J. Am. Chem. Soc. 1992, 114, 6003-6006

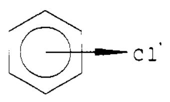
Inverted Regioselectivities in the Reactions of Chlorine Atoms with Heteroarylmethanes

Rajive K. Khanna,[*,†] **Becky Armstrong,**[†] **Hong Cui,**[†] **and James M. Tanko**[‡]

Contribution from the Department of Chemistry and Biochemistry, University of Southern Mississippi, Hattiesburg, Mississippi 39406-5043, and Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061-0212.
Received January 15, 1992. Revised Manuscript Received April 3, 1992

Abstract: The relative reactivities of the two methyl groups of 2,6-dimethylquinoline (2,6-DMQ) and 2,7-dimethylquinoline (2,7-DMQ) toward several radicals were assessed by intramolecular competitions. The regioselectivities observed for *t*-BuO$^\bullet$ and Br$^\bullet$ (k_6/k_2, $k_7/k_2 > 1$) are consistent with electrophilic characteristics of these radicals and estimates of relative stability of the resulting radicals. In contrast, Cl$^\bullet$ displays inverted selectivities (k_6/k_2, $k_7/k_2 < 1$) suggesting a directive effect of the DMQ nitrogen. Complexation of Cl$^\bullet$ by the N lone pair of dimethylquinolines, followed by a novel intramolecular hydrogen abstraction through a 5-center cyclic transition state, explains the regioselectivities observed in these reactions. Although bromine atoms also complex with heteroaromatics, these Br$^\bullet$ complexes have a low reactivity toward benzylic hydrogens. Evidence from intermolecular competition experiments, laser flash photolysis studies, semiempirical MO calculations, and dimethylbutane quenching experiments is presented in support of the proposed intramolecular hydrogen abstraction process.

In the late 1950's Russell[1,2] demonstrated that the selectivities in free radical chlorinations, using molecular chlorine, can be dramatically enhanced by conducting the reactions in aromatic solvents and CS_2. For example,[2] for photochlorinations of 2,3-dimethylbutane with Cl_2 at 25 °C, the tertiary-to-primary selectivity on a per hydrogen basis increases from 4.2 in pure alkane to 59 in 8 M benzene. The enhanced selectivity was attributed to a chlorine atom–benzene π-molecular complex (**1**) in equilibrium with free chlorine atoms. These observations were subsequently confirmed and extended by Walling[3] and others.[4,5]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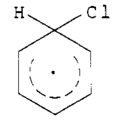
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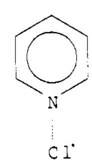
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In 1983, Skell[6] demonstrated that the arene/Cl$^\bullet$ complex was not in equilibrium with free chlorine atoms under all conditions and suggested an alternative σ-type structure (**2**, the 6-chlorocyclohexadienyl radical) for the complex. In 1985, the Ingold group[7] generated the benzene/Cl$^\bullet$ complex, utilizing laser flash photolysis, from a variety of Cl$^\bullet$ precursors. These authors favored, on the basis of their kinetic and spectroscopic observations, Russell's original proposal that benzene/Cl$^\bullet$ was a π-complex.[7-9]

Recently Breslow[10] described the use of pyridine ester templates to direct selective free radical chlorinations of steroids[11] and attributed the excellent selectivity observed in these reactions to a loose σ^*-type complex of Cl$^\bullet$ with pyridine nitrogen (**3**).[12] The transient absorption spectrum of the pyridine/Cl$^\bullet$ complex[12] differs drastically from that of the benzene/Cl$^\bullet$ complex and cyclohexadienyl-type radicals and is consistent with the proposed σ^*-type structure.[13] Ab initio calculations[12] suggest a planar structure with a long N-Cl 3-electron bond.

We have investigated the complexes of chlorine atoms with quinoline and its derivatives, utilizing transient spectroscopy and steady state techniques. In this paper we present evidence for a novel intramolecular hydrogen atom abstraction process, occurring through 5-center or 6-center cyclic transition states, in chlorine atom complexes of methylquinolines. Our results demonstrate that this intramolecular reaction results in a dramatic inversion of regioselectivity in photochlorination reactions of dimethylquinolines with Cl_2. We also find that the reactions of $(CH_3)_3CO^\bullet$ and Br$^\bullet$ with heteroarylmethanes are not governed by spatial restrictions imposed by the nitrogen.

