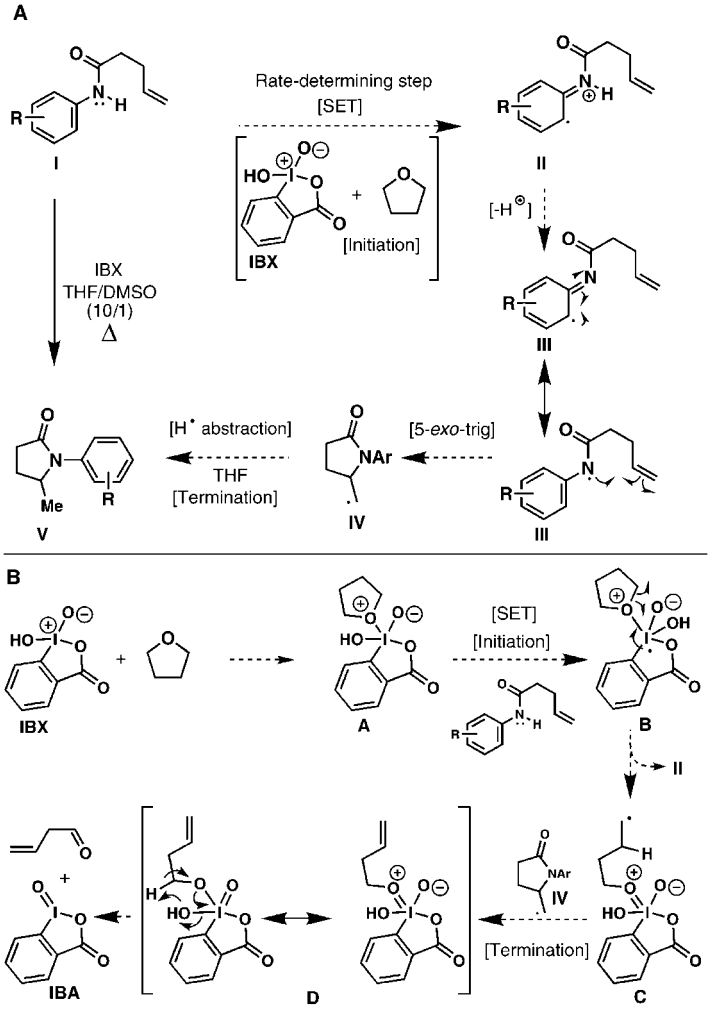
[13] The term self-replication is limited to linear structures whose replication is based on the template chemistry of nucleic acids; the term self-reproduction is a more general one, valid for all structures including micelles and vesicles; and the term autopoietic self-reproduction is for the particular case in which reactions leading to self-reproduction take place within the boundary of the reproductive unit (e.g. within the boundary of a vesicle).
[14] E. Blöchliger, M. Blocher, P. Walde, P. L. Luisi, *J. Phys. Chem. B* **1998**, *102*, 10383 – 10390.
[15] M. Schroeder, *Chem. Rev.* **1980**, *80*, 187 – 213.
[16] M. Minato, K. Yamamoto, J. Tsuji, *J. Org. Chem.* **1990**, *55*, 766 – 768.
[17] W. P. Griffith, A. C. Skapski, K. A. Woode, M. J. Wright, *Inorg. Chim. Acta* **1978**, *31*, L413 – L414.
[18] H. C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483 – 2547.
[19] H.-L. Kwong, C. Sorato, Y. Ogino, H. Chen, B. K. Sharpless, *Tetrahedron Lett.* **1990**, *31*, 2999 – 3002.
[20] T. Oberholzer, K. H. Nierhaus, P. L. Luisi, *Biochem. Biophys. Res. Commun.* **1999**, *261*, 238 – 241.
[21] T. Oberholzer, M. Albrizio, P. L. Luisi, *Chem. Biol.* **1995**, *2*, 677 – 682.

Mechanistic Studies of Periodinane-Mediated Reactions of Anilides and Related Systems**

K. C. Nicolaou,* Phil S. Baran, Remo Kranich, Yong-Li Zhong, Kazuyuki Sugita, and Ning Zou

We have recently reported a series of novel synthetic technologies for the facile construction of complex polycycles,[1] diverse heterocycles,[2] amino-sugars,[3] and α,β-unsaturated carbonyl compounds[4] induced by hypervalent iodine reagents (*o*-iodoxybenzoic acid (1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide, IBX) and Dess – Martin periodinate (DMP)). This spate of reactions, which arose from a discovery made during the total synthesis of the CP molecules,[5] necessitated an in-depth mechanistic investigation to gain further understanding of the sequence of processes involved. Herein we present divergent mechanistic pathways for these IBX- and DMP-mediated reactions based on isotope labeling, kinetic studies, cyclic voltammetry measurements, NMR spectroscopic analysis, and designed cascade reactions.

