Intermediates in nucleophilic aromatic substitution

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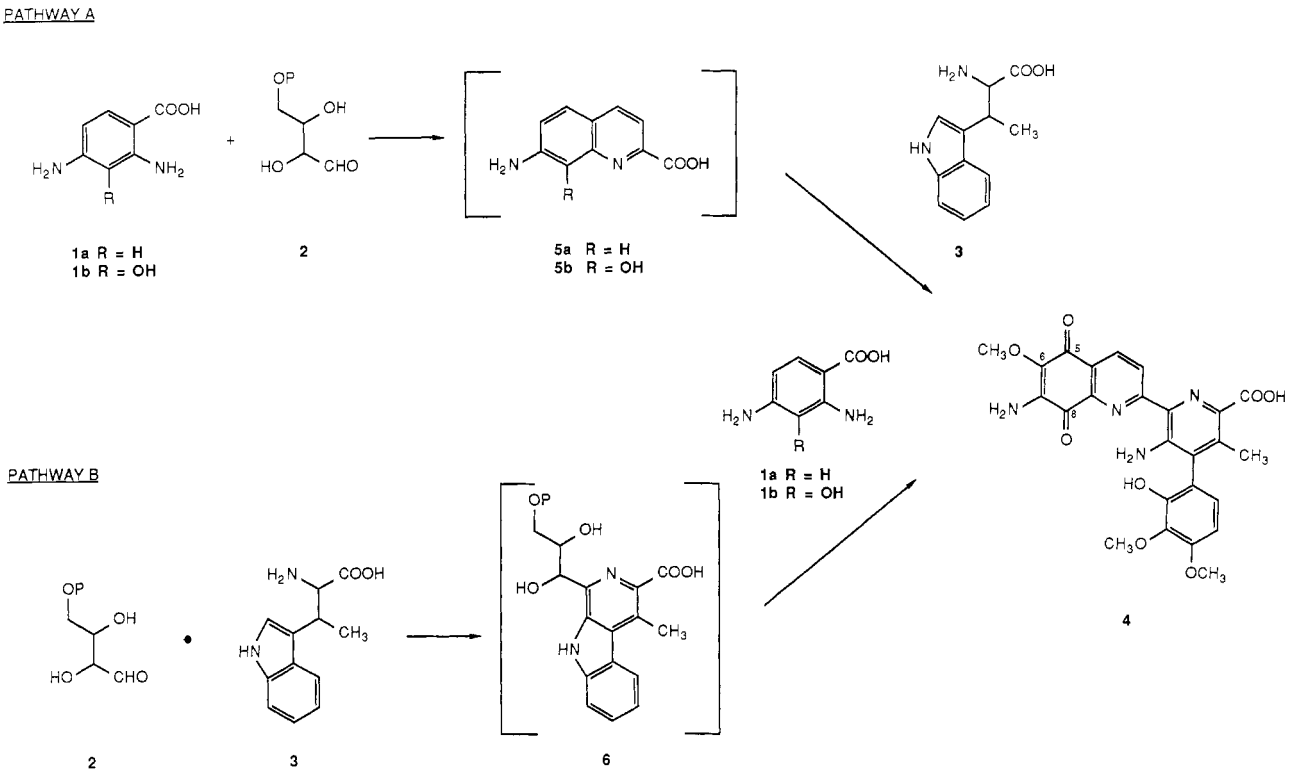
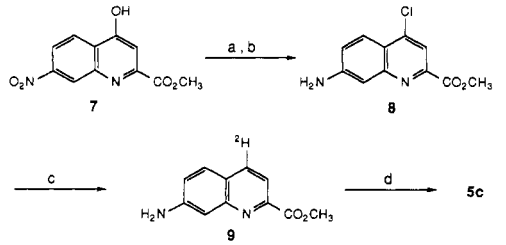
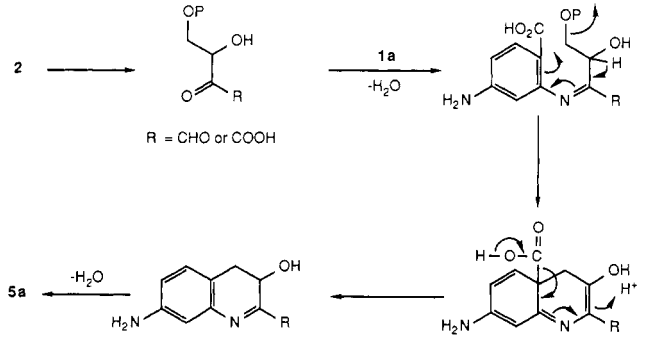
Scheme I