Experimental Section

General Considerations. ^{13}C NMR and ^1H NMR spectra were obtained on a 200-MHz Bruker AC-200 spectrometer. GC analyses were performed on a Hewlett Packard HP 5890A instrument equipped with a FID detector and an HP 3396 reporting integrator. Analyses were accomplished on a J&W scientific DB-1 capillary column (30 m × 0.25 mm).

Materials. CCl_4 was dried over KOH for 24 h, decanted, distilled from phosphorus pentoxide, and stored over fresh molecular sieves. Pyridine and quinoline were dried over KOH, distilled, and stored over molecular sieves. $(CH_3)_3COCl$ was prepared immediately before use from *tert*-butyl alcohol and sodium hypochlorite by Walling's method.[14] *N*-Bromosuccinimide (NBS) was recrystallized from water and dried in vacuo. Azobisisobutyronitrile (AIBN) was purchased from Kodak. All other chemicals were purchased from Aldrich Chemical Co., and used as such.

Intramolecular Competitions. Reactions were performed under argon atmosphere in silicon-septa sealed round-bottomed flasks. In competitive chlorinations with $(CH_3)_3COCl$ at 70 °C, DMQ (0.5–2.5 mmol) and a weighed amount of AIBN (0.2 mol % of DMQ) were placed in a sealed 20-mL flask (equipped with a Teflon-coated magnetic bar) with 10 mL of dry CCl_4. The flask was covered with aluminum foil and then a weighed amount of $(CH_3)_3COCl$ (10 mol %) was added using a glass

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[†] University of Southern Mississippi.

[‡] Virginia Polytechnic Institute and State University.

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syringe. The mixture was degassed by the freeze–pump–thaw technique (flushed with argon in the thaw cycle) and placed in a controlled-temperature bath. After the reaction was complete (30–60 min), the flask was cooled and 0.25 mL of the reaction mixture was transferred to an NMR tube containing 0.25 mL of $CDCl_3$ (with TMS). ^1H NMR analysis of the solution was performed immediately. GC analysis of the reaction mixture was performed using biphenyl as the internal standard. The reactions (in the absence of AIBN) at 40 °C were irradiated with a 200-W sunlamp (at a distance of 2 ft from the reaction vessel) for 25–30 min. In competitive brominations at 70 °C, NBS (10 mol %) and benzoyl peroxide (2 mol %) were used; at the reaction temperature of 22 °C, the reaction mixture was irradiated with a 450-W medium-pressure mercury-vapor lamp for 30 min. Competitive chlorinations were carried out as follows: Chlorine (10% in a stream of argon) was slowly bubbled (total flow = 5 mL/min) through deoxygenated solutions containing 0.5–2.5 mmol of DMQ in CCl_4 at room temperature in the dark (flask wrapped in aluminum foil) for 5–10 min. The rate of flow of each gas and the total flow were measured by using a bubble flow-meter in a well-vented hood. The sealed reaction flasks were placed in a controlled-temperature bath and the reaction was initiated with the light from a 200-W sunlamp placed at a distance of 30 in. Upon completion of the reaction (10–15 min), the reaction mixture was analyzed by ^1H NMR and capillary GC.

The ratios of the two side-chain halogenated products in the reaction mixtures were obtained from ^1H NMR spectroscopy and capillary GC. The average ^1H NMR chemical shift values (TMS) for the methylene protons of the monohalogenated products are as follows. In chlorinations: 2,6-DMQ, δ 4.64 (s, 6-CH_2Cl), 4.76 (s, 2-CH_2Cl); 2,7-DMQ, δ 4.70 (s, 7-CH_2Cl), 4.77 (s, 2-CH_2Cl); in brominations: 2,7-DMQ, δ 4.59 (s, 7-CH_2Br), 4.63 (s, 2-CH_2Br).

Intermolecular Competitions. Relative reactivities were determined by capillary GC, using biphenyl as an internal standard, and using the relation

$$\text{relative reactivity} = (\ln A/A_0)/(\ln B/B_0)$$

where A_0 and B_0 are the peak areas of the two quinolines relative to the internal standard prior to reaction and A and B are the same quantities after reaction. Analyses were performed in triplicate.

