Homolytic Alkylation of Protonated Heteroaromatic Bases by Alkyl Iodides, Hydrogen Peroxide, and Dimethyl Sulfoxide†

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A new general process of selective, homolytic alkylation of heteroaromatic bases of great synthetic interest is described. It is based on the reaction of alkyl iodides with hydrogen peroxide and heterocyclic compounds in DMSO, catalyzed by an Fe(II) salt. It is shown that the iodine abstraction from the alkyl iodide by the methyl radical, generated from the solvent, is the key point of the overall process. Combined enthalpic and polar effects contribute to the high selectivity: the enthalpic factor governs the equilibria of the iodine abstraction, and the polar factor determines the reactivity toward the protonated heterocyclic ring.

In 1968 we showed, in a preliminary report,[1] that a variety of selective reactions could be realized by taking advantage of the polar effects arising from the nucleophilic character of carbon-centered radicals in reactions with electron-deficient substrates (olefins conjugated with electron-withdrawing groups, protonated heteroaromatic bases, quinones, etc.). Electron-poor olefins and heteroaromatic bases were revealed to be particularly interesting for the synthetic involvements: the alkylation of these olefins has shown a large synthetic potentiality,[2] and the substitution of heteroaromatic bases by nucleophilic carbon-centered radicals has been developed as one of the most important general reactions in heteroaromatic series,[3] due to the high regio- and chemoselectivity, the availability of numerous and inexpensive radical sources, which can be successfully applied, and the simple experimental conditions. It reproduces most of the numerous aspects of the Friedel–Crafts aromatic substitutions, but with opposite reactivity and selectivity.

In this Account, we describe a new method of homolytic alkylation using alkyl iodides as a source of alkyl radicals. The method is particularly useful because of the generality of the reaction, the good results, the inexpensive reagents, and the simple experimental conditions. We have already briefly mentioned this new synthetic approach in a preliminary report.[4]

Results and Discussion

Alkyl iodides have been largely utilized as a source of alkyl radicals by iodine abstraction under reductive conditions,[2b] particularly organometallic radicals (i.e., trialkyltin, eq 1, or reducing metal salts, eq 2). The high

$$R\text{–}I + {}^{\bullet}SnR_3 \rightarrow R^{\bullet} + I\text{–}SnR_3 \quad (1)$$

$$R\text{–}I + Cr^{2+} \rightarrow R^{\bullet} + Cr^{3+} + I^{-} \quad (2)$$

rates make eq 1 and 2 very selective; they have been successfully utilized to reduce alkyl radicals (eq 3) or in

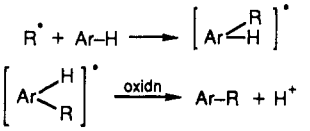
$$R^{\bullet} + HSnR_3 \rightarrow RH + {}^{\bullet}SnR_3 \quad (3)$$

$$R^{\bullet} + S \rightarrow R\text{–}S^{\bullet} \quad (4)$$

$$R\text{–}S^{\bullet} + HSnR_3 \rightarrow R\text{–}SH + {}^{\bullet}SnR_3 \quad (5)$$

reductive alkylation of unsaturated substrates (eq 4 and 5) in chain processes. These selective sources of alkyl radicals, however, are not suitable for the aromatic substitution, characterized by an oxidative alkylation (Scheme I). To be useful for the heteroaromatic substitution, the radical source must have oxidative character. Thus we have considered a different approach, based on the iodine-transfer reaction of eq 6. The synthetic success of this

Scheme I



$$R^{\bullet} + Ar\text{–}H \longrightarrow \left[Ar\!\!<^{R}_{H}\right]^{\bullet}$$

$$\left[Ar\!\!<^{H}_{R}\right]^{\bullet} \xrightarrow{\text{oxidn}} Ar\text{–}R + H^{+}$$

$$R\text{–}I + R'^{\bullet} \rightleftharpoons R^{\bullet} + R'\text{–}I \quad (6)$$

approach is due to the fundamental fact that small differences in the energies of the C–I bonds are reflected in large differences of the rates and equilibria of eq 6.