Scheme II



Scheme III



analogous to the biosynthesis of tryptophan from anthranilic acid and ribose diphosphate.[21]

In order to further probe this remarkable pathway, testing of **1b**, 7-amino-8-hydroxyquinoline-2-carboxylic acid (**5b**), and 7-amino-5-hydroxyquinoline-2-carboxylic acid as potential later intermediates is currently under investigation.

Acknowledgment. Strains of *S. flocculus* were originally obtained from Dr. John DeZeeuw of Pfizer and Co., Inc., Groton, CT. Rodger Kohnert and John Wityak are thanked for obtaining the ^{15}N and ^{2}H NMR spectra. This work was supported by Public Health Service Grant GM31715 to S.J.G. The multinuclear Bruker AM 400 NMR spectrometer was purchased in part through grants from the National Science Foundation (CHE-8216190) and from the M.J. Murdock Charitable Trust to Oregon State University.

(20) For examples of quinoline biosynthesis from anthranilic acid and "acetate", see: Herbert, R. B. *The Biosynthesis of Secondary Metabolites*; Chapman and Hall: New York, 1981; pp 131-132. For examples from tryptophan metabolism, see: Luckner, M. *Secondary Metabolism in Microorganisms, Plants, and Animals*; Springer-Verlag: New York, 1984; pp 404-406.

(21) Lehninger, A. L. *Biochemistry*; Worth: New York, 1975; p 709.

Intermediates in Nucleophilic Aromatic Substitution

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Bimolecular nucleophilic aromatic substitution by anions in polar hydroxylic solvents is generally written as rate-limiting formation of a Meisenheimer, or σ, complex,[1,2] but π-complexes[3] are also postulated reaction intermediates.[4]

Unexpectedly, reported rate constants for formation of Meisenheimer complexes from OH^- and a nitroarene or quinazoline

(1) (a) Bunnett, J. F. *Q. Rev., Chem. Soc.* **1958**, *12*, 1. (b) Buncel, E.; Norris, A. R.; Russell, K. F. *Ibid.* **1968**, *22*, 123.

(2) Strauss, M. J. *Chem. Rev.* **1970**, *70*, 667. Terrier, F. *Ibid.* **1982**, *82*, 78.

(3) (a) Miller, R. E.; Wynne-Jones, W. F. K. *J. Chem. Soc.* **1959**, 2377. (b) Allen, C. R.; Brook, A. J.; Caldin, E. F. *Ibid.* **1961**, 2171 and references cited therein.

(4) Tamaru, K.; Ichikawa, M. *Catalysis by Electron Donor-Acceptor Complexes*; Wiley: New York, 1975; p 53.