Quenching Experiments. The reactivities of the 6-methylquinoline/Cl• and 2-methylquinoline/Cl• complexes toward the primary and tertiary hydrogens of 2,3-dimethylbutane (DMB) were measured as follows: Chlorine (10% in Ar) was slowly bubbled (total flow = 5 mL/min) through deoxygenated solutions containing 0.1 M DMB and appropriate amounts of the quinoline (0.25–1.0 M) in CCl_4 at room temperature in the dark for 5 min. The reaction was initiated with the light from a 200-W sunlamp. Upon completion of the reaction (10 min), the chlorinated products were analyzed in triplicate by GC. Under these conditions the conversion of DMB was limited to ca. 10%.

Laser Flash Photolysis.[15] The excitation source used was a Lumonics Hyper EX-440 excimer laser which produces a 10–15 ns pulse duration of <60 mJ at 351 nm (XeF fill). An Applied Photophysics excimer based nanosecond flash spectrometer equipped with a LKS-1400 control unit, F 3.4 grating monochromator, 150-W arc lamp, 1-kV photomultiplier power supply, and either an IP28 or a R928 photomultiplier tube was the monitoring system. The transient traces initially captured by a Phillips/Fluka PM 3323 digital oscilloscope were then transferred to an Archimedes Acorn microcomputer for storage and processing. Experiments were carried out in static systems with samples contained in suprasil cells. These were usually deoxygenated by bubbling with argon. Laser dose attenuation experiments (with neutral density filters) were routinely carried out.

MO Calculations. Semiempirical MO calculations were performed using the AM1 approximation developed by Dewar et al.[16] and implemented through MOPAC, v. 5.0 (QCPE 455). Full geometry optimizations were performed on the parent quinolines. For the open-shell species, geometries were optimized using UHF, followed by a single-point calculation using the half-electron approximation.[17,18]

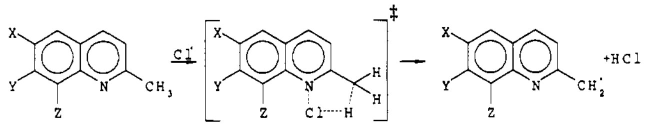
Results and Discussion

Table I. Relative Side-Chain Reactivities[a] of 2,6-DMQ and 2,7-DMQ toward Several Radicals

radical	T, °C	k_6/k_2	k_7/k_2
$(CH_3)_3CO^\bullet$	70[b]	1.8	1.7
$Br^\bullet$	70[c]	4.0	3.9
	22[d]		5.7
$Cl^\bullet$	40[e]	0.30	0.31
	22[e]		0.21
	40[f]	0.58	0.55

[a] Ratios of products, at low conversions (10–15%), estimated by ^1H NMR and capillary GC. The polyhalogenated materials do not exceed 10% of monohalides. [b] $(CH_3)_3COCl/CCl_4$; initiated thermally with AIBN in the dark (ref 20). [c] *N*-Bromosuccinimide (NBS)/CCl_4; initiated thermally with dibenzoyl peroxide (ref 19). [d] NBS/CCl_4; photoinitiated (450-W medium-pressure mercury vapor lamp). [e] Cl_2/CCl_4; photoinitiated (200-W sunlamp). No reaction was observed in the dark. [f] $(CH_3)_3COCl/CCl_4$; photoinitiated (200-W sunlamp). Under these conditions, ca. 80% of the reaction is propagated by chlorine atom chain (ref 14).

Scheme I. Intramolecular Hydrogen Transfer in Dimethylquinolines



2,6-DMQ : X = CH_3; Y = Z = H

2,7-DMQ : Y = CH_3; X = Z = H

2,8-DMQ : Z = CH_3; X = Y = H

Intramolecular Competitions. The relative reactivities of the two methyl groups of 2,6-dimethylquinoline (2,6-DMQ) and 2,7-dimethylquinoline (2,7-DMQ) toward $(CH_3)_3CO$; $Br^\bullet$, and $Cl^\bullet$ were assessed by intramolecular competition experiments under several conditions, using $(CH_3)_3COCl$,[14] *N*-bromosuccinimide (NBS),[19] and Cl_2, respectively, as halogenating agents in CCl_4 solvent. A 10-fold excess of the quinoline substrate was used in each run to limit the side-chain polyhalogenated material to 10–15% of monohalides. The relative side-chain reactivities were given by the ratios of the side-chain halogenated products, estimated by ^1H NMR and capillary GC. We find that the observed regioselectivities, at low DMQ concentrations (<0.25 M) are independent of substrate concentrations. The results are summarized in Table I.