For the IBX-mediated ring closures of anilides and related systems to N-heterocycles, we had previously proposed a pathway predicated on single electron transfer (SET) as shown in Scheme 1 (**I** → **II** → **III** → **IV** → **V**).[3] To confirm this



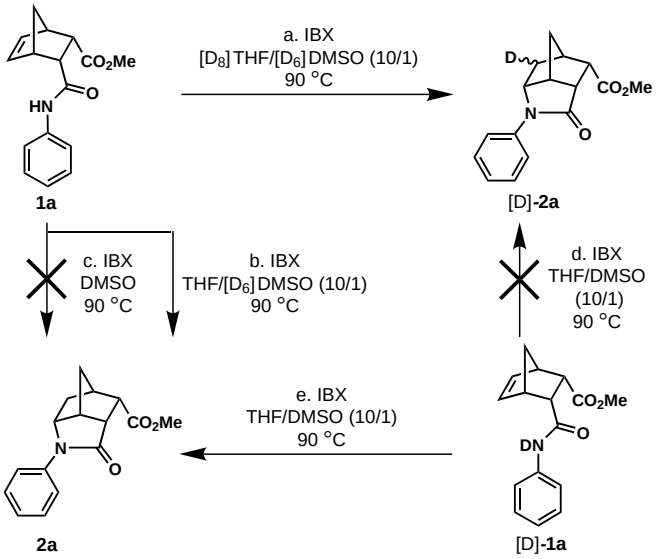
Scheme 1. Proposed mechanism of the IBX-mediated ring closure of anilides and related systems to N-heterocycles (**I** → **V**). SET = single electron transfer, IBX = *o*-iodoxybenzoic acid.

hypothesis it was critical to first determine whether the hydrogen atom which must quench the proposed radical that would result from cyclization (**IV** → **V**, Scheme 1) originated from the substrate itself, IBX, or the solvent. Thus, when the reaction of **1a** (Scheme 2) with IBX was performed in [D_8]THF/[D_6]DMSO (10/1), deuterium was detected (NMR) in product [D]-**2a** at the carbon atom as predicted from the proposed mechanism. Carrying out the reaction of **1a** in THF/[D_6]DMSO (10/1) or of [D]-**1a** (see Scheme 2) in THF/DMSO (10/1) led to **2a** containing no deuterium. When the experiment was carried out without a hydrogen-donating solvent (such as THF or dioxane) present (for example, in neat DMSO), no reaction was observed.[6] This peculiar solvent dependence led us to conclude that the solvent actually plays a role in this reaction, besides being a source of

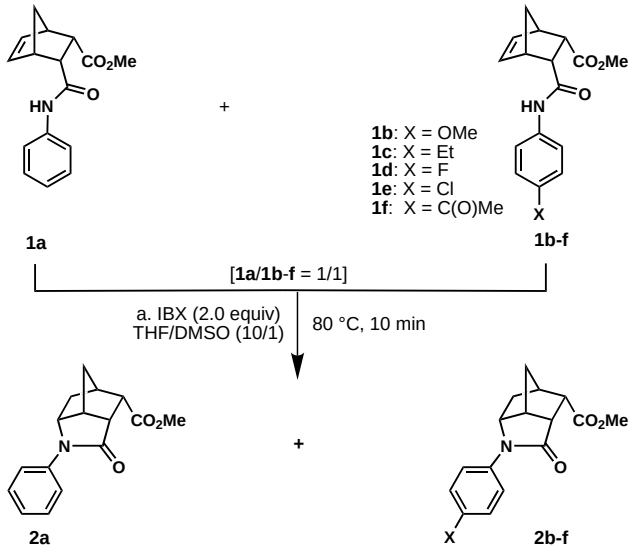
[*] Prof. Dr. K. C. Nicolaou, P. S. Baran, Dr. R. Kranich, Dr. Y.-L. Zhong, Dr. K. Sugita, Dr. N. Zou
Department of Chemistry
and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
and
Department of Chemistry and Biochemistry
University of California San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)
E-mail: kcn@scripps.edu

[**] Professors M. G. Finn, A. Eschenmoser, and M. E. Newcomb are gratefully acknowledged for valuable discussions and suggestions. We thank Dr. D. H. Huang and Dr. G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. We would also like to thank Dr. G. Vasilikogiannakis for helpful discussions and an anonymous referee for critical suggestions. Financial support for this work was provided by The Skaggs Institute for Chemical Biology, the National Institutes of Health (USA), a predoctoral fellowship from the National Science Foundation (P.B.), postdoctoral fellowships from ArrayBiopharma (N.Z.) and Bayer AG (R.K.), and grants from Abbott, Amgen, ArrayBiopharma, Boehringer – Ingelheim, Glaxo, Hoffmann – LaRoche, DuPont, Merck, Novartis, Pfizer, and Schering Plough.

