$S_{RN}1$ Mechanism in Heteroaromatic Nucleophilic Substitution. Reactions of 2-Chloroquinoxaline and 4-Chloroquinazolines with Ketone Enolates[1a,b]

David R. Carver,[1c] James S. Hubbard, and James F. Wolfe*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

Received July 13, 1981

Reaction of 2-chloroquinoxaline (**1**) with *O*-potassio-3,3-dimethyl-2-butanone (**2**) in liquid NH_3 affords 1-(quinoxalin-2-yl)-3,3-dimethyl-2-butanone (**3**) via a thermal $S_{RN}1$ mechanism and 2-*tert*-butylfuro[2,3-*b*]quinoxaline (**4**) via a competing ionic, addition–substitution process. When the $S_{RN}1$ component of this dual mechanistic scheme is inhibited by di-*tert*-butyl nitroxide, only furoquinoxaline **4** is produced. *O*-Potassio-2,4-dimethyl-3-pentanone (**5**) reacts in a similar fashion with **1** to give $S_{RN}1$ products, 2-(quinoxalin-2-yl)-2,4-dimethyl-3-pentanone (**6**) and 2-isopropylquinoxaline (**8**), along with quinoxalino[3,4-*b*]-2,2,5,5-tetramethylcyclopentanone (**7**), which results from addition–substitution. Reaction of **1** with *O*-potassio-3-methyl-2,4-pentanedione (**9**) affords low yields of 2-(quinoxalin-2-yl)butanone (**10**) by a sluggish $S_{RN}1$ pathway. Reactions of 4-chloroquinazoline (**11a**) and 4-chloro-2-phenylquinazoline (**11b**) with enolate **2** provide excellent yields of the respective 4-quinazolinyl ketones **12a,b** via an apparent S_NAr mechanism.

Although numerous reports of nucleophilic substitution involving 2-chloroquinoxaline[2] and 4-chloroquinazolines[3] have been published, there is currently no evidence that these heteroaromatic systems have the capability of undergoing substitution via the $S_{RN}1$ mechanism.[4] Recent findings in our laboratories[5-7] and elsewhere[8] have demonstrated that this mechanism obtains in reactions of ketone enolates and certain other nucleophiles with 2-chloroquinoline,[6] 2-, 3-, and 4-halopyridines,[5] 2-, 4-, and 5-halopyridimidines,[7,8] 3-chloropyridazines,[7] and 2-chloropyrazine.[7] The proposed initiation (eq 1) and

Scheme I

$$\text{Het-X} + \text{N}^- \rightarrow [\text{Het-X}]^{-}\cdot + \text{N}\cdot \quad (1)$$

$$[\text{Het-X}]^{-}\cdot \rightarrow \text{Het}\cdot + \text{X}^- \quad (2)$$

$$\text{Het}\cdot + \text{N}^- \rightarrow [\text{Het-N}]^{-}\cdot \quad (3)$$

$$[\text{Het-N}]^{-}\cdot + \text{Het-X} \rightarrow \text{Het-N} + [\text{Het-X}]^{-}\cdot \quad (4)$$

propagating steps (eq 2–4) of this radical-chain process are given in Scheme I, where Het-X is an appropriate heteroaromatic substrate and N^- represents a generalized nucleophile capable of initiating the chain process by electron transfer. Ketone enolates have proved to be excellent nucleophiles for testing the $S_{RN}1$ reactivity of halogenated heteroaromatics. In fact, the relative reactivity of certain halogenated, π-deficient heteroaromatics with potassium ketone enolates in liquid NH_3 is related to the reduction potential of the substrate as reflected in the polarographic measurement of the reduction potential ($E_{1/2}$) of the parent heterocycle.[7] In order to further test this relationship as a predictive tool and to determine if the $S_{RN}1$ pathway is

Table I. Reactions of 1 and 11a,b with Ketone Enolates

expt	substrate	enolate	conditions[a,b]	product	yield, %
1	11	2	dark	3	70
				4	15
2	1	2	dark[c]	3	70
				4	9
3	1	2	dark[d]	3	70
				4	11
4	1	2	dark, inhibited[c,e]	3	38
				4	18
5	1	2	dark, inhibited[d,e]	3	26
				4	27
6	1	2	dark, inhibited[f]	3	nil
				4	43
					(58)[g]
7	1	2	dark[h]	3	*i*
				4	nil
8	1	5	dark	6	31
				7	28
				8	17
9	1	5	dark, inhibited[f]	7	*j*
10	1	5	dark[h]	6	43
11	1	9	dark	1	47
				10	15
12	1	9	*hν*	1	45
				10	17
13	1	9	dark, inhibited[k]	1	51
				10	3
14	11a	2	dark	12a	95
15	11a	2	dark, inhibited[f]	12a	95
16	11b	2	dark	12b	93
17	11b	2	dark, inhibited[f]	12b	97

[a] Reaction time was 15 min unless designated otherwise. [b] Ratio of enolate to substrate was 3.75:1 unless designated otherwise. [c] Reaction time 3 min. [d] Reaction time 1 min. [e] 20 mol % of DTBN was used as an inhibitor. [f] 100 mol % of DTBN was used as inhibitor. [g] Crude reaction mixture treated with NiO_2 in refluxing benzene. [h] Ratio of enolate to substrate was 1:1. [i] Ketone **3** was the only product detected by GC, but the yield was not determined. [j] Cyclopentanone **7** was the only product detected by GC, but the yield was not determined. [k] 15 mol % of DTBN was used as an inhibitor.