It is interesting to note that in the reactions with $(CH_3)_3COCl$, different results are obtained depending on the conditions employed. Thus, competitive experiments with $(CH_3)_3COCl$, initiated thermally with AIBN in the dark at 70 °C, show regioselectivities of k_6/k_2, $k_7/k_2 > 1$, whereas photoinitiated reactions with the same reagent display inverted regioselectivities. Walling[14,20] had reported earlier that in thermally initiated (AIBN) chlorinations of benzylic substrates with $(CH_3)_3COCl$, $(CH_3)_3CO^\bullet$ serves as the hydrogen atom abstracting species, but in photochlorinations using the same reagent ca. 80% of the reaction is propagated by chlorine atom chain, and the HCl formed in the reaction is neutralized in a fast reaction with $(CH_3)_3COCl$. Our results are in agreement with these observations.

The regioselectivities observed for $Br^\bullet$ and t-$BuO^\bullet$ are consistent with the electrophilic properties of these radicals[21,22] together with the charge densities in 2,6-DMQ (0.956 at C-6; 0.815 at C-2) and 2,7-DMQ (0.933 at C-7; 0.810 at C-2) which we have estimated from ^{13}C NMR shifts[23,24] of the respective aromatic

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[22] Electrophilic radicals ($Cl^\bullet$, $Br^\bullet$, $(CH_3)_3CO^\bullet$) have low-energy SOMO's (ionization potential of $Cl^\bullet$ = +13 eV) and thus should preferentially attack electron-rich sites with high-energy HOMO's, in these early transition state reactions. See: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1989; pp 186–188.

carbons by using the equation proposed by Olah[23] for a variety of cyclic, aromatic 2, 6, and 10 π-electron systems: $\delta = 288.5 - 159.5\rho$, where ρ is the charge density and δ is the ^{13}C chemical shift of the aromatic carbon. Furthermore, our estimates of the relative stability of the resulting quinolylmethyl radicals from semiempirical MO calculations (AM1/UHF)[16] predict hydrogen abstraction from 6-CH_3, and 7-CH_3 to be more favorable than 2-CH_3 by 2.8 and 2.4 kcal mol^{-1} in 2,6-DMQ and 2,7-DMQ, respectively. Thus, $(CH_3)_3CO^•$ and $Br^•$ display "normal" regioselectivities of k_6/k_2, $k_7/k_2 > 1$.

The *inverted* regioselectivities observed with $Cl^•$ suggest a directive effect of the DMQ nitrogen. Thus, complexation of $Cl^•$ by the nitrogen lone pair of DMQ, analogous to the pyridine/$Cl^•$ complex proposed by Breslow and Turro,[12] followed by a novel intramolecular hydrogen abstraction through a 5-center cyclic transition state (Scheme I), explains the regioselectivities observed in photochlorinations with Cl_2. In support, we find that the photochlorination of 2,8-dimethylquinoline (2,8-DMQ), where the methyl at C-8 is also in close proximity to the N lone pair, displays the regioselectivity of $k_{8\text{-Me}}/k_{2\text{-Me}} = 1.72$, with Cl_2 in CCl_4 at 22 °C. Apparently, hydrogen abstraction from the methyl group at C-8 ($\rho = 0.959$) by the complexed $Cl^•$, through a lower energy 6-center transition state, occurs in preference to atom abstraction from the methyl group at C-2 ($\rho = 0.810$) with a 5-center transition state.[25] However, steric hindrance in 2,8-DMQ may prevent $Cl^•$ from binding to the N lone pair and thus the observed regioselectivity may simply reflect the relative reactivity of free chlorine atoms toward the two methyl groups. It is pertinent to note that $(CH_3)_3CO^•$ shows a regioselectivity of $k_{8\text{-Me}}/k_{2\text{-Me}} = 2.5$ in reactions (AIBN, 70 °C) with 2,8-DMQ. Furthermore, semiempirical MO calculations (AM1/UHF)[16] predict hydrogen atom abstraction from 8-CH_3 to be more favorable than 2-CH_3 by ca. 4.0 kcal mol^{-1}.

Intermolecular Competitions. Intermolecular competition reactions of 2-methylquinoline (2-MeQ) and 8-methylquinoline (8-MeQ) with Cl_2 at 22 °C show a relative reactivity of $k_{8\text{-MeQ}}/k_{2\text{-MeQ}} = 1.8$. Since the intramolecular and intermolecular selectivity ratios for the 8-CH_3 and 2-CH_3 positions are about the same, we suggest that this ratio may reflect the relative reactivity of the complexed $Cl^•$ toward 8-CH_3 and 2-CH_3 via 6-center and 5-center transition states, respectively.