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Scheme I

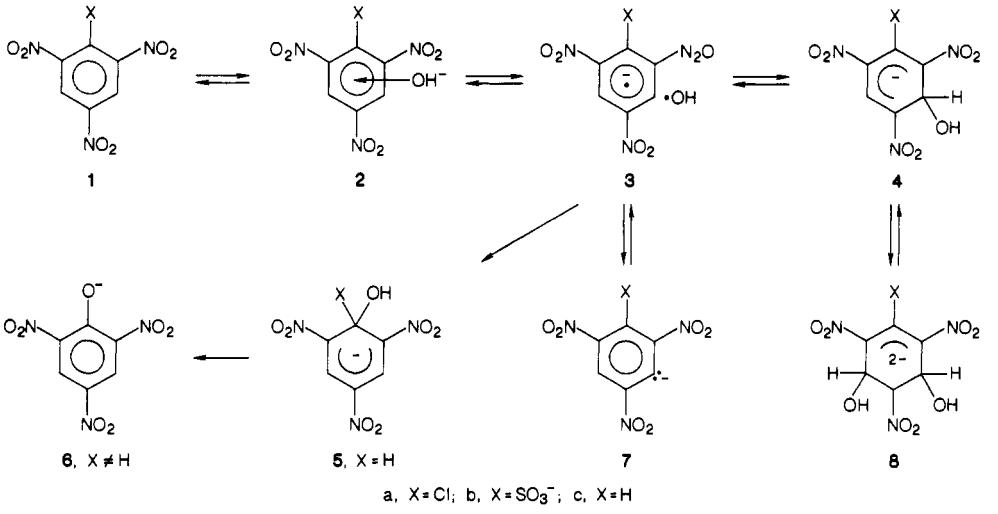

Table I. Relaxation Times of Reactions of 1,3,5-Trinitrobenzene and its Derivatives[a]

	X = Cl		X = SO_3^-		X = H	
reaction	λ, nm	$1/\tau$, s^{-1}	λ, nm	$1/\tau$, s^{-1}	λ, nm	$1/\tau$, s^{-1}
disappearance of **2**	490	550[b] (520[c])	495	570 (670)	500	ca. 800 (615)[b]
appearance of **3**	260	500[b] (450[c])	260	520 (600)	258	(590)[b]
disappearance of **3**	260	7.4 (32[c])	260	4.1 (2.0)	258	25 (215)[b]
fast formation of **6**	360	7.7 (30[c])	360	3.5 (1.7)		
formation of **4**	490	8.1 (32[c])	495	4.4 (1.8)	500	27 (230)[b]
slow formation of **6**	360	0.08[d] (0.048[d])	360	0.02[f] (0.012[g])		
disappearance of **4**	490	0.087 (0.042)	495	0.02 (0.010)		
formation of **8**	274	0.050[e]				
very slow formation of **6**	360	0.0028[e]				
disappearance of **8**	274	0.0027[e]				

[a] Reactions of $(NO_2)_3C_6H_2X$ at 25 °C with aqueous 0.5 M OH^- unless specified. Values in parentheses are in H_2O–Me_2SO 1:1 v/v, 0.2 M OH^-, and λ is the wavelength at which reactions were followed; relaxation times, τ, were determined at the specified wavelengths. [b] 0.25 M OH^-. [c] 0.15 M OH^-. [d] ca. 70% of overall reaction. [e] 2.5 M OH^-. [f] 96% of overall reaction. [g] 89% of overall reaction.

are larger than for reactions of OH^- with chloro derivatives,[5-7] suggesting a complex mechanism. We have reinvestigated reactions of OH^- with picryl chloride (**1a**) and sulfonate (**1b**) and 1,3,5-trinitrobenzene (**1c**) in H_2O or H_2O–Me_2SO 1:1 v/v at 25 °C and made preliminary observations on reactions of other activated aromatic substrates.