(1) (a) This research was generously supported by the National Science Foundation (Grants CHE 74-20520 and CHE-8022538). (b) Presented in part at the Second Chemical Congress of the North American Continent, Las Vegas, NV, Aug 1980; Abstract ORGN 71. (c) Abstracted from the Ph.D. dissertation of D.R.C., Virginia Polytechnic Institute and State University, Aug 1979.

(2) (a) Cheeseman, G. W. H.; Werstink, E. S. G. *Adv. Heterocycl. Chem.* **1978**, *22*, 367. (b) Lont, P. J.; van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 85. (c) Anderson, R. K.; Cheeseman, G. W. H. *J. Chem. Soc., Perkin Trans. 1* **1974**, 129. (d) Carter, S. D.; Cheeseman, G. W. H. *Tetrahedron* **1978**, *34*, 981. (e) Iijima, C.; Hayashi, E. *Yakugaku Zasshi* **1972**, *92*, 729. Leaving groups other than halides were employed in this study. (f) Hayashi, E.; Miuagishima, T. *Ibid.* **1968**, *88*, 303. (g) Hayashi, E.; Miuagishima, T. *Ibid.* **1967**, *87*, 826.

(3) (a) Armarego, W. L. F. *Adv. Heterocycl. Chem.* **1979**, *24*, 1. (b) Armarego, W. L. F. *Ibid.* **1963**, *1*, 253. (c) Higashino, T.; Tamura, Y.; Nakayama, K.; Hayashi, E. *Chem. Pharm. Bull.* **1970**, *18*, 1262. (d) Scherrer, R. A.; Beatty, H. R. *J. Org. Chem.* **1972**, *37*, 1681.

(4) (a) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. (b) Wolfe, J. F.; Carver, D. R. *Org. Prep. Proc. Int.* **1978**, *10*, 224.

(5) Komin, A. P.; Wolfe, J. F. *J. Org. Chem.* **1977**, *42*, 2481.

(6) (a) Wolfe, J. F.; Green, J. C.; Hudlicky, T. *J. Org. Chem.* **1972**, *37*, 3199. (b) Hay, J. V.; Hudlicky, T.; Wolfe, J. F. *J. Am. Chem. Soc.* **1975**, *97*, 374. (c) Hay, J. F.; Wolfe, J. F. *Ibid.* **1975**, *97*, 3702.

(7) Carver, D. R.; Komin, A. P.; Hubbard, J. S.; Wolfe, J. F. *J. Org. Chem.* **1981**, *46*, 294.

(8) Oostveen, E. A.; van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 441.

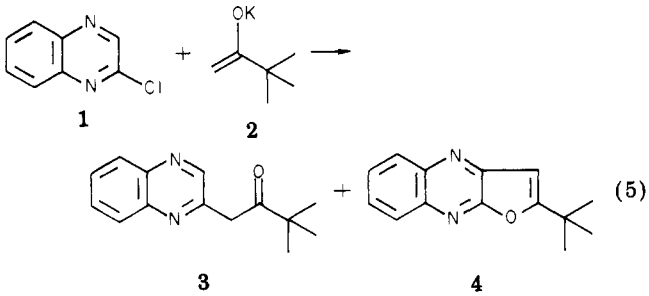
0022-3263/82/1947-1036$01.25/0

viable with substituted quinoxalines and quinazolines, we have investigated reactions of 2-chloroquinoxaline (1) and 4-chloroquinazolines (11a,b) with several enolate nucleophiles.

Results

With 2-Chloroquinoxaline (1). Reactions of 1 with *O*-potassio-3,3-dimethyl-2-butanone (2), *O*-potassio-2,4-dimethyl-3-pentanone (5), and *O*-potassio-3-methyl-2,4-pentanedione (9) are summarized in Table I and eq 5–7.