In contrast, an intermolecular competition reaction of 2-methylquinoline (2-MeQ; 0.1 M) and 6-methylquinoline (6-MeQ; 0.1 M), with Cl_2 at 22 °C, shows a relative reactivity of $k_{6\text{-MeQ}}/k_{2\text{-MeQ}} = 0.53$. However, in the presence of added pyridine (5 M) a selectivity of $k_{6\text{-MeQ}}/k_{2\text{-MeQ}} = 2.50$ is observed. We suggest that pyridine effectively competes with the quinolines for chlorine atoms and that under these conditions the pyridine/$Cl^•$ complex abstracts hydrogen atoms intermolecularly.

Laser Flash Photolysis. Excimer laser excitation (351 nm, 10 ns, 15 mJ) of Cl_2 in CCl_4 with quinoline (Q) yields the absorption spectrum of the quinoline/$Cl^•$ complex (λ_{max} at 372 nm, with no detectable long-wavelength band). This spectrum is consistent with the notion that the Q–$Cl^•$ complex is a σ^*-type complex, similar to the reported[12] pyridine/$Cl^•$ complex. We have estimated the rate constant for formation of the Q/$Cl^•$ complex from the total signal observed at 370 nm (A_{370}) and the rate of growth of the signal (k_{exptl}), with varying amounts of quinoline (2.5–7.5 mM), using the relationships

$$1/A_{370} = \alpha + \alpha(k_0/k_{\text{formation}})(1/[Q])$$

$$k_{\text{exptl}} = k_0 + k_{\text{formation}}[Q]$$

where k_0 includes all pseudo-first-order modes of chlorine atom decay.[7] We find that the rate constant so obtained ($k_{\text{formation}} = 1.2 \times 10^{10}\ M^{-1}\ s^{-1}$)[26] is larger than that for the abstraction of benzylic hydrogens by free chlorine atoms ($k \sim 5 \times 10^9\ M^{-1}\ s^{-1}$ with toluene[27] at 40 °C). Assuming that the rate constants for the formation of 2,6-DMQ/$Cl^•$ and 2,7-DMQ/$Cl^•$ complexes are similar in magnitude to that obtained for the Q/$Cl^•$ complex, we conclude that the complexation of $Cl^•$ by dimethylquinolines can effectively compete with hydrogen atom abstraction by free chlorine atoms from these substrates. Chlorine atom complexes with 2,6-DMQ, 2,7-DMQ, and 2,8-DMQ could not be observed, evidently as a consquence of rapid decay of these species via the intramolecular hydrogen atom abstraction pathway.

Laser flash photolysis of solutions of Br_2 (1.0 mM) in CCl_4 containing pyridine yield the pyridine/$Br^•$ complex (λ_{max} at 398 and 411 nm with no detectable long-wavelength band) with $k_{\text{formation}} = 1.6 \pm 1.5 \times 10^8\ M^{-1}\ s^{-1}$. The formed complex has a lifetime of ca. 20 μs in neat pyridine (12.5 M) which remains unchanged in the presence of toluene (<0.5 M; without degassing to suppress $Br^•$ recycling), suggesting that the $Br^•$/pyridine complex has a low reactivity[28] toward benzylic hydrogens of toluene. It should be noted that the reaction of toluene with free bromine atoms ($k \sim 2 \times 10^5\ M^{-1}\ s^{-1}$ at 40 °C)[29] in equilibrium with the complex is not expected to contribute significantly to the decay of the complex since the concentration of free bromine atoms, under these conditions, is expected to be very low. In view of the low reactivity of the pyridine/$Br^•$ complex, we propose that although bromine atoms may also complex with dimethylquinolines, these complexes do not decay by a fast intramolecular hydrogen atom abstraction pathway.

MO Calculations. Semiempirical molecular orbital calculations (AM1/UHF)[16] predict planar geometries for the quinoline/$Cl^•$, 2-methylquinoline/$Cl^•$, and 2,8-DMQ/$Cl^•$ complexes, with an N–Cl bond length of ca. 1.83 Å.[30] Relative heats of formations from these calculations indicate that both the Q/$Cl^•$ complex ($\Delta H^\circ_{\text{relative}} = 0.0$ kcal mol^{-1}) and the 2-MeQ/$Cl^•$ complex ($\Delta H^\circ_{\text{relative}} = +0.6$ kcal mol^{-1}) are of comparable stability, and the 2,8-DMQ/$Cl^•$ complex is 6 kcal mol^{-1} less stable, presumably due to steric effects.

