrium. The *addition* of benzenesulfinite to **2** (below) likewise gives **1A-*d*** at first, but **1B-*d*** dominates at equilibrium. The rationalization involves the putative carbanion intermediate **5**. The energy advantage of **5** over **6** at the RHF/6-31+G(2d,p) level was **5** kcal (somewhat less at lower levels of theory).[24] For the methanesulfonyl analog (**4**), the energy preference is 3.7 kcal.[24] No participation of the sulfone group with the anion could be discerned in the quantum calculations, that is, from NBO approximation of the carbanion lone pair → (S—O)* interaction, or the lp → (C—S)* interactions, both of which were negligible.[25]



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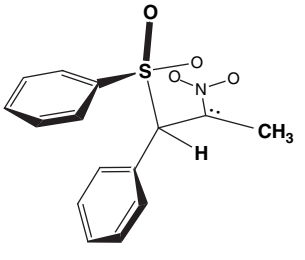

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One of the sulfone oxygens shields the upper face of **5**. Approach of the hydrogen donor to the lower face (giving **1A**) is unimpeded, whereas approach to the upper face of **5** (giving **1B**), encounters steric inhibition. In addition, a slight contra-steric non-planarity of the carbanionic center appears in some higher level calculations on the anion derived from **4** (e.g., bPB/DN* and SWVN/DN* in Spartan).[21] The methyl and nitro in **5** are slightly tilted upward which would further favor approach of the proton donor to the lower face. The 'HOMO density' image provided by Spartan (the initial graphic for this publication) shows a markedly higher 'HOMO density' on the lower face of **5** (blue in color). It is as if the sulfonyl group repels electron density to the lower side of the carbanion carbon. Initial protonation of the nitro group giving an acinitro compound, followed by tautomerism encounters the same intermediates and would be subject to the same effects.[10,26–29]

ADDITIONS

Anionic additions to activated alkenes have received little attention with regard to mechanism, despite their wide synthetic utility. By the Principle of Microscopic Reversibility,[30] *addition* of benzenesulfinite to the alkene **2** to form **1A** and **1B** should be the mechanistic reverse of the *elimination* process. As a practical matter, an acidic hydrogen donor is necessary for these *addition* reactions. Thymol (pK_a*ca*. 10) is ineffective. Acetic acid (pK_a*ca*. 5) works, but the reaction is slow. Trifluoroacetic acid (pK_a 0.3) enables rapid reaction.

In general microscopic reversibility appears to be upheld. In the presence of trifluoroacetic acid, (DMSO*d6* as solvent, no D_2O), the initial *addition* product is largely **1A**, although **1B** dominates at equilibrium. In some cases, **3** forms as well. In the presence of CD_3COOD, as proton donor, the addition reaction is very slow, and **1A** again dominates at first, by a small margin. With TFA in DMSO*d6*:D_2O (10:1 v/v) as solvent, the *addition* reaction is again slow.

The question arises as to mechanism of *addition*. An initial attack of acid on the nitroalkene **2** followed by attack of benzenesulfinite on the carbocation is inconsistent with the presence of the electron withdrawing nitro group. *Addition* to propenylbenzene, which lacks the nitro group, did not occur. The remaining possibilities are: (1) a termolecular process involving attack of benzenesulfinite and more or less simultaneous hydrogen donation by the acid (similar to the *Ade3* mechanism in electrophilic additions),[31] (2) a two-step mechanism involving attack of benzenesulfinite in the first step, followed by protonation of the intermediate anion by the hydrogen donor, and (3) a single electron transfer process in various ramifications.[9,32–37] Mechanism (1) is inconsistent with the studies of the elimination process in which D for H *exchange* occurs in one isomer, but not the other. If mechanism (1) were in effect, *equilibration* of isomers would require a separate reaction. These processes seem best explained via a carbanionic intermediate, either via mechanism (2) or a carbanion ultimately formed in one of the variants of mechanism (3). The qualitatively greater reaction rate as acid strength increases suggests that the second step of mechanism (2) is rate determining. This means only that the rate of protonation of the anion **5** is

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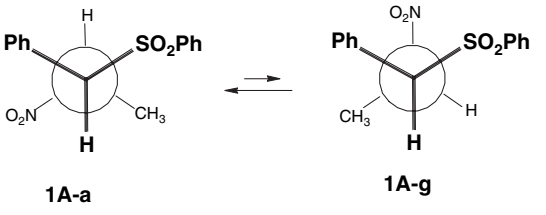
slower than reversion of the anion to the alkene **2**. However, it is not possible to distinguish definitively between mechanisms (2) and (3). Dinitrobenzene did not inhibit the *addition* or *elimination* reactions.[9]

Calculations [RHF/6–31+G(2d,p) and UHF/6–31G+(2d,p) (DK = 1)] place the direct two-electron addition to form a carbanion intermediate **5** [mechanism (2)] 3.5 kcal lower in energy than an electron transfer process yielding a nitro alkene radical-anion and a benzenesulfonyl radical [mechanism (3)]. These simulations involved intermediates (not transition states) since there is no obvious way to simulate the transition state for electron movement. The optimization of the radical-anion with counterpoise correction failed repeatedly in our hands. The older 'massage' type of calculation using single-point calculations on previously optimized structures suggests that the BSSE correction is *ca*. 0.5 kcal for each fragment.[38] This would reduce the energy difference in mechanism (1) *versus* (3) to *ca*. 2.5 kcal. On a kinetic basis, the entropic advantage of single electron transfer should favor mechanism (3) further. In any case, mechanism (3) appears to be roughly competitive to mechanism (2) in energy.