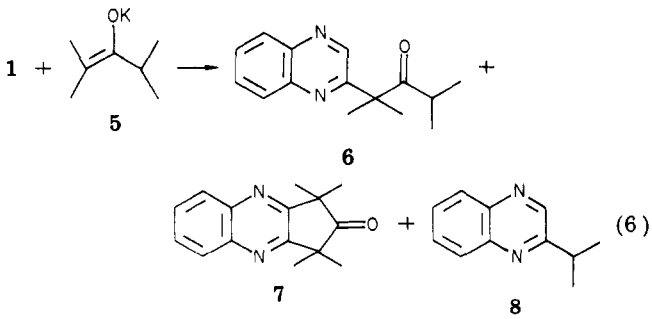
Unlike $S_{RN}1$ reactions of halogenated quinolines, pyridines, and pyrimidines with enolates 2 and 5, which require photostimulation for successful displacement of halide, exposure of substrate 1 to 3.75 equiv of enolate 2 in liquid NH_3 resulted in complete consumption of 1 after 15 min in the dark. Two products, the expected ketone 3 (70%) and furoquinoxaline 4 (15%), were formed (eq 5). Similar



(5)

results were obtained with reaction periods of 3 and 1 min or when the reaction was irradiated with near-ultraviolet light. When 20 mol % of the radical scavenger, di-*tert*-butyl nitroxide (DTBN),[9] was added to the enolate solution prior to introduction of substrate 1, the yield of 3 decreased to 38% in a 3-min dark reaction and to 26% after 1 min. Yields of furoquinoxaline 4 in these two reactions were 18% and 27%, respectively (expts 4 and 5). Formation of ketone 3 was completely inhibited by 100 mol % of DTBN in a 15-min dark reaction, while the yield of 4 increased to 43% (Expt 6). In a similar inhibited reaction, the yield of 4 was raised to 58% by treatment of the crude product mixture with nickel peroxide.[10] Ketone 3 was eliminated from consideration as the progenitor of 4 by the finding that 3 was recovered unchanged after exposure to KNH_2 in liquid NH_3 for 15 min.

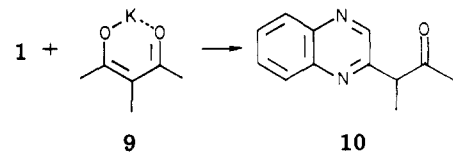
Reaction of 1 with 3.75 equiv of enolate 5 in the dark gave ketone 6 (31%) along with quinoxalino[*b*]cyclopentanone 7 (28%) and 17% of 2-isopropylquinoxaline (8) (eq 6). Irradiation did not accelerate the reaction or



(6)

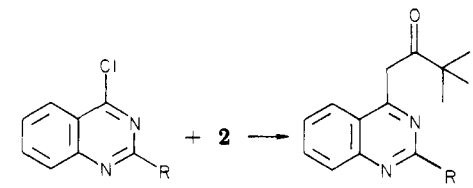
change this distribution of products appreciably. Inhibition of the dark reaction with 100 mol % of DTBN resulted in formation of 7 but not 6 or 8 (expt 9). When 1 was allowed to react with 1 equiv of enolate 5 in the dark, ketone 6 was produced in 43% yield; however, neither 7 nor 8 could be detected (expt 10). The remainder of the reaction product was a colorless oil that darkened rapidly upon reaching room temperature and did not give any characterizable products. Ketone 6 was not converted to 7 on treatment with KNH_2 in liquid NH_3.

Reaction of 1 with enolate 9 in the dark gave 3-(quinoxalin-2-yl)-2-butanone (10) in 15% yield along with recovered 1 (eq 7). Addition of 15 mol % of DTBN reduced the yield of 10 to 3%. Irradiation of the uninhibited reaction had no effect on the yield of 10 (expts 11–13).



(7)

With 4-Chloroquinazolines 11a,b. Results obtained from reactions of 4-chloroquinazoline (11a) and 4-chloro-2-phenylquinazoline (11b) with pinacolone enolate (2) are presented in Table I and eq 8. Both 11a and 11b afforded



(8)

excellent yields of ketones 12a and 12b, respectively, after 15 min in the dark. Neither of these reactions was inhibited by 100 mol % of DTBN (expts 14–17).

Discussion

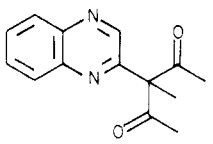
In an earlier study[7] we reported that 2-chloropyrazine was the most reactive of five types of halogenated heteroaromatics, undergoing facile $S_{RN}1$ reactions with ketone enolates in liquid NH_3 without the need for photostimulation. If, as it appeared from those results, the reduction potentials of heteroaromatics can be used to predict the relative $S_{RN}1$ reactivity of such substrates, then comparison of the reduction potential of quinoxaline ($E_{1/2}$ = −1.09 V)[11] with that of pyrazine ($E_{1/2}$ = −1.57 V)[11] would suggest that 1 should be even more reactive than 2-chloropyrazine. The inhibitory influence of DTBN on the reactions of 1 with enolates 2 and 5 leaves little doubt that the $S_{RN}1$ mechanism provides the major route to ketones 3 and 6. The observation that 100 mol % of DTBN was necessary to completely suppress formation of 3, while similar reactions of 2-chloropyrazine could by inhibited by 10–15 mol % of DTBN,[7] can be attributed to an increased rate of initiation with 1 relative to the latter substrate. The ease of electron transfer to 1 also provides a possible explanation for what appears to be the first example of an aromatic $S_{RN}1$ reaction involving a β-dicarbonyl enolate (9). Less easily reduced aromatic substrates have shown a definite lack of reactivity with such nucleophiles.[6c,12] Apparently enolate 9 undergoes a sluggish $S_{RN}1$ reaction with 1 to afford 13, which then under the reaction conditions suffers cleavage to form 10. It is unlikely that 10 arises through cleavage