In dilute aqueous NaOH (0.01–0.05 M), disappearance of **1a** followed at 240 nm and appearance of picrate ion (at 360 nm) were second order (k_2 = 0.46 M^{-1} s^{-1}) and no intermediates were seen. With [OH^-] = 0.1–0.75 M, we saw a species absorbing at ca. 490 nm[8] (**2a**, Scheme I), but its formation was too fast to be followed on a stopped-flow spectrometer (cf. ref 3b). It disappeared with a reciprocal relaxation time,[10] $1/\tau$, of ca. 500 s^{-1} in 0.1–0.5 M OH^-, and a new species (**3**) formed with a similar $1/\tau$ followed at 260 nm. This species disappeared with first-order kinetics giving both picrate ion (λ_{max} = 360 nm) and a Meisenheimer complex (**4a**, λ_{max} = 490 nm). Values of $1/\tau$ were essentially the same following decreasing absorbance at 260 nm or increasing at 360 or 490 nm. They vary with [OH^-] in the range 5–10 s^{-1} in 1–0.1 M OH^-. Complex **4a** was then slowly transformed into picrate ion (**6**) with $1/\tau$ = 0.03–0.08 s^{-1} in 1–0.1 M OH^- followed at 360 or 490 nm. Under our conditions most of the picrate ion is formed by this reaction path (Table I and Scheme I). Similar overall behavior was observed with **1b** and in aqueous Me_2SO. A second Meisenheimer complex can form from **1a**,[2] because with [OH^-] > 1 M we saw a species absorbing at 274 nm,[11] which slowly disappeared to give **6** with $1/\tau$ = 0.068–0.0027 s^{-1}, in 1–2.5 M OH^-, followed at 274 or 360 nm.

Picrate ion (**6**) can be formed in three steps: (i) very rapidly by partitioning of the transient species **3a** into **6**[12] and **4a**; (ii) by return of **4a**, via **3a**; (iii) by the very slow disappearance of the dianionic complex **8a**.

Reaction of **1a** (or **1b**) is accompanied by hydrogen exchange, because by NMR (300 MHz) we saw rapid exchange of two aromatic protons in 0.682 M NaOD in Me_2SO–D_2O (57%). If reaction of **1a** in Me_2SO–D_2O (34:66 v/v 1 M OD^-) is stopped after 30 s, isolated **1a** is fully exchanged (from mass spectrometry). Thus in these conditions exchange is faster than chemical reaction, but with substrates such as **1c** which rapidly form Meisenheimer complexes (or final reaction products), exchange is less important. Therefore we assume that exchange involves interconversion of **3** and anion **7** and that **7** is not on the overall reaction path, cf. ref 13.

The postulated Scheme I intermediate **2** is shown as a π-complex, cf. ref 3. The second intermediate **3**, is written as a charge-transfer complex of a pair of radicals with a benzenoid structure, rather than as an anion. When X = H, as with **1c**,

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(6) (a) Hinze, W. L.; Liu, L. J.; Fendler, J. H. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1751. (b) Bunton, C. A.; Romsted, L. S.; Savelli, G. *J. Am. Chem. Soc.* **1979**, *101*, 1253.

(7) (a) Bunting, J. W.; Perrin, D. D. *J. Chem. Soc. B* **1967**, 950. (b) Barlin, G. B.; Yung, A. C. *Ibid.* **1971**, 2323.

(8) Gan observed a similar intermediate of 1,3,5-trinitrobenzene and OH^- in cationic micelles[9] but did not follow its formation or disappearance.

(9) Gan, L. H. *Can. J. Chem.* **1985**, *63*, 598.

(10) Bernasconi, C. *Relaxation Kinetics*; Academic Press: New York, 1976.

(11) This species also absorbs at higher wavelengths, but this absorbance could not be separated from those of picrate ion and monoanionic Meisenheimer complex. It is probably the dihydroxy species **8**.[2]

(12) This reaction probably goes via the short-lived 1-complex **5**, which is not observed spectrally unless X ≡ H; i.e., reaction is addition rather than substitution.

(13) Buncel, E.; Zabel, A. W. *Can. J. Chem.* **1981**, *59*, 3177 and references cited therein.

attainment of equilibrium with Meisenheimer complex involves intermediates **2c** and **3c**, which can be observed spectrally. We have also made similar observations for reactions of OH^- with 2,4-dinitrobenzene, 2,4-dinitronaphthalene, quinazoline, 3,5-dinitropyridine, and 5-nitropyridine and -pyrimidine and their halo derivatives.