At first we started with the most favorable thermodynamic and kinetic conditions by using aryl radicals generated by oxidant precursors for the iodine abstraction[5] (eq 7). The rate is close to the diffusion-controlled limit,

$$R\text{–}I + Ar^{\bullet} \xrightarrow{k} R^{\bullet} + Ar\text{–}I \qquad k > 10^9\ M^{-1}\ s^{-1} \quad (7)$$

and the equilibrium is completely shifted to the right. Thus it is a very selective source of alkyl radicals, also considering the fact that most of the possible competitive reactions of the aryl radicals are 2–4 orders of magnitude slower (in the range of 10^5–10^7 M^{-1} s^{-1}).

We have obtained good results in several cases of heteroaromatic substitution by using aroyl peroxides or diazonium salts as sources of aryl radicals;[5] there are, however, some structural limitations. With aroyl peroxides the reaction does not work with tertiary alkyl iodides because it does not lead to aryl radicals, due to competitive ionic reactions.

A further general limitation occurs with substrates with activated C–H bonds or unsaturated systems (olefinic or aromatic) of high electron availability; in these cases, the iodine abstraction does not occur because the reactions of

† Dedicated to Professor D. H. R. Barton on the occasion of his 70th birthday.

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Table I. Equilibrium Constants for Reaction 8 ($Me^{\bullet} + RI \rightleftarrows MeI + R^{\bullet}$)

R	K
Et	20.1
i-Pr	468
t-Bu	1.7×10^4

the aroyloxy radical, $ArCOO^{\bullet}$, initially formed, with the substrate (hydrogen abstraction, addition to the unsaturated system), are faster than the decarboxylation,[6] and aryl radicals are not formed.

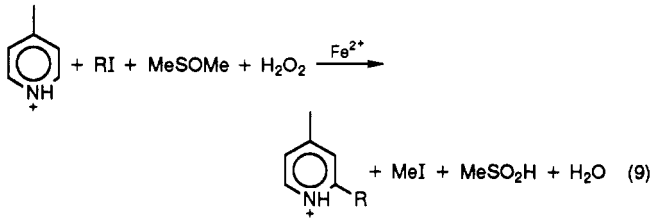
The main limitation with diazonium salts is due to the high rate of addition of nucleophilic alkyl radicals to the diazonium group, which competes with the heterocyclic substitution leading to the free-radical diazo coupling reaction.[7] To overcome this competition, it is necessary to keep the stationary concentration of the diazonium salt low during the reaction.

Thus, a more general, simple, and cheap source of alkyl radicals from alkyl iodides would have been of undoubted interest. In pursuing this aim, we have found of great interest the recent kinetic and thermodynamic results reported by Griller and co-workers[8] for the reaction of the methyl radical with alkyl iodides (eq 8). The rate con-

$$Me^{\bullet} + I\text{–}R \rightleftarrows Me\text{–}I + R^{\bullet} \qquad (8)$$

stants are normally $>10^6\ M^{-1}\ s^{-1}$, higher than most of the other possible competitive reactions of the methyl radical, and the equilibrium constants are strongly affected by the stability of the alkyl radical (Table I). Thus, in principle, it was possible to use a source of methyl radicals to generate alkyl radicals of any kind according to the equilibria of eq 8.

Following this idea we have developed a new, effective general method of substitution of protonated heteroaromatic bases, based on the reaction of alkyl iodides with hydrogen peroxide in DMSO and an Fe(II) salt. The reaction is very fast, and the stoichiometry is shown by eq 9. The results with a variety of heteroaromatic bases and



alkyl iodides are summarized in Table II. The reaction can be successfully applied also to complex molecules, as iodo sugars that lead to C-nucleosides interesting for their biological activity.[9]

A complex, but selective, redox chain is working in reaction 9. The first interaction involves the well-known redox decomposition of H_2O_2 by an Fe(II) salt (eq 10).

$$H_2O_2 + Fe^{2+} \rightarrow HO^{\bullet} + HO^{-} + Fe^{3+} \qquad (10)$$

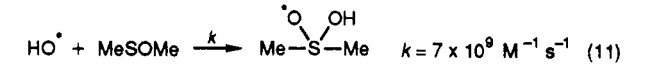
The high reactivity and the low selectivity of the hydroxyl radical with a large variety of organic and inorganic compounds are controlled by using DMSO as solvent. The hydroxyl radical reacts quickly with DMSO[10] (eq 11), and