Quenching Experiments. Photochemically initiated free radical chlorination (Cl_2) of 2,3-dimethylbutane (DMB) is reported[7] to show a selectivity ($S = k_{\text{tertiary}}/k_{\text{primary}}$ per hydrogen) of 2.8 in CCl_4 and low DMB concentrations (<0.1 M). In the presence of benzene[1-9] and pyridine[12] solvents (which reversibly complex chlorine atoms and thereby decrease their reactivity), the selectivity ratio, S, increases dramatically with an increase in the concentration of these additives. We observe a similar increase in S in the presence of 6-methylquinoline; selectivities at a low DMB concentration (vs 6-MeQ concentrations) are 31 (0.25 M) and 52 (0.5 M). In contrast, the selectivity ratio is unaffected in the presence of and with an increase in the concentration of 2-methylquinoline, although the yield of chlorinated products from DMB decreases as expected. The selectivities (vs 2-MeQ concentrations) are 3 (0 M), 4 (0.25 M), 6 (0.5 M), and 8 (1.0 M) and confirm that the 2-MeQ/$Cl^•$ complex reacts almost exclusively by a fast intramolecular hydrogen transfer reaction (vide supra) and thus has a short lifetime.

Summary and Conclusions

Chorine atoms are complexed by the N lone pair of heteroaromatic solvents such as pyridine and quinoline with rate constants larger than $1.0 \times 10^{10}\ M^{-1}\ s^{-1}$. The presence of an ab-

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[24] The charge densities, thus obtained, are in close agreement with the calculated SCF charge densities in methylquinolines. See: Gleicher, G. J. *Tetrahedron* **1977**, *33*, 1921–1923.

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[30] For 2-MeQ-$Cl^•$, another potential energy minima was found in which the Cl was ca. 40° out of the plane of the aromatic ring. This complex was ca. 6 kcal/mol higher in energy than the planar form. A larger value (2.27 Å) for the N–Cl bond length in the pyridine/$Cl^•$ complex is reported[12] from ab initio calculations.

stractable hydrogen in close proximity to the N lone pair, as in 2- or 8-methylquinolines, leads to a fast intramolecular hydrogen abstraction by the complexed chlorine atom through novel cyclic transition states. This intramolecular reaction results in unexpected regioselectivities in the reactions of Cl$^•$ with heteroarylmethanes. Although bromine atoms also complex with heteroaromatic solvents, these complexes have a low reactivity toward benzylic hydrogens. Consequently, Br$^•$ shows normal regioselectivities in reactions with heteroarylmethanes, similar to the normal regioselectivities displayed by radicals such as $(CH_3)_3CO^•$ which are not known to complex with heteroaromatic solvents.

Acknowledgment. Support of this research by the National Science Foundation EPSCoR program is gratefully acknowledged. We thank Professor Glen Russell for many helpful discussions.

Registry No. 2,6-DMQ, 877-43-0; 2,6-DMQ, 93-37-8; 2,8-DMQ, 1463-17-8; 2-MeQ, 91-63-4; 8-MeQ, 611-32-5; 6-MeQ, 91-62-3; *tert*-butoxy, 3141-58-0; at. bromine, 10097-32-2; at. chlorine, 22537-15-1; pyridine, 110-86-1; quinoline, 91-22-5; 2,3-dimethylbutane, 79-29-8.

Supplementary Material Available: Transient absorption spectra of quinoline/Cl$^•$ and pyridine/Br$^•$ complexes (2 pages). Ordering information is given on any current masthead page.