Scheme I accords with other evidence, e.g., formation of a 3-Meisenheimer complex from OMe^- and **1a** in MeOD.[14] Radical reactions often accompany nucleophilic addition and substitution and anion radicals are known in similar systems.[15] If O_2 is bubbled into an equilibriated solution of **1c** and **5c** in aqueous 0.5 M OH^-, **6** is formed with a similar $1/\tau$ (2.2×10^{-4} s^{-1}) as for the disappearance of the Meisenheimer complex (2.5×10^{-4} s^{-1}), and O_2 should trap **3c**, but not the other species.[16] There is rapid hydrogen exchange at C-2 of 1,3-dinitrobenzene in Me_2SO–D_2O (66:34 v/v, 0.053 M OD^-), but with heating to 50 °C all the proton NMR signals disappear, probably due to line broadening. All reappear on cooling, except at C-2.[17]

Some of the reported rate constants for reaction of OH^- with **1a,b** are in fact for conversion of a 3-Meisenheimer complex (**4a,b**) into picrate ion.[5a,18] To this extent care has to be taken in comparing reactivities of arenes and chloroarenes with OH^-. However, the data in Table I suggest that some steps are faster with **1c** than with **1a,b**, with a complex dependence on solvent composition and $[OH^-]$.

Acknowledgment. Support by the National Science Foundation (Chemical Dynamics Program) and CNR (Rome) is gratefully acknowledged.

(14) Crampton, M. R.; El Ghanani, M. A.; Khan, H. A. *Tetrahedron* **1972**, *28*, 3299.
(15) Russell, G. A.; Janzen, E. G. *J. Am. Chem. Soc.* **1964**, *86*, 1807. Bellobono, T. R.; Gamba, A.; Sala, G.; Tampieri, M. *Ibid.* **1972**, *94*, 5781. Mariani, C.; Modena, G.; Piazzo, G. P.; Scorrano, G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1187.
(16) Isolated Meisenheimer complexes are not reported to react readily with O_2.[2]
(17) 1,3-Dinitrobenzene does not form a Meisenheimer complex in OD^-–D_2O, but one forms with OH^- in aqueous Me_2SO.
(18) Gibson, B.; Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2* **1979**, 648. Bunton, C. A.; Ihara, Y.; Wright, J. L. *J. Org. Chem.* **1976**, *41*, 2520.

Synthesis of Covalently Linked Double-Helical Cross Sections Representative of Purine–Purine and Pyrimidine–Pyrimidine Duplexes

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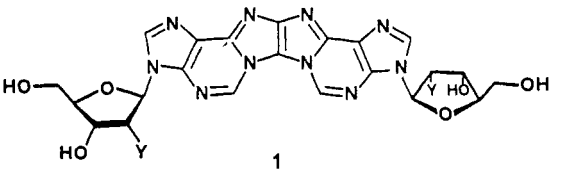
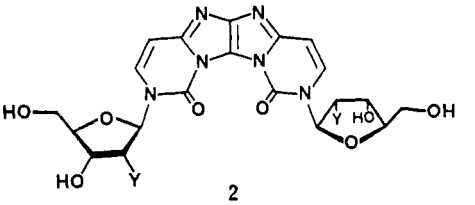
We have introduced the concept of covalently linked cross sections with molecular architecture similar to Watson–Crick hydrogen-bonded base pairs in a double helix, and we have shown how these can be synthesized conveniently.[1] The covalent cross sections possess 1,3,4,6-tetraazapentalene as the central linking system, the geometry of which mimics closely that of the doubly hydrogen bonded eight-membered central ring of a normal Watson–Crick cross section. In fact, it would be difficult to construct a closer mimic because of the excellent fit (within 0.2 Å, purine C1′ to pyrimidine C1′) and the coincidence of polarity of the two central ring systems. Great interest in the effect of DNA distortion on binding and biological activity has stimulated us to provide a covalently linked purine–purine cross section **1** with dimensions such as would be produced in the pairing of A with I, capable of generating a bulge in a double-helical RNA or DNA. We also provide a covalently linked pyrimidine–pyrimidine cross section **2** such as might be produced in the hypothetical pairing of C with U or T, namely, a pinched-in RNA or DNA cross section. Fixed-cross-section entities have not been available before this.