Table II. Alkylation of Heteroaromatic Bases by Alkyl Iodides, H_2O_2, and DMSO

heteroaromatic base	alkyl iodide	orientatn	convrsn,[a] %	yields,[b] %
lepidine	isopropyl	2	90	88
lepidine	isobutyl	2	93	91
lepidine	cyclohexyl	2	88	92
lepidine	*n*-propyl	2	75	82
lepidine	*n*-butyl	2	73	78
lepidine	*tert*-butyl	2	98	86
quinaldine	isopropyl	4	95	96
quinaldine	cyclohexyl	4	94	97
quinaldine	*n*-butyl	4	72	81
quinoline	isopropyl	2 (25%), 4 (36%), 2,4 (39%)	97	94
quinoline	isobutyl	2 (27%), 4 (38%), 2,4 (35%)	95	92
quinoline	cyclohexyl	2 (23%), 4 (33%), 2,4 (44%)	98	91
quinoline	*n*-propyl	2 (36%), 4 (39%), 2,4 (25%)	78	82
quinoline	*n*-butyl	2 (40%), 4 (43%), 2,4 (17%)	75	77
quinoline	*tert*-butyl	2	96	87
isoquinoline	isopropyl	1	86	88
isoquinoline	cyclohexyl	1	79	84
acridine	isopropyl	9	78	92
acridine	cyclohexyl	9	83	96
4-cyanopyridine	isopropyl	2 (67%), 2,6 (33%)	86	95
4-cyanopyridine	cyclohexyl	2 (62%), 2,6 (38%)	92	93
4-cyanopyridine	*tert*-butyl	2 (58%), 2,6 (42%)	96	94
4-acetylpyridine	isopropyl	2 (68%), 2,6 (32%)	85	95
4-methylpyridine	cyclohexyl	2	35	99
pyrazine	cyclohexyl	2	45	78
quinoxaline	cyclohexyl	2 (68%), 2,3 (32%)	86	81
benzothiazole	cyclohexyl	2	38	87

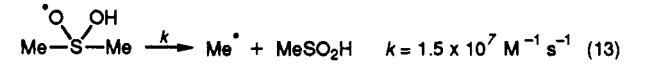
[a] Percentage of converted heteroaromatic base. [b] Yield based on the converted base.

the possible, fast, competitive and unselective reactions with other substrates, including alkyl iodides[11] (eq 12), are minimized by the excess of the solvent. The radical ad-



$$R\text{–}I + {}^{\bullet}OH \xrightarrow{k} R\text{–}\dot{I}\text{–}OH \quad k > 10^9\ M^{-1}\ s^{-1} \qquad (12)$$

duct of DMSO undergoes a fast β-scission[10] (eq 13), acting as a selective source of methyl radicals. The iodine ab-



straction by the methyl radical from the alkyl iodide (eq 8) is fast and successfully competes with other possible reactions of the same radical: it occurs according to the equilibria reported in Table I. However, the fact that the equilibria of eq 8 are shifted to the right is not in itself a sufficient condition to have a high selectivity because the reaction rates of Me and R radicals can be quite different. Thus, when the enthalpic factor governs the reactivity, as in the iodine abstraction (eq 8), the methyl radical is more reactive than primary, secondary, tertiary, and in general α-substituted alkyl radicals; that can counterbalance the unfavorable equilibria. The radical source becomes selective in the heteroaromatic substitution because the polar effects are very important. The addition rates of the alkyl

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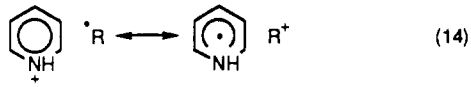
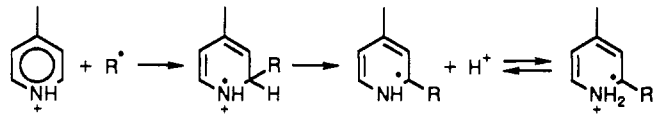
radicals to protonated heteroaromatic bases are strongly affected by the nucleophilic character of the radicals with transition states more similar to charge-transfer complexes than to the intermediate radical adduct[3,12] (eq 14). Thus



(14)

the enthalpic factor governs the equilibria of eq 8 (Table I), whereas the polar factor governs the selectivity of the reaction of the alkyl radical with the heterocyclic ring (eq 14). Since the alkyl radicals without electron-withdrawing groups in the α-position are more nucleophilic than the methyl radical, both factors work in the same direction; that is, the radical R$^\bullet$ is favored in the equilibrium of eq 8 for enthalpic reasons, it is more reactive than the methyl radical with the heterocyclic compounds for polar reasons, and a highly selective substitution has been achieved. With secondary and tertiary alkyl iodides only the radical R$^\bullet$ of the equilibrium 8 is involved in the substitution without significant formation of methyl derivatives. Also with primary alkyl iodides, characterized by less favorable equilibrium (Table I) and polar effects, the substitution substantially takes place with the primary alkyl radical and only traces (<2%) of methyl-substituted derivatives are formed. In this last case, the equilibrium of eq 8 can be further improved by using an excess of alkyl iodide at temperatures higher than 42 °C so that the methyl iodide can be removed during the reaction.