(9) (a) Hoffman, A. K.; Feldman, A. M.; Geblum, E.; Hodgson, W. G. *J. Am. Chem. Soc.* **1964**, *86*, 639. (b) Nelson, S. F.; Bartlett, P. D. *Ibid.* **1966**, *88*, 143.

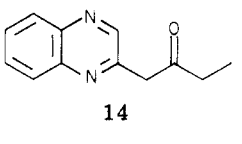
(10) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497.

(11) Wiberg, K. B.; Lewis, T. P. *J. Am. Chem. Soc.* **1970**, *92*, 7154.

(12) (a) Bunnett, J. F.; Sundberg, J. E. *J. Org. Chem.* **1976**, *41*, 1702. (b) Rossi, R. A.; Bunnett, J. F. *Ibid.* **1973**, *38*, 3020.



13



14

of protonated **9** to form a mixture of 2-butanone enolates followed by $S_{RN}1$ reaction of these salts with **1**. If this were the case, ketone **14** should also have been present in the reaction mixture;[5,12b] however, this product could not be detected. The rather poor material balance in these reactions may result from competing ionic addition of enolate **9** at the 3-position of **1**, followed by decomposition of the resulting dihydro adduct during work up (vide infra).

Failure of DTBN to inhibit reactions of quinazolines **11a,b** with enolate **2** was somewhat surprising, since the reduction potential of quinazoline ($E_{1/2}$ = −1.22 V)[11] would suggest that **11a,b** should undergo $S_{RN}1$ reactions with a degree of facility comparable to or greater than that for 2-chloropyrazine. In previous cases of DTBN inhibition of heteroaromatic $S_{RN}1$ reactions we have tacitly assumed that this reagent functions by radical trapping. However, it is conceivable that inhibition may result from either or both of the redox reactions shown in eq 9 and 10. The

$$[\text{Het-X}]^{-}\cdot + R_2NO\cdot \rightarrow \text{Het-X} + R_2NO^{-} \quad (9)$$

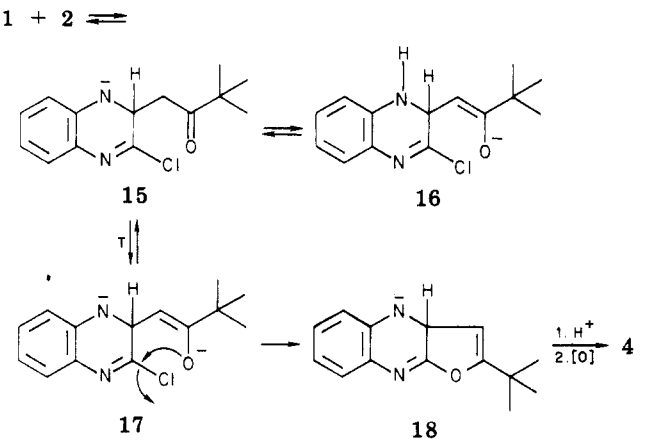
$$[\text{Het-N}]^{-}\cdot + R_2NO\cdot \rightarrow \text{Het-N} + R_2NO^{-} \quad (10)$$

present studies involving **1** and **11a,b** provide strong evidence that DTBN does not exert its inhibitory action in this manner. For example, since the reduction potential of quinazoline is more negative than that of quinoxaline, the radical anions shown in eq 9 and 10 with Het = 4-quinazolinyl should be more effective reducing agents toward DTBN than the corresponding radical anions having Het = 2-quinoxalinyl. Therefore, inhibition by electron transfer should be more pronounced with **11a,b** than with **1**. In fact, just the opposite trend is observed.