EXPERIMENTAL PART

Addition of sodium benzenesulfinate to 2-nitro-1-phenylprop-1-ene (**2**) gave the high melting and low melting addition products **1A** and **1B**. Neither the needles of the high melting isomer, nor the cubes of the low melting isomer were adjudged suitable for crystallographic structure determination. These were distinguished in the following way. The NMR vicinal coupling constants were rather high: high melting isomer, $J_{AB} = 10.7$ Hz ($CDCl_3$); low melting isomer, $J_{AB} = 8.5$ Hz ($CDCl_3$). The calculated coupling constants were 10.6 and 10.5 Hz, respectively. No basis for judgment exists from calculated *J* values. However, the solvent effect seemed determinative. The major conformers are shown below:



In fairly low dielectric constant media, $CDCl_3$, DK = 4.8, the most favored conformers have anti-vicinal hydrogens, as molecular mechanics calculations indicate. For **1A**, the dominant conformation (**1A-a**) has the added advantage that dipole repulsion between nitro and the sulfone group is minimized. For **1B**, the gauche conformer, **1B-g**, has some importance, since dipolar repulsion of nitro *versus* sulfone is reduced, although there are three gauche interactions between sizable groups. In **1B-a**, there are fewer gauche interactions, but dipolar repulsion is significant. In higher dielectric constant media (DMSO*d6*, DK = 48), dipolar repulsion is attenuated or rendered less significant.[39–42] So, 1A is increasingly populated by conformers, such as **1A-g**, and the average vicinal coupling constant decreases, $J_{AB} = 9.9$ Hz. For **1B**, conformer **1B-a** becomes more highly populated, since dipolar repulsion is of less significance, and J_{AB} increases to 10.4 Hz. Molecular mechanics simulations at various dielectric constants agree with the above findings in general trends.[19] In $CDCl_3$, the chemical shift of the methyl group is δ2.17 ppm for **1A**, compared to δ1.51 ppm for **1B**, since the phenyl group shields methyl for the major conformer of **1B-a**, but not **1A-a**. The similarity of the chemical shifts for **4A,B** to **1A,B** shows that the benzenesulfonyl aromatic group has little influence.

PREPARATIONS

Compound **2** was prepared by the solventless method of Knoevenagel.[43] Condensations in solution did not work well in our hands. General method for preparing compounds **1A** and **1B**: Compound **1A** (Ar = Ph), was prepared by placing the appropriate alkene, in this case **2**, 0.60 g (3.6 mmol) with sodium benzenesulfinite, 0.80 g (4.9 mmol) in dimethyl sulfoxide (minimum water present), 20 mL, plus trifluoroacetic acid, 0.1 mL with short warming to *ca*. 60 °C, then allowing to stand at room temperature for *ca*. 1 day. Water was added, and a precipitate formed upon long standing. The mixture was extracted with methylene chloride (2 × 50 mL), and the combined organic layers extracted twice with water/ammonium sulfate, dried (magnesium sulfate), filtered, and the solvent evaporated. The remaining material was recrystallized using the triangle scheme (lead fractions, using ethanol as initial solvent, moving to ether/hexane mixtures for late fractions. The high melting fraction, **1A**, totaled 0.32 g, mp 148.5–150.0 °C (needles). NMR (DMSO*d6*): δ1.78 (d, 3, CH_3), 5.18 (d, 1, CHPh, $J = 9.9$ Hz), 5.56 (dq, 1, $CHNO_2$, $J = 7$, 9.9 Hz), 7.1–7.6 (m, 10, Ph). High resolution mass spectrometry: calculated for $C_{15}H_{14}NO_4S$ *m/z* 305.0722, observed *m/z* 305.0728, (variance, 2.1 ppm). Compound **1B** was obtained from late fractions, and totaled 0.034 g. When recrystallized to purity it showed mp 118.5–119.2 °C (cubes). NMR(DMSO*d6*): δ1.29 (d, 3, CH_3),

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5.21 (d, 1, CHPh, $J = 10.4$ Hz), 5.64 (dq, 1, $CHNO_2$, $J = 7$,10.4 Hz), 7.2–7.7 (m,10,Ph). High resolution mass spectrometry: for $C_{15}H_{14}NO_4S$, calculated *m/z* 305.0722, observed *m/z* 305.0719 (variance, 1.0 ppm). Later fractions returned **2** as an uncrystallizable oil.