The redox chain is effective, due to the high oxidizability of the pyridinyl type radical intermediate[13] (eq 15 and 16).



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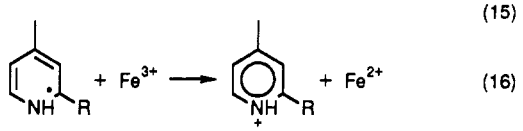

(16)

The amount of hydrogen peroxide utilized is larger than stoichiometric because it is consumed also in side reactions, which do not involve the heteroaromatic base. The reduction of the hydroxyl radical by an Fe(II) salt (eq 17) and the reaction with the alkyl iodide (eq 12) do not appear to be particularly important in view of the high rate constant of eq 11 and of the large excess of DMSO. Likely it is consumed in the reduction of the radical adduct of DMSO (eq 18) and in the oxidation of the sulfinic to the sulfonic acid (eq 19). Also the hydrogen abstraction from sulfinic acid by the methyl radical (eq 20) would appear to be a significant side reaction.[14]

$$HO^\bullet + Fe^{2+} \rightarrow HO^- + Fe^{3+} \quad (17)$$

(18)

$$MeSO_2H + H_2O_2 \rightarrow MeSO_3H + H_2O \quad (19)$$

$$MeSO_2H + Me^\bullet \xrightarrow{k} MeSO_2^\bullet + CH_4 \qquad k \sim 10^6\ M^{-1}\ s^{-1} \quad (20)$$

The Fe(II) salt should not be consumed, due to the catalytic character of the overall process, in which the Fe(II) salt, consumed in eq 10, is regenerated in eq 16. However, a certain amount of Fe(II) salt is consumed, probably more by eq 18 than by eq 17 (both are termination steps of the redox chain). A fundamental question arising from these results concerns the selectivity of the iodine abstraction from alkyl iodides by carbon-centered radicals because the synthetic success is essentially based on this selectivity. The rate sequence of iodine abstraction cannot be ascribed to steric effects, which should lead to an opposite behavior in the series of primary, secondary, and tertiary alkyl iodides, and not even to polar effects, which should increase the reactivity with the nucleophilic character of the abstracting alkyl radical (for example, the rate of chlorine abstraction from CCl_4 by alkyl radicals, particularly sensitive to polar effects, increases from methyl (17 $M^{-1}\ s^{-1}$) to *tert*-butyl ($49.10^3\ M^{-1}\ s^{-1}$),[15] exactly the opposite behavior observed for the iodine abstraction). Clearly this selectivity must be ascribed to the enthalpic factor. Now the question is why a small difference in the energies of the C–I bonds (56.5 kcal/mol for Me–I and 52.1 kcal/mol for *t*-Bu–I),[8] which is obviously reflected in the enthalpy of the iodine abstraction, determines such a high kinetic selectivity (Table I). The fact is striking if we compare the iodine abstraction with the hydrogen abstraction from C–H bonds by alkyl radicals, in which larger differences of the energies of the C–H bonds are reflected in lower kinetic selectivity. Also the absolute rate constants in hydrogen abstraction by the methyl radical from C–H bonds (10^2–$10^3\ M^{-1}\ s^{-1}$)[16] are much lower than those of iodine abstraction ($>10^6\ M^{-1}\ s^{-1}$), even if the hydrogen abstractions are more exothermic. Under complete thermodynamic control, this behavior would be explained by the fact that small variations in bond strengths are completely exploited. However, for processes under kinetic control, thermochemistry will only be partially reflected in the transition states,[17] as shown by the Evans–Polanyi ($E_a = \alpha\Delta H^\circ + C$) and similar relationships.[18] A reasonable explanation for both selectivity and absolute rates is that thermochemistry is reflected in the transition states of the iodine abstraction more than in the transition states of the hydrogen abstraction.