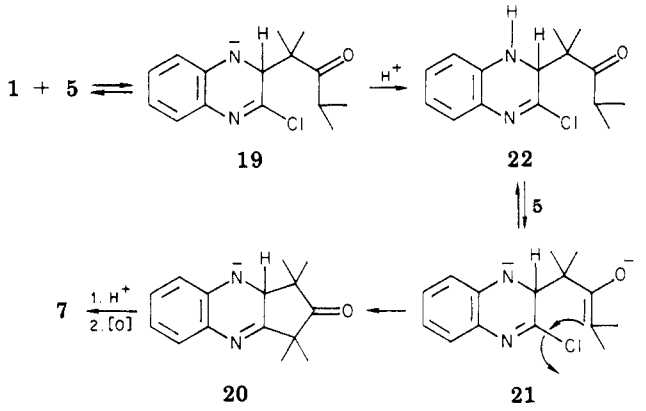
It appears that the reactions of enolate **2** with **11a,b** take place by an ionic addition–elimination (S_NAR) mechanism similar to that observed with **11a** and other nucleophiles.[3,13] A comparative study of S_NAR reactions of **1** and **11a** with nitrogen nucleophiles has revealed tht **11a** is ca. 5×10^4 more reactive toward ionic substitution than **1**.[13] The higher S_NAR reactivity of **11a** can be ascribed to the 1,3-arrangement of heteroatoms, which allows stabilization of an intermediate σ complex by delocalization of negative charge directly onto either of two nitrogen atoms, while the 1,4-arrangement of heteroatoms in the σ complex derived from **1** has only one nitrogen atom positioned for effective resonance delocalization of negative charge.[13] As a result, the high S_NAR reactivity of **11a,b** allows ionic substitution to proceed at a rate which comfortably exceeds that of the $S_{RN}1$ process. This represents the first instance of successful competition of ionic substitution with radical-chain substitution in a heteroaromatic system, although we have previously observed competitive nucleophilic additions in reactions of enolates with 2-chloropyrimidine and 3-chloro-6-methoxypyridazine.[7]

It is interesting to note that when the $S_{RN}1$ reaction of **1** with enolate **2** was inhibited by an equimolar amount (based on **1**) of DTBN, the only product obtained was furoquinoxaline **4** (expt 6). It is possible to rationalize production of **4** as resulting from ionic displacement of chloride to form **3**, followed by lateral enolization, addition of the resulting carbanion to the 3-position of **3**, and

Scheme II



Scheme III



subsequent oxidation of the resulting 3,4-dihydro derivative during workup. However, this route is discredited by failure of **3** to give **4** upon treatment with KNH_2. Therefore, the series of reactions shown in Scheme II is proposed to account for production of **4**. Addition of enolate **2** to C_3 of **1** to form intermediate **15** is analogous to reactions of oxygen[2c] and nitrogen[2d] nucleophiles with **1**. Dianion **17**, rather than monoanion **16**, is probably the intermediate which undergoes ring closure, since **4** was not formed when **1** was treated with 1 equiv of enolate **2**. This experiment gave only ketone **3**. Thus, excess **2** presumably effects lateral ionization of **15** to give **17**. The enhanced yield of **4** obtained on treatment of the crude, inhibited reaction mixture with nickel peroxide presumably results from oxidation of protonated **18**. Formation of cyclopentanone **7** from **1** and enolate **5** is assumed to occur as shown in Scheme III. Again, dianion **20** appears to be necessary for cyclization, as shown by the observation that a 1:1 molar ratio of **1** to enolate **5** gives only ketone **6**. Attempts to trap intermediate **19** as the dihydroquinoxaline **22** or the fully aromatic analogue of **22** by shortening the reaction period and then quenching with acid or acid and nickel peroxide produced only **7** and intractable tar.

Finally, it should be emphasized that when the $S_{RN}1$ mode of substitution with **1** and enolates **2** and **5** is inhibited, the only isolated products are those arising from ionic addition at the 3-position of **1**. Thus, the $S_{RN}1$ mechanism provides the *only* route to ipso substitution with **1** and these nucleophiles. Similar requirements apply to 2-chloropyrimidine,[7] which undergoes mainly ionic addition when the $S_{RN}1$ pathway is prevented. These observations have important synthetic implications, for now that the $S_{RN}1$ mechanism is recognized as operational with

(13) Chapman, N. B.; Russel-Hill, D. Q. *J. Chem. Soc.* **1956**, 1563.

1, the mode of reaction, i.e., radical chain substitution or ionic addition, can be controlled by appropriate choice of reaction conditions.

Experimental Section

General Methods. All reactions were conducted under an atmosphere of nitrogen; quenching and processing of reaction mixtures were performed under atmospheric conditions unless otherwise noted. All photostimulated reactions were conducted in a Rayonet RPR-240 photochemical reactor equipped with four 12.5-W bulbs emitting maximally at 350 nm.[4b] Gas chromatographic (GC) analyses and separations were accomplished on a Varian Associates 90-P or 1200 instrument using columns of 2% Carbowax 20M on Chromosorb supports at 153–235 °C. Determinations of GC yields were accomplished with benzoate and phthalate esters as internal standards. ^{1}H NMR spectra were determined on a JEOL JMN-PS-100 or Varian EM-390 spectrometer at 100 or 90 MHz, respectively, with tetramethylsilane as an internal reference. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Infrared spectra were produced on a Beckman IR-20A-X spectrophotometer. Elemental microanalyses were performed by Galbraith Laboratories. Melting points were observed with a Thomas-Hoover apparatus and are uncorrected.