Compound **1B** (Ar = 4-anisyl) was prepared similarly, except that acetic acid was used as solvent, mp 114.4–116.0°C. High resolution FAB: for $C_{16}H_{17}NO_5S$, calculated $(m + H)^+$ 335.0900, observed $(m + H)^+$ 336.0912 (variance, 2.0 ppm). For this and subsequent compounds, the NMR spectrum was extremely similar to **1A** or **1B**.

Compound **1A** (Ar = 4-CH_3Ph) was prepared similarly, although only the high melting isomer was obtained, mp 128.0–128.5 °C. The other diastereomer was present, but difficult to separate from **2**. High resolution mass spectromectry: for $C_{16}H_{17}NO_4S$, calculated *m/z* 319.0878, observed *m/z* 319.0873 (variance, 1.8 ppm).

Compound **1A** (Ar = 4-ClPh) was prepared similarly, mp 146.0–147.5 °C. High resolution mass spectrometry: for $C_{15}H_{14}ClNO_4S$, calculated *m/z* 339.0332, observed *m/z* 339.0321 (variance, 3.4 ppm).

Compound **1B** (Ar = 3-NO_2Ph) was prepared similarly, mp 149.7–152.8 °C. High resolution mass spectrometry: for $C_{15}H_{14}N_2O_6S$; the molecular ion at *m/z* 350.0573 was not observed. The [*m*-NO_2] peak was prominent at *m/z* 304.0630 (variance 4.6 ppm).

Compound **3** (Ar = 4-ClPh) was prepared by treating **2** (Ar = 4-ClPh), (2.0 g, 10.1 mmol), with sodium benzenesulfinite (1.7 g, 10.1 mmol) in DMSO (20 mL) and acetic acid (1 mL) with occasional gentle heating (*ca*. 40–50 °C) for *ca*. 5 days. The reaction mixture was poured into water and extracted back-and-forth into methylene chloride, dried (sodium sulfate), and the solvent evaporated. After much difficulty, crystallization was induced from ethanol, after which this material (0.44 g) was recrystallized from ethanol, mp 75.0–75.9 °C. High resolution FAB: for $C_{10}H_{13}O_2S$, calculated *m/z* 292.032479, observed *m/z* 292.032998 (variance, 1.8 ppm). ^{1}H NMR ($CDCl_3$): δ1.71 (d, 3, CH_3, $J = 7.0$ Hz), 7.0–7.7 (m, 10, aromatic plus olefinic hydrogens). ^{13}C NMR: 14.9 (CH_3), 128.4, 128.7, 128.8, 132.0, 133.2, 138.6 (aromatic plus alkene carbons).

Compound **4B** was prepared by treating **2** (1.0 g, 6.1 mmol) with sodium methanesulfinite (0.82 g, 8 mmol) in DMSO solvent (20 mL) (over molecular sieve) and TFA (0.1 mL). Work up, as before, and two recrystallizations from ethanol gave 4B, mp 156.9–157.4 °C, 0.15 g. The other diastereomer was present, but was very hard to separate from unreacted **2**. Chromatography on alumina should be avoided. Chromatography on silica gel gave additional **2** only. High resolution FAB: for $C_{10}H_{13}NO_4S$, calculated $(m + H)^+$ 244.0638, observed $(m + H)^+$ 244.0651 (variance, 2.9 ppm). NMR ($CDCl_3$): δ1.50 (d, 3, $CHCH_3$, $J = 7$ Hz), 2.71 (s, 3, CH_3SO_2), 4.98 (d, 1, CHPh, $J =$ 8.0 Hz), 5.50 (dq, 1, $CHNO_2$, $J = 7$, 8.0 Hz), 7.43 (apparent s, 5, Ph).

TIME STUDY OF THE REACTIONS

The time study plot (as well as regular runs) was made using a sample made up from *ca*. 15 mg of substrate in 0.6 mL DMSO-d6/0.06 mL D_2O with 15 mg of sodium benzenesulfinite. The progress of the reaction was followed by NMR integration of peaks whose position was known from independent determination. The determinations were made at intervals of minutes at the beginning, lengthening to weeks as equilibrium was approached. The disappearance of starting material was similarly determined. Repeated trials gave very similar results.

COMPUTATIONAL METHODS

For molecular mechanics calculations, several computational packages were tested, PCModel,[44] ChemSite,[45] and Chem3DPro.[46] PCModel (MMX force field) provided results most consistent with NMR determinations of conformation and with equilibrium data. The MM2 force field was not completely parameterized for this structure, which adversely affected Chem3DPro. The molecular dynamics option was used (300 K) to establish the dominant conformations. The title graphic was determined with PCSpartanPro, at the RHF/6-31+G* level (the 'HOMO density' mode of visualization). The 'HOMO density' was checked with density functional methods available in the Spartan package, SVWN/DN* and pBP/DN* (similar to B3LYP). The SVWN/DN* basis set often provides quite different data, but in this case, the 'HOMO densities' were reasonably similar. In general, the preferred basis set for all calculations was B3LYP/6-31+G(2d,p), where possible to the normal four-parameter criterion for termination used by Gaussian.[24] The data was checked at a range of basis sets to ensure that no anomalies were present. Considerable attention was devoted to finding the most favorable conformation.

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