An alternative explanation based on an addition–elimination process,[19] involving an intermediate radical adduct, R–I$^\bullet$–Me, has as only circumstantial evidence the fact that the hydroxyl radical adds rapidly to the alkyl iodides (eq 12). However, the hydroxyl is quite a particular radical, and it can be hazardous to extrapolate its behavior to carbon-centered radicals.

The method of alkylation of heterocyclic compounds by alkyl iodides appears to be particularly useful because of the numerous applications. Practically all the primary, secondary, and tertiary alkyl radicals without electron-withdrawing groups bonded to the radical center can be easily generated according to eq 8 and successfully utilized for the heteroaromatic substitution. The presence of electron-withdrawing groups in the α-position inhibits the addition to the heterocyclic ring; for example, carboxymethyl radical $^\bullet CH_2COOR$, generated from the corresponding iodoacetate, does not react with protonated heteroaromatic bases, but it adds to electron-rich aromatics and olefins. All the heteroaromatic bases with at least one

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(19) Personal suggestion of D. H. R. Barton.

α or γ free position can be successfully utilized. Moreover, the experimental conditions are extremely simple and mild (the reaction is exothermic and completed in a few minutes, starting at room temperature), and the reagents and the catalyst are particularly inexpensive.

Preliminary results[4,20] have shown that other simple sources of methyl radicals ((AcO_2), t-BuOOH, $(t\text{-BuO})_2$, MeCOMe + H_2O_2, MeCOOH + $S_2O_8^{2-}$) are also suitable for the alkylation of heteroaromatic bases by alkyl iodides and for several other selective reactions. Nucleophilic alkyl radicals, generated from alkyl iodides, can in fact also be utilized in the selective alkylation of diazonium salts, pyrylium salts, iminium salts, quinones, electron-poor olefins, biacetyl, and oximes, whereas electrophilic radicals (with electron-withdrawing groups in the α-position; in these cases, the iodine abstraction by the methyl radical is still easier[21] compared with the unsubstituted alkyl iodides) can be utilized for the oxidative alkylation of olefins and aromatics.

Experimental Section

All the reaction products were identified by comparison (GLC, NMR, MS) with authentic samples, previously prepared by a different procedure developed by us[22] (alkylation by silver-catalyzed decarboxylation of carboxylic acid by peroxydisulfate).

General Procedures. (i) Secondary Alkyl Iodides. H_2O_2 (30%; 7.5 mmol) was added dropwise over 2 min at room temperature to a stirred solution of 2.5 mmol of heteroaromatic base, 2.5 mmol of H_2SO_4, and 0.3 mmol of $FeSO_4{\cdot}7H_2O$ in 25 mL of DMSO. A fast reaction took place, and the temperature rose to 40–50 °C. Additional $FeSO_4$ (0.2–0.4 mmol) was added in small portions until the temperature kept on rising (in any case, a moderate excess of $FeSO_4$ has no significant influence on the yields). The solution was stirred for 15 min, diluted with water, made basic with NaOH, and extracted with CH_2Cl_2. The reaction products were analyzed by GLC with the same procedures previously utilized (quinaldine or lepidine as internal standard).[22] The GLC of the low-boiling reaction products, carried out in the case of isopropyl iodine and lepidine, revealed the presence of 1.7 mmol of methyl iodide. No significant product of methylation of the heteroaromatic base was observed.

(ii) Primary Alkyl Iodides. The procedure is similar to i with the difference that more H_2O_2 (13 mmol) and alkyl iodide (13 mmol) were utilized; the temperature spontaneously rose to 70–80 °C, and 1–2% of methylation of the heteroaromatic base was observed as a byproduct.

(iii) Tertiary Alkyl Iodides. Tertiary alkyl iodides react with DMSO at room temperature, giving the corresponding oxyalkylsulfonium iodides. Procedure i has been slightly modified in order that the alkyl iodide is always present in the reaction medium. Thus 7.5 mmol of 30% H_2O_2 and 7.5 mmol of the tertiary alkyl iodide were separately and simultaneously added dropwise over 5 min to a stirred solution of 2.5 mmol of heteroaromatic base, 2.5 mmol of H_2SO_4, and 0.5 mmol of $FeSO_4{\cdot}7H_2O$ in 25 mL of DMSO at room temperature. The solution was stirred for an additional 15 min and worked up as in procedure i. No product of methylation of the heteroaromatic base was observed.