All solvents were of commercial quality except for those purified as noted. Liquid ammonia was commercial, anhydrous grade and was used without further purification.

Chromatographic separations were performed on silica gel. Preparative TLC plates were made from EM Merck PF-254 Type 60 silica gel. Analytical TLC separations were carried out on Eastman 13181 silica gel plates with a fluorescent indicator (No. 6060) with polymer backing. Other TLC separations were carried out on Merck HF-254 (Type 60) silica gel (Catalog No. 7739) mechanically spread on glass microscope slides. Column chromatography was accomplished by using a low-pressure column and reservoir under 10–25 lb of nitrogen pressure with Woelm 126 silica gel (<0.063 mm). For a typical reaction mixture a column packing of 2.2 × 20 cm was used, with fractions taken every 30 mL. The solvent mixture was adjusted so that the desired component had an R_f of 0.3 on analytical TLC plates. Column fractions were assayed by TLC.

Reactions was carried out by one of the following procedures. Exceptions to these general methods are noted for individual reactions.

Procedure A. Photostimulated Reactions. For the photostimulated reactions, 150–175 mL of anhydrous ammonia was introduced directly into an appropriate reaction vessel.[1c,4b] Under positive nitrogen pressure, 11.25 mmol of potassium metal was dropped into the ammonia. Addition of a few milligrams of ferric nitrate hydrate catalyzed amide formation. After amide formation was complete, an anhydrous ethereal solution of the ketone (11.25 mmol) was added dropwise. After mixing of the solution was complete (magnetic stirring with a bare metal magnet), the lamps were turned on. Addition of the substrate (3.00 mmol) in 10 mL of ether was accomplished in 1 min. After irradiation, the reaction mixture was quenched by pouring the liquid ammonia solution directly onto solid ammonium chloride (3.5 g) contained in a 2-L beaker. The reaction vessel was washed twice with 100 mL of ether, and the washes were combined with the ammonia solution. Evaporation of the ammonia was accomplished on a warm hot plate wet with ethanol (to help transfer heat and prevent ice formation). Brief boiling of the remaining ether removed residual ammonia. Filtration of the ethereal solution from the solid salts was then performed. Crushing the salts with a spatula and four triturations with 50 mL each of ether gave good extraction in most cases. Drying ($MgSO_4$) and evaporation of the ether afforded crude products.

Procedure B. Dark Reactions. To a 250-mL, three-necked, 24/40 ₮ flask fitted with two nitrogen bubblers and an addtion funnel was added 150–175 mL of anhydrous liquid ammonia run in directly from the tank via a Tygon tube. Potassium amide (11.25 mmol) was generated as described in procedure A, followed by addition of the ketone (11.25 mmol) in 7–10 mL of ether. Before the substrate (3.00 mmol in 10 mL of ether) was added, the flask was wrapped with several layers of black cloth, and the room lights were extinguished. Subsequent workup was identical with that described in procedure A. The following experiments detail isolation of specific reaction products. Inhibited reactions were conducted by adding an ethereal solution of the appropriate heteroaromatic and DTBN to the enolate solution.

Dark Reaction of 1 with Enolate 2. Procedure B gave a crude product mixture which was analyzed by GC (225 °C). 1-(Quinoxalin-2-yl)-3,3-dimethyl-2-butanone (**3**) was isolated by preparative GC as light yellow needles: mp 88–90 °C (lit.[2e] mp 93.5 °C): IR (neat) 3060 (w, CH), 1705 cm^{-1} (m, C=O); ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 9 H, *t*-Bu), 4.16 (s, 1.3 H, CH_2), 5.55 (s, 0.66 H, enol CH), 7.23, 7.56, 7.89 (m, 4 H, aromatic ring H), 8.12 (s, 0.66 H, enol quinoxaline H_3), 8.59 (s, 0.33 H, keto quinoxaline H_3), 14.0 (br s, 0.66 H, enol OH).

2-*tert*-Butylfuro[2,3-*b*]quinoxaline (**4**) was isolated by preparative GC and recrystallized from hexane to afford pale yellow needles: mp 95 °C (lit.[2e] mp 98 °C); IR (neat) 3080 (w, CH), 3060 (w, CH), 1621 cm^{-1} (w, C=O); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H, *t*-Bu), 6.63 (s, 1 H, furan H_3), 7.61 (m, 2 H, aromatic ring H_6 and H_7), 8.02 (m, 2 H, aromatic ring H_5 and H_8). Reactions of **3** and 1 min duration were carried out in a similar manner.