  1433-7851/01/4001-0202 $ 17.50+.50/0



Scheme 2. The role of THF as a hydrogen atom donor in the IBX-mediated cyclization of anilides. Reagents and conditions: a) IBX (4.0 equiv), $[D_8]$THF/$[D_6]$DMSO (10/1), 90 °C, 24 h, 24%; b) IBX (1.0 equiv), THF/$[D_6]$DMSO (10/1), 80 °C, 10 min, 15% conversion (NMR); c) IBX (4.0 equiv), DMSO, 90 °C, 24 h; d) and e) IBX (4.0 equiv), THF/DMSO (10/1), 90 °C, 24 h, 40% (**2a**).



Scheme 3. Competition reactions of equimolar mixtures of **1a** and **1b–f**. Reagents and conditions: a) IBX (2.0 equiv), THF/DMSO (10/1), 80 °C, 10 min.

hydrogen as shown in Scheme 1B. A viable scenario might involve coordination of THF to IBX, which would lead to intermediate **A** (Scheme 1B). This intermediate would act as an extraordinary oxidant which could then initiate the cyclization by SET to furnish intermediates **II** (Scheme 1A) and **B** (Scheme 1B). Rearrangement of **B** to **C** followed by hydrogen abstraction by **IV** would lead to product **V** in addition to **D**, which should rapidly lead to IBA and 3-butenal. Notably, treatment of THF with only IBX at 90 °C for 24 h led to the isolation of 2-iodobenzoic acid along with polymeric material and compounds containing aldehyde residues, as judged by ^{1}H NMR spectroscopy. In addition, when IBA was employed in the cyclization (**I**→**V**) no reaction was observed.

Further support of the proposed mechanism (Scheme 1) was gained upon a systematic evaluation of the kinetics of the reaction with substrates designed to probe the electronic effects of aromatic substituents on the rates of the entire process (**I**→**V**) and of step **III**→**IV** (see below). Thus, by synthesizing a series of aromatic amides differing in substitution at the *para* position (**1b–f**, Scheme 3)[7] the stage was set to compare the different overall reaction rates and to arrive at a Hammett plot. Competing equimolar mixtures of **1a** and **1b**, **1c**, **1d**, **1e**, or **1f** were heated with two equivalents of IBX in THF/DMSO (10/1) at 80 °C for 10 min (Scheme 3). The ratios between the unsubstituted product **2a** and the *para*-substituted products **2b–f** were determined by ^{1}H NMR spectroscopy. Electron-donating substituents [namely, X = OMe (**1b**) and Et (**1c**)] resulted in an increase in the rate of the cyclization, whereas electron-withdrawing substituents caused a decrease in the reaction rate [namely, X = Cl (**1e**) and C(O)Me (**1f**)] or had no significant effect on the rate [X = F (**1d**)] relative to that of the unsubstituted substrate. For amides of type **1** with X = NO_2 or CF_3, no reaction occurred under the conditions described in Scheme 3.

The Hammett plot,[8] based on the ratio of the reaction rate constants (k_s/k_u) and σ_p^+ parameters,[9] gave a linear graph with a negative slope ($\rho = -1.4$, $R^2 = 0.97$; Figure 1).[10] This ρ value is typical for a radical reaction[8] and indicates a lower electron density in the transition state relative to the initial

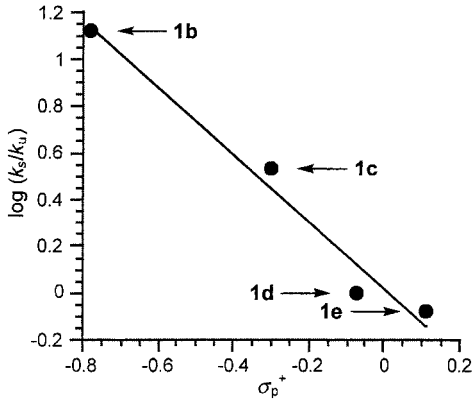
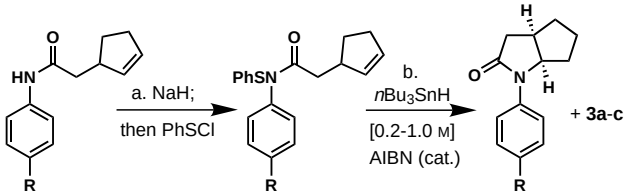


Figure 1. Hammett plot for the reaction shown in Scheme 3 (**1**→**2**). See ref. [9] for more details.

ground state of the substrate. It supports the assumption that the first step of the reaction involves SET from the aromatic ring of the amide to IBX to form a radical anion/radical cation pair as shown in Scheme 1. After loss of a proton, radical cation **II** is converted into radical **III** as shown in Scheme 1. The latter amidyl radical (**III**) then cyclizes onto the double bond in a 5-*exo-trig* fashion, to furnish carbon-centered radical species **IV** which is quenched by the transfer of a hydrogen radical from THF (see above).