1



2

a, Y = OH
b, Y = H

The synthetic Scheme (Scheme I) that culminated in **1a** consisted of three steps from 2′,3′,5′-tri-*O*-acetyladenosine (**3a**) plus final O-deprotection. The intermediate **4a**[2] obtained from **3a** and chloroketene diethyl acetal as described previously[1] was condensed with additional **3a** in the presence of an acid catalyst to give **5a**. The conversion to **5a** was improved to 17% by the use of 0.5 equiv of *p*-toluenesulfonic acid instead of 0.2 equiv.[1] The yield of the highly fluorescent **6a** on oxidative cyclization of **5a** was significantly increased to 40% over that realized with iodobenzene diacetate in trifluoroethanol–nitromethane. This was effected by the use of 2-nitroiodobenzene diacetate in a solvent mixture of 1,1,1,3,3,3-hexafluoro-2-propanol or 1,1,1,3,3,3-hexafluoro-2-methyl-2-propanol and nitromethane. The structures of the intermediates were confirmed by elemental, ^1H NMR, and FAB mass spectral analysis. The symmetry of **6a** was evident from the dramatic simplification of its ^1H NMR spectrum in comparison with that of its immediate precursor **5a**. Particularly diagnostic is the downfield shift[2] of the NMR signal for the proton on the pyrimidine ring observed in the conversion of **3a** to **5a** (0.46 ppm) and again in the conversion of **5a** to **6a** (0.61 ppm). The presence of a plane of symmetry in **6a**, consistent with the assigned structure, was established by its ^{13}C spectrum, in which the chemical shifts of the different junctional carbons 6a and 13a appeared at 111.41 and 152.51 ppm, respectively, and that of the identical junctional carbons 12b and 14a appeared at 141.45 ppm. The structure of **6a** was further established by $^1H/^{13}C$ short-range[3] and long-range[4,5] NMR correlation studies and by high-resolution FAB mass spectrometry.

Complete deacetylation of **6a** was achieved in methanolic ammonia during 1 h at 0 °C followed by 2.5 h at room temperature to give 3,10-di-β-D-ribofuranosylpurino[1″,6″:1′,2′]-imidazo-[4′,5′:4,5]imidazo[2,1-*i*]purine (**1a**) (80%).[6] The 3,10-bis(2′-deoxy-β-D-ribofuranosyl) analogue **1b** (68% yield in deacetylation) was synthesized by a similar sequence starting with 3′,5′-di-*O*-acetyl-2′-deoxyadenosine. Structures of the intermediates and final product **1b** in this sequence were established by the same analytical and spectroscopic means as in the series of reactions leading to **1a**. The precedents[1,7] for the oxidative cyclization step were modified as described above for **1a**.

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(2) Leonard, N. J.; Cruickshank, K. A. *J. Org. Chem.* **1985**, *50*, 2480.
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(5) Sato, Y.; Geckle, M.; Gould, S. J. *Tetrahedron Lett.* **1985**, *26*, 4019.
(6) We are grateful to Dr. Kurt L. Loening, Director of Nomenclature, Chemical Abstracts Service for his assistance in providing acceptable IUPAC/CA names for the compounds described herein.
(7) Cruickshank, K. A.; Sumoto, K.; Leonard, N. J. *Tetrahedron Lett.* **1985**, *26*, 2723.

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