A Hausdorff Chirality Measure

Andrzej B. Buda and Kurt Mislow*

Contribution from the Department of Chemistry, Princeton University, Princeton, New Jersey 08544. *Received February 27, 1992*

Abstract: Chirality is a property that is independent of its physical and chemical manifestations. It is therefore possible to quantify chirality without any reference to pseudoscalar observables. In this paper we propose a new measure of chirality that is based on Hausdorff's concept of distances between sets and that is a natural choice as a measure for molecular models that represent structures as sets of atomic coordinates. This *Hausdorff chirality measure*, a continuous and similarity-invariant function of an object's shape, is zero if and only if the object is achiral. We have applied this measure to study the chirality of tetrahedral shapes—classical models of tetracoordinate carbon atoms—and have identified the extremal (most chiral) shapes for every chiral subsymmetry of T_d that can be realized by a tetrahedron. Our calculations show that the degree of chirality of the extremal objects increases with a decrease in symmetry, although the most symmetric chiral tetrahedron, with D_2 symmetry, already possesses 87% of the maximal chirality value available for tetrahedra, and that the shape of the most chiral tetrahedron, with C_1 symmetry, is very close to that of the most chiral C_2 tetrahedron. The properties and the applicability of the Hausdorff chirality measure are compared with those of other measures of chirality that are based on common-volume or root-mean-square approaches.

Attempts to give a quantitative meaning to molecular chirality can be dated almost as far back as van't Hoff's and LeBel's proposition to extend the structural formulas of chemistry into three-dimensional space. In 1890 Guye introduced the first function designed to correlate a pseudoscalar property, i.e., optical rotation, with the molecular structure of chiroids—the first example of a chirality function in chemistry.[1] Chirality, however, is an inherent molecular property that depends only on symmetry and that is independent of its physical and chemical manifestations. It should therefore be possible to quantify chirality, i.e., to construct a chirality measure, without reference to any experimental data. Indeed, recent years have witnessed much interest in the development of such chirality measures.[2]

In his original definition, Kelvin formulated the concept of chirality as an *abstract* property of *geometric* objects: "I call any geometrical figure, or group of points, *chiral*... if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself".[3,4] Although enantiomorphs (Q and Q') cannot be superposed by any rotation-translation, they can be placed upon each other (superimposed or overlapped) so that at least parts of them coincide. If one can establish a measure for the degree of overlap, then the means are available, in general, to optimize the overlap by rotation and translation of one enantiomorph with respect to the other. Once maximal overlap is achieved, the degree of overlap no longer depends on the relative orientation of the enantiomorphs and is only a function of the geometric shape; it might therefore serve to measure the chirality of an object (and its mirror image). Not every mathematical function, however, is suitable for such a measure.[2] In order to be called a *degree of chirality* a real-valued function $f(Q)$ should have the following properties:[5] (1) $f(Q)$ is a continuous function of Q, (2) $0 \leq f(Q) \leq 1$, (3) $f(Q) = 0$ if and only if Q is achiral, and (4) $f(Q)$ is similarity-invariant. The first requirement is a direct consequence of the fact that $f(Q)$ is a function of the shape of Q: the shape of a geometric object can, in principle, change in a continuous way, and such changes should be reflected in the continuous changes of $f(Q)$. The function should yield the same value for objects that have the same shape but that differ in size: this is achieved by the invariance of $f(Q)$ under similarity transformations.[6] In addition, as a *degree* of chirality, $f(Q)$ should be dimensionless and normalized to the interval [0, 1].

It should be noted that Kelvin's definition of chirality, when analyzed from an algebraic point of view, also implicitly contains a proposition for a measure of chirality, $k(Q)$, which can be paraphrased as follows: if any geometrical figure, or group of points, can be brought to coincide with its mirror image, then $k(Q)$

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(1) Guye, P.-A. *Compt. Rend.* (*Paris*) **1890**, *110*, 714. Guye, P.-A. *Ibid.* **1893**, *116*, 1378, 1451, 1454. See also: Crum Brown, A. *Proc. R. Soc. Edinburgh* **1890**, *17*, 181.

(2) For a critical discussion and review, see: Buda, A. B.; Auf der Heyde, T.; Mislow, K. *Angew. Chem., Int. Ed. Engl.*, in press. This review also describes highlights of the present work.

(3) Kelvin, W. T. *Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light*; Clay, C. J.: London, 1904; p 619.

(4) From Kelvin's definition it follows that the chirality of an object (e.g., a geometric figure, a group of points, the geometric model of a molecule) is a function of the object's *shape*. Thus, to achieve chirality it is not sufficient to assign different labels to parts of an achiral object. For example, an irregular tetrahedron is chiral, but a regular tetrahedron in which the four different vertices are distinguished by different labels (indices) is not.

(5) See also: Grünbaum, B. *Proc. Symp. Pure Math., Am. Math. Soc.* **1963**, *7*, 233.

(6) A similarity transformation is a transformation that preserves angles in a transformed object, Q.