Based on the pioneering work of Newcomb and co-workers in the area of amide-centered radicals,[11–13] we were able to use *N*-(phenylthio)amides[12] **4a–c** derived from **3a–c**[7] (Scheme 4) to deduce whether the rate-limiting step of the reaction was **I**→**II** or **III**→**IV**. Three reactions for each amide

  1433-7851/01/4001-0203 $ 17.50+.50/0



3a: R = H
3b: R = OMe
3c: R = F
3d: R = C(O)Me
3e: R = CF_3

4a: R = H
4b: R = OMe
4c: R = F

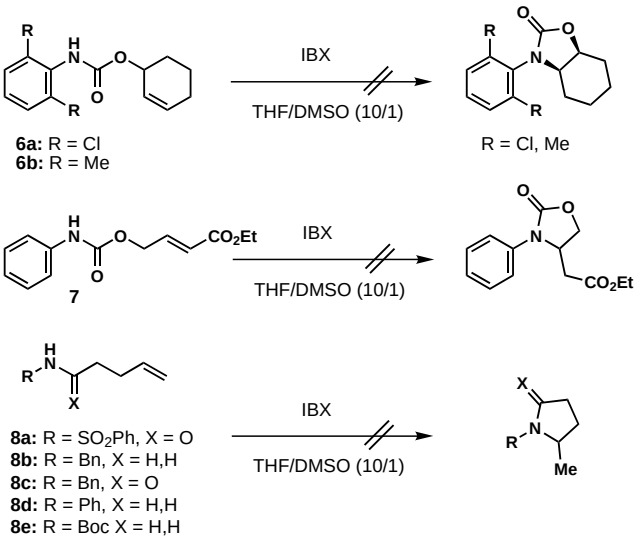
5a: R = H
5b: R = OMe
5c: R = F

Scheme 4. Synthesis of *N*-(phenylthio)amides **4a**–**c** and their tin hydride-mediated conversion into cyclized (**5a**–**c**) and uncyclized (**3a**–**c**) amides. Reagents and conditions: a) NaH (1.3 equiv), THF, reflux, 4 h; then PhSCl (ca. 1 equiv, added until yellow color of PhSCl persists), −78 °C, 1 h, 74–86 %; b) nBu$_3$SnH (0.2–1.0 M), toluene, 65 °C, 2–5 h, 85–92 % total yield of cyclized and uncyclized anilide.

were conducted at 65 °C in toluene in the presence of excess nBu$_3$SnH at concentrations ranging from 0.2 to 1.0 M. The relative yields of cyclized product (**C**, **5a**–**c**) and acyclic amide (**A**, **3a**–**c**) were determined by HPLC. From the ratio of **C**:**A** and by assuming that the rate of trapping of tin hydride is the same for all of the radicals[11–13] the relative rate constants for cyclization of the amide centered radicals could be inferred. The relative rates of cyclization were determined to be (0.66 ± 0.1), (0.30 ± 0.1), and (0.40 ± 0.1) M for **4a**, **4b**, and **4c**, respectively. Since the opposite trend is observed when the overall rate (see above) is evaluated, and because the amidyl radical cyclization is quite rapid in all cases (**4a**–**c**), we conclude that SET from the aromatic nucleus of the anilide to IBX/THF (**I**→**II**) is the rate-determining step of the reaction.

Since the first SET step (**I**→**II**) is likely irreversible, we gauged the oxidation potentials of a series of anilides (**3a**–**e**, Scheme 4). By performing cyclic voltammetry on CH_2Cl_2 solutions, the *p*-substituted anilides were determined to be more difficult to oxidize than ferrocene by the following amounts: 1.20 V (**3a**), 0.82 V (**3b**), 1.23 V (**3c**), 1.48 V (**3d**), and $\geq$1.57 V (**3e**).[14] A direct correlation of the measured oxidation potentials with the observed relative rates of the reactions (see above) was immediately apparent. Thus, anilides with lower oxidation potentials (**3a**–**c**) proceeded rapidly while anilides with higher oxidation potentials proceeded only sluggishly (**3d**) or not at all (**3e**).[15]

Scheme 5 illustrates a number of unexplained failures of this IBX reaction previously encountered in our laboratories which can now be rationalized in light of these new findings. The need for an open position *ortho* to the nitrogen atom is evident since substrates **6a** and **6b** do not undergo reaction. This could be explained by an increase in the oxidation