Inhibited Dark Reactions of 1 with Enolate 2. Procedure B was modified by adding 90 mg (20 mol %) of DTBN to the ethereal solution of 1 before adding it to the enolate. Also, the reaction time was shortened to 3 min. GC analysis was conducted at 225 °C.

Increasing the reaction period to 15 min and using 100 mol % (3.00 mmol, 432 mg) of DTBN resulted in a 43% yield of **4**. No trace of substitution product **3** could be found by GC analysis. Repeating the reaction and stripping the crude product of volatile material produced a red gum. This was dissolved in 150 mL of benzene and treated with 3.0 g of NiO_2 at reflux for 2.5 h.[10] Kugelrohr distillation of the crude product afforded 58% of furoquinoxaline **4** [130 °C (0.15 torr)]. Recrystallization from hexene gave pale yellow needles, mp 96 °C.

Dark Reaction of 1 with Enolate 5. Procedure B yielded a blood red solution at the end of the reaction period that quenched to a light yellow solution. GC analysis and collection at 192 °C gave three major components with retention times of 7.5, 21.6, and 28.6 min, respectively. The first peak was identified as 2-isopropylquinoxaline (**8**):[14] IR (neat) 3060 (w, CH), 1495 (m), 1463 (m), 1090 (m), 765 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.43 (d, 7 Hz, 6 H, isopropyl), 3.30 (septet, 7 Hz, 1 H, isopropyl), 7.64 (m, 2 H, quinoxaline H_6 and H_7), 7.96 (m, 2 H, quinoxaline H_5 and H_8), 8.71 (s, H, quinoxaline H_3). Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.26. Found: C, 76.57; H, 7.18; N, 16.45.

The second compound (a white solid) to be collected was identified as quinoxalino[3,4-*b*]-2,2,5,5-tetramethylcyclopentanone (**7**): mp 146–147 °C; IR (neat) 3050 (w, CH), 1640 cm^{-1} (s, C=O); ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 12 H, $(CH_3)_4$), 7.68 (m, 2 H, quinoxaline H_6 and H_7), 8.03 (m, 2 H, quinoxaline H_5 and H_8). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.96; H, 6.91; N, 11.48.

The third eluted compound was obtained as an oil and identified as 2-(quinoxalin-2-yl)-2,4-dimethyl-3-pentanone (**6**): IR (neat) 3060 (w, CH), 1705 cm^{-1} (s, C=O); ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 7 Hz, 6 H, isopropyl), 1.63 (s, 6 H, $(CH_3)_2$), 2.70 (septet, J = 7 Hz, 1 H, isopropyl), 7.64 (m, 2 H, quinoxaline H_6 and H_7), 7.93 (, 2 H, quinoxaline H_5 and H_8), 8.68 (s, 1 H, quinoxaline H_3). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.48; H, 7.52; N, 11.45.

Reducing the equivalency of enolate **5** to 1 from 3.75:1 to 1:1 gave a 43% yield of substitution product **6**. No traces of **8** or **7** were detected.

Reaction of *O*-Potassio-3-methyl-2,4-pentanedione (9) with 1. Procedure B gave a dark red solution which by GC analysis and collection at 198 °C gave acetamide (70–162 mg), recovered starting material 1 (47%), and 15% of 3-(quinoxalin-2-yl)-2-butanone (**10**): mp 60–64 °C; IR (neat) 3050 (w, CH), 1685 cm^{-1} (s, C=O); ^{1}H NMR ($CDCl_3$) δ 1.64 (d, J = 7 Hz, 3 H, α-CH_3), 2.22 (s, 3 H, CH_3), 4.20 (q, J = 7 Hz, 1 H, CH), 7.68 (m, 2 H, quinoxaline H_6 and H_7), 7.97 (m, 2 H, quinoxaline H_5 and H_8) 8.72 (s, 1 H, quinoxaline H_3). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04;

(14) Conrad, M.; Hock, K. *Ber.* **1899**, *32*, 1209.

N, 13.99. Found: C, 71.72; H, 6.02; N, 13.74.

Photostimulated reaction of enolate **9** with **1** was conducted according to procedure A to give, by GC analysis, a 45% recovery of starting material **1** and a 17% yield of ketone **10**.

Inhibited dark reaction of enolate **9** with **1** by procedure B, modified by adding 15 mol % (0.065 g) of DTBN to the 2-chloroquinoxaline, gave by GC analysis a 51% recovery of **1** and <3% of **10**.

Treatment of 3 and 6 with Potassium Amide. By use of 17.6 mg of potassium and a small amount of ferric nitrate, 0.45 mmol of KNH_2 in 50 mL of NH_3 was prepared. Quinoxalinyl ketone **3** (102 mg, 0.45 mmol) in ether (10 mL) was added to the amide to give a bright orange solution. Stirring for 15 min, quenching, and extraction as described in procedure A gave an 85% recovery of **3** and no detectable trace of **4**. Similar treatment of ketone **6** gave only recovered **6**.