Registry No. DMSO, 67-68-5; i-PrI, 75-30-9; i-BuI, 513-38-2; PrI, 107-08-4; BuI, 542-69-8; t-BuI, 558-17-8; H_2O_2, 7722-84-1; $FeSO_4$, 7720-78-7; lepidine, 491-35-0; quinaldine, 91-63-4; quinoline, 91-22-5; isoquinoline, 119-65-3; acridine, 260-94-6; 4-cyanopyridine, 100-48-1; 4-acetylpyridine, 1122-54-9; 4-methylpyridine, 108-89-4; pyrazine, 290-37-9; quinoxaline, 91-19-0; benzothiazole, 95-16-9; cyclohexyl iodide, 626-62-0; 2-isopropyllepidine, 91879-71-9; 2-isobutyllepidine, 123005-14-1; 2-cyclohexyllepidine, 56947-80-9; 2-propyllepidine, 99878-27-0; 2-butyllepidine, 30980-47-3; 2-*tert*-butyllepidine, 97691-25-3; 4-isopropylquinaldine, 123005-15-2; 4-cyclohexylquinaldine, 37597-46-9; 4-butylquinaldine, 37520-55-1; 2-isopropylquinoline, 17507-24-3; 4-isopropylquinoline, 17507-25-4; 2,4-diisopropylquinoline, 22493-98-7; 2-isobutylquinoline, 93-19-6; 4-isobutylquinoline, 7661-51-0; 2,4-diisobutylquinoline, 123005-16-3; 2-cyclohexylquinoline, 1613-43-0; 4-cyclohexylquinoline, 33357-38-9; 2,4-dicyclohexylquinoline, 123005-17-4; 2-propylquinoline, 1613-32-7; 4-propylquinoline, 20668-44-4; 2,4-dipropylquinoline, 33538-25-9; 2-butylquinoline, 7661-39-4; 4-butylquinoline, 74808-78-9; 2,4-dibutylquinoline, 123005-18-5; 2-*tert*-butylquinoline, 22493-94-3; 1-isopropylisoquinoline, 20922-03-6; 1-cyclohexylisoquinoline, 33538-11-3; 9-isopropylacridine, 33538-07-7; 9-cyclohexylacridine, 35242-12-7; 4-cyano-2-isopropylpyridine, 33538-10-2; 4-cyano-2,6-diisopropylpyridine, 33538-08-8; 4-cyano-2-cyclohexylpyridine, 40114-95-2; 4-cyano-2,6-dicyclohexylpyridine, 83001-42-7; 2-*tert*-butyl-4-cyanopyridine, 33538-09-9; 4-cyano-2,6-di-*tert*-butylpyridine, 37581-48-9; 4-acetyl-2-isopropylpyridine, 123005-19-6; 4-acetyl-2,6-diisopropylpyridine, 123005-20-9; 2-cyclohexyl-4-methylpyridine, 15787-48-1; 2-cyclohexylpyrazine, 53190-45-7; 2-cyclohexylquinoxaline, 40115-00-2; 2,3-dicyclohexylquinoxaline, 123005-21-0; 2-cyclohexylbenzothiazole, 40115-03-5.

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Ethylene Dications Substituted with Electron-Donating Groups

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Direct spectroscopic observations were made of substituted ethylene dications bearing π-stabilizing groups such as an aryl, a hydroxy, or a methoxy group in a strong acid, trifluoromethanesulfonic acid (TFSA). Based on the spectroscopic evidence, we reached the following conclusions. (1) 1,1-Diaryl-2-hydroxy-2-methoxyethylene dications, 1,1-diaryl-2,2-dihydroxyethylene dications, and 1,1,2-triaryl-2-hydroxyethylene dications are *discrete* intermediates in the electrocyclization reaction to yield the fluorene and phenanthrol in TFSA. (2) Several dications bearing methoxy substituents on the aromatic rings are formed in trifluoroacetic acid (TFA). (3) NMR spectra suggested the nonplanar structures of O-protonated α-carbonyl diarylmethyl dications at the central C–C bond. (4) 1,2-Diaryl-1,2-dihydroxyethylene dications and 1-aryl-1,2,2-trihydroxyethylene dications are very stable. Ab initio MO calculations showed that 1,2-dihydroxyethylene dications are more stable than 1,1-dihydroxyethylene dications.

The generation and detection of small doubly charged cations in the gas phase are well-established owing to modern experimental techniques such as charge stripping (CS) mass spectrometry.[1] The properties of such ions can

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