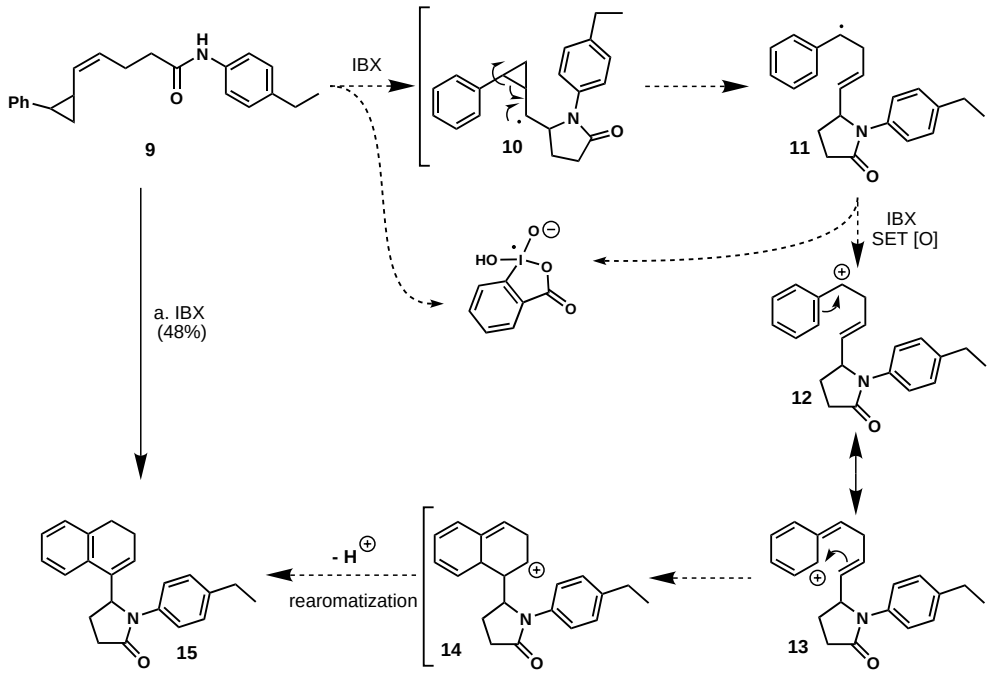
6a: R = Cl
6b: R = Me

R = Cl, Me

7

8a: R = SO_2Ph, X = O
8b: R = Bn, X = H,H
8c: R = Bn, X = O
8d: R = Ph, X = H,H
8e: R = Boc X = H,H

Scheme 5. Nonparticipating substrates for the IBX-mediated cyclization which supports the proposed mechanism of Scheme 1.

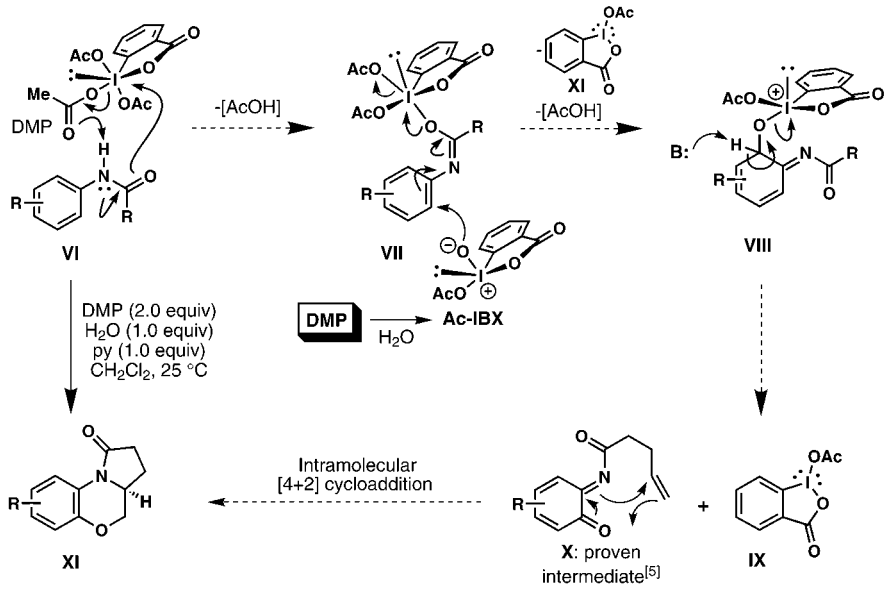


9 10 11 12 13 14 15

Scheme 6. Cascade cyclization of **9** to **15**. Reagents and conditions: a) IBX (4.0 equiv every 24 h), THF/DMSO (10/1), 90 °C, 48 h, 48 %.

  1433-7851/01/4001-0204 $ 17.50+.50/0

potential caused by deconjugation of the lone pair on the nitrogen atom from the arene ring,[16] a decreased rate of 5-*exo-trig* cyclization, or simply a lack of deprotonation of the radical cation (**II** → **III**). The mildly electrophilic nature of the nitrogen-centered radical[11, 13] is evident since α,β-unsaturated ester **7** failed to react (Scheme 5). The notion that only anilides can react with IBX in this manner is supported by the fact that substrates **8a**, **8c**, and **8e** are unresponsive to the conditions, while **8b** and **8d** lead rapidly only to decomposition products.



Scheme 7. Proposed mechanistic aspects of the DMP-cascade reaction of anilides (**VI**) to polycycles (**XI**).

Additional evidence pointing to a radical-based mechanism for this process is provided by the designed cascade reaction depicted in Scheme 6. Thus, when cyclopropylanilide **9**[11] was treated with IBX in the usual manner[2] for 48 h the novel tetracycle **15** was obtained in 48% yield. This striking transformation can be explained by invoking a radical mechanism involving formation of species **10**, as predicted by Scheme 1, and which initiates rupture of the adjacent cyclopropyl ring to give the benzylic radical **11**. Oxidation of this radical (**11**) leads to cation **12** which is then followed by cationic cyclization to **14** via resonance structure **13**. Finally, rearomatization and loss of a proton leads to the observed product **15** (Table 1).

Our present investigation into the mechanism of the DMP-induced cyclization of anilides and related substrates to N,O-heterocycles led us to revise our original proposals[1] to the one depicted in Scheme 7. Indeed, upon addition of freshly prepared DMP to a solution of *N*-phenylacetamide in $CDCl_3$ a dark brown coloration appeared along with new ^{1}H NMR signals, whereas TLC analysis revealed only starting materials and minor decomposition products, which indicate the formation of a transient intermediate (presumably a complex of type **VII**, Scheme 7). Furthermore, the participation of two periodinane species (DMP and Ac-IBX) as postulated in the proposed mechanism was supported by the observation that no product was formed in the presence of 1–3 equivalents of DMP alone (strictly anhydrous conditions) or Ac-IBX alone (freshly prepared).[17] Recognition of the key synergy between DMP and Ac-IBX in this cascade led to the proposition that enough water was needed to convert half of the DMP to Ac-IBX, and prompted the use of pyridine as a facilitator of the reaction. These mechanistic insights inspired further modifications of the reaction conditions leading to a refined process requiring room temperature, dichloromethane as solvent, and a minimum of 2.0 equivalents of DMP (optimally 4.0 equivalents), 1.0 equivalent of H_2O (optimally 2.0 equivalents), and 1.0 equivalent of pyridine, the latter accelerating the reaction but not essential.[18]

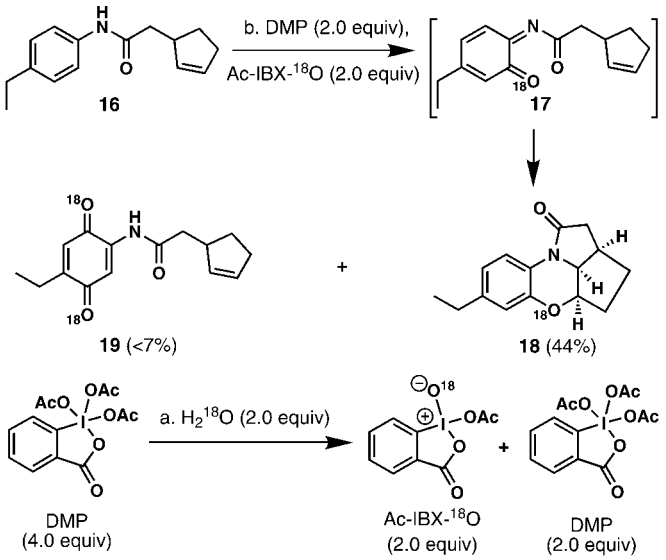
Table 1. Selected data for compounds **15** and **19**.

15: $R_f = 0.42$ [silica gel, ethyl acetate:hexane (1:2)]; IR (film): $\tilde{\nu}_{max} = 2966$, 2923, 2869, 1695, 1609, 1512, 1453, 1394, 1362, 1292, 1217, 1131, 1104, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.49$ (d, $J = 8.5$ Hz, 2H), 7.27–7.24 (m, 3H), 7.21–7.18 (m, 2H), 7.11 (d, $J = 8.5$ Hz, 2H), 5.88 (d, $J = 4.6$ Hz, 1H), 5.22 (d, $J = 8.1$ Hz, 1H), 2.75–2.66 (m, 3H), 2.58 (q, $J = 7.5$ Hz, 2H), 2.51–2.42 (m, 1H), 2.23 (m, 2H), 1.99 (br t, $J = 10.6$ Hz, 1H), 1.18 (t, $J = 7.5$, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.9$, 137.2, 133.7, 132.7, 129.0, 128.1 (2C), 128.0 (2C), 127.3 (2C), 126.6 (2C), 121.9, 120.7, 60.5, 31.2, 28.2, 28.0, 25.8, 22.7, 15.5; HR-MS (matrix-assisted laser desorption/ionization (MALDI)-FTMS): calcd for $C_{22}H_{23}NONa$ [M+H$^+$]: 318.1858, found: 318.1857.

19: yellow needles; $R_f = 0.61$ [silica gel, ethyl acetate:hexane (1:2)] m.p. 77–79 °C ($CHCl_3$); IR (film) $\tilde{\nu}_{max} = 3330$, 2934, 1710, 1692, 1665, 1644, 1609, 1503, 1464, 1454, 1328, 1174, 1096, 898, 723 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 8.03$ (br s, 1H), 7.55 (s, 1H), 6.54 (t, $J = 1.5$ Hz, 1H), 5.84–5.80 (m, 1H), 5.70–5.65 (m, 1H), 3.25–3.12 (m, 1H), 2.57–2.31 (m, 6H), 2.25–2.08 (m, 1H), 1.60–1.41 (m, 1H), 1.13 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 187.9$, 183.2, 171.5, 153.2, 137.8, 133.0, 132.3, 128.2, 114.9, 43.9, 42.1, 31.8, 29.5, 22.3, 11.6; HR-MS (MALDI) calcd for $C_{15}H_{17}NO(^{18}O)_2$ [M+H$^+$]: 264.1366, found: 264.1487.

Further compelling evidence of the participation of Ac-IBX in the process as a nucleophile that attacks intermediate **VII** (Scheme 7) was gathered by preparing Ac-IBX-^{18}O (DMP + $H_2{}^{18}O$) and employing it in the reaction of substrate **16** (Scheme 8). Thus, treatment of anilide derivative **16** with DMP and Ac-IBX-^{18}O (1.0 equivalent of each) in dichloromethane at 25 °C led to ^{18}O-labeled polycycle **18** (44% yield) as confirmed by mass spectrometric analysis. This observation supports the notion that the newly installed oxygen atom arises from Ac-IBX, rather than from H_2O, air, or the substrate itself. Initial attempts to intercept the postulated *o*-azaquinone intermediate **17** were unsuccessful; however, we were able to isolate and characterize a minor product in this reaction, the *p*-quinone structure **19** (Table 1) containing two ^{18}O atoms (mass spectrometry analysis). This intriguing observation and the understanding of the relation between the fleeting *o*-azaquinone **17** and quinone **19** led to the design of

  1433-7851/01/4001-0205 $ 17.50+.50/0



Scheme 8. ^{18}O-labeling studies with the DMP-cascade reaction. Isolation of labeled polycycle **18** and quinone **19** from anilide **16**. Reagents and conditions: a) $H_2{}^{18}O$ (2.0 equiv), CH_2Cl_2, 25 °C, ultrasound, 1 min; then 25 °C, 10 min; b) solution of Ac-IBX-^{18}O/DMP, **16** (1.0 equiv), CH_2Cl_2, 25 °C, 4 h.

a series of new reactions which will be described in the following communication.[19]

In conclusion, through this study we have provided supporting evidence for a mechanistic rationale of the previously reported unique interactions[1–4] of periodinane reagents (DMP, IBX, and Ac-IBX) with anilide and related substrates. The mechanistic understanding of these intriguing processes is expected to lead to the design of new reactions for the construction of novel molecular diversity and to enrich the enabling technologies for combinatorial chemistry, chemical biology, and medicine.

Received: August 14, 2000
Revised: November 2, 2000 [Z15628]

[1] K. C. Nicolaou, Y.-L. Zhong, P. S. Baran, *Angew. Chem.* **2000**, *112*, 636; *Angew. Chem. Int. Ed.* **2000**, *39*, 622.
[2] K. C. Nicolaou, Y.-L. Zhong, P. S. Baran, *Angew. Chem.* **2000**, *112*, 639; *Angew. Chem. Int. Ed.* **2000**, *39*, 625.
[3] K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, J. A. Vega, *Angew. Chem.* **2000**, *112*, 2625; *Angew. Chem. Int. Ed.* **2000**, *39*, 2525.
[4] K. C. Nicolaou, Y.-L. Zhong, P. S. Baran, *J. Am. Chem. Soc.* **2000**, *122*, 7596.
[5] a) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, H.-S. Choi, W. H. Yoon, Y. He, K. C. Fong, *Angew. Chem.* **1999**, *111*, 1774; *Angew. Chem. Int. Ed.* **1999**, *38*, 1669; b) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, K. C. Fong, Y. He, W. H. Yoon, H.-S. Choi, *Angew. Chem.* **1999**, *111*, 1774; *Angew. Chem. Int. Ed.* **1999**, *38*, 1669.
[6] A reddish-brown color was formed immediately; however, repeated attempts to isolate a new compound failed. ^1H and ^{13}C NMR spectroscopic analysis of the crude mixture showed the major component to be starting material. In most cases, starting material could be recovered in >75% yield.
[7] Synthesized by a 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)-mediated coupling of the corresponding (commercially available, Aldrich) carboxylic acid and substituted anilines.
[8] For σ_p^+ values, see P. Zuman, R. C. Patel, *Techniques in Organic Reaction Kinetics*, Krieger Publishing Company, Malabar, FL, **1992**, p. 230. For a discussion of Hammett plots, see T. H. Lowry, S. K. Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper & Row, New York, **1987**.
[9] k_u: Rate constant of the reaction **1a**→**2a**, k_s: rate constants of the reactions **1b**–**f**→**2b**–**f**. Since the σ_p^+ parameter for the acetate group was not defined in ref. [8], substrate **1f** was not plotted. For the determination of ρ the following expression[8] was used: $k_s/k_u = \log[1 - s_r/s_t]/\log\,[1 - u_r/u_t]$. ρ = reaction constant; u_r and s_r = mmols of anilide **1a** and *p*-substituted anilides **1b**–**e**, respectively, that reacted, or by analogy, mmols of products **2a** and **2b**–**e** formed; u_t and s_t = initial mmols of anilide **1a** and *p*-substituted anilides **1b**–**e**, respectively.
[10] R. Higgins, C. S. Foote, H. Cheng, *ACS Symp. Ser.* **1968**, *77*, 102.
[11] J. H. Horner, O. M. Musa, A. Bouvier, M. Newcomb, *J. Am. Chem. Soc.* **1998**, *120*, 7738; M. Newcomb, N. Tanaka, A. Bouvier, C. Tronche, J. Horner, O. M. Musa, F. N. Martinez, *J. Am. Chem. Soc.* **1996**, *118*, 8505; M. Newcomb *Tetrahedron* **1993**, *49*, 1151, and references therein.
[12] J. L. Esker, M. Newcomb, *Tetrahedron Lett.* **1993**, *34*, 6877.
[13] J. L. Esker, M. Newcomb in *Advances in Heterocyclic Chemistry*, *Vol. 58* (Ed.: A. R. Katritzky), Academic Press, New York, **1993**, p. 1.
[14] Anodic peak potentials, 0.2 M nBu$_4$NBF$_4$ in CH_2Cl_2, Pt disk electrode, Pt wire auxiliary and pseudo-reference electrodes, 23 °C, 200 mV s^{-1}, referenced to internal ferrocene at +0.30 V; irreversible and rapid fouling of the electrode was observed and, therefore, measured potentials are on the first scan only (reproducible on several independent runs). Professor M. G. Finn is gratefully acknowledged for his assistance in these measurements. For a systematic study of the bond dissociation energies of the N–H bonds in anilines, and their oxidation potentials, see F. G. Bordwell, X.-M. Zhang, J.-P. Cheng, *J. Org. Chem.* **1993**, *58*, 6410.
[15] The recognition that IBX behaves as a general SET reagent suggests a SET-based mechanism (rather than the initially proposed ionic mechanism) for the reaction described in ref. [4]. Furthermore, a new IBX-mediated benzylic oxidation reaction based on a SET rationale was devised, and will be reported in due course.
[16] For an insightful study of steric inhibition of resonance, see S. Böhm, O. Exner, *Chem. Eur. J.* **2000**, *6*, 3391, and references therein.
[17] a) For the first report of Ac-IBX, see D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277; b) water-induced acceleration of the DMP reagent (leading to Ac-IBX) was also observed in the context of alcohol oxidation: S. D. Meyer, S. L. Schreiber, *J. Org. Chem.* **1994**, *59*, 7549; c) see also: S. D. Munari, M. Frigerio, M. Santagostino *J. Org. Chem.* **1996**, *61*, 9272.
[18] Complete details of this optimization will be given in the full account of this work.
[19] K. C. Nicolaou, K. Sugita, P. S. Baran, Y.-L. Zhong, *Angew. Chem.* **2001**, *113*, 213; *Angew. Chem. Int. Ed.* **2001**, *40*, 207.

  1433-7851/01/4001-0206 $ 17.50+.50/0