Dark Reaction of Enolate 2 with 4-Chloroquinazoline (11a). 4-Chloroquinazoline (**11a**) was synthesized by the method of Armarego.[15] Procedure B gave 95% of 1-(quinazolin-4-yl)-3,3-dimethyl-2-butanone (**12a**) as yellow crystals after recrystallization from hexane–toluene: mp 118–119 °C; IR ($CDCl_3$) 3060 (w, CH), 1625 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 1.27 (s, 9 H, *t*-Bu), 6.20 (s, 1 H, enol CH), 7.57 (m, 5 H, aromatic), 14.7 (br s, 1 H, enol OH). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.78; H, 7.13; N, 12.33.

Procedure B was modified by adding 0.45 g (100 mol %) of DTBN to **11a** before addition to the enolate. This resulted in yellow crystals of **12a** (95%) isolated by recrystallization as in the previous experiment.

Dark Reaction of Enolate 2 with 4-Chloro-2-phenylquinazoline (11b). Procedure B gave a yellow solid, which upon recrystallization from toluene–hexane afforded a 93% yield of 1-(2-phenylquinazolin-4-yl)-3,3-dimethyl-2-propanone (**12b**): mp 153–157 °C; IR ($CHCl_3$) 3400 (br, enol), 3080, 3020 (CH), 1680 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 1.30 (s, 9 H, *t*-Bu), 6.22 (s, 1 H, enol CH), 7.43 (m, 7 H, aromatic), 8.17 (m, 2 H, aromatic), 15.57 (br s, 1 H, enol OH). Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.84; H, 6.68; N, 9.17.

Procedure B was repeated, but 100 mol % (0.45 g) of DTBN was added to the ethereal solution of **11b** before addition to the enolate. This afforded light yellow crystals, which were recrystallized from toluene–hexane to give 97% of **12b**.

Registry No. **1**, 1448-87-9; **2**, 51742-96-2; **3**, 37053-07-9; **4**, 37053-02-4; **5**, 51689-86-2; **6**, 80360-33-4; **7**, 80360-34-5; **8**, 80360-35-6; **9**, 72610-66-3; **10**, 80360-36-7; **11a**, 5190-68-1; **11b**, 6484-25-9; **12a**, 80360-37-8; **12b**, 80360-38-9; potassium amide, 17242-52-3.

(15) Armarego, W. L. F. *J. Appl. Chem.* **1961**, *11*, 70.

Solvolytic and Stable Ion Studies of 1,1′-Diadamantylmethyl Cations[1a]

George A. Olah,*[1b] G. K. Surya Prakash,[1b] Gao Liang, Paul v. R. Schleyer,*[1c] and W. David Graham[1d]

Hydrocarbon Research Institute, University of Southern California, Los Angeles, California 90007, and the Institut für Organische Chemie der Friedrich-Alexander-Universität Erlangen-Nürnberg, 8520, Erlangen, Federal Republic of Germany

Received October 22, 1981

A series of 1,1′-diadamantylmethyl carbocation systems were studied under solvolytic and stable ion conditions. At low temperatures in superacid solutions, tertiary 1,1′-diadamantylmethyl derivatives (except *tert*-butyl-1,1′-diadamantylmethyl) gave the corresponding static carbenium ions. From the ^1H and ^{13}C NMR spectroscopic data, the ion from secondary 1,1′-diadamantylmethyl precursors is assigned the rearranged 4-(1-adamantyl)-3-homoadamantyl cation structure. However, this species is not static but undergoes fast Wagner–Meerwein shifts even at very low temperatures (≈−140 °C) to give a set of six equivalent carbenium ions. There is no evidence for bridging. In solvolysis, the relatively low α-CH_3/H rate ratios of the 1,1′-diadamantylmethyl and di-*tert*-butylmethyl systems strongly suggest that both secondary substrates undergo anchimerically assisted ionization of modest magnitude.

Introduction

While primary systems typically solvolyze by nucleophilic displacement (S_N2) and tertiary systems by ionization to carbocations (S_N1),[2] the solvolysis mechanism of secondary systems was not fully understood mechanistically until the importance of nucleophilic solvent assistance was recognized.[3] The overall solvolysis rate constant (k_t) can be treated as the sum of the solvent assisted rate constant (k_s) and neighboring group or anchimeric assisted rate constant (k_Δ).[3] The limit as k_Δ and k_s tend toward zero is k_c (the rate constant for an anchimerically and nucleophilically unassisted process).

Earlier work established the 2-adamantyl system (**1**, R = H) as a standard for limiting secondary solvolysis, i.e., with k_s/k_c and k_Δ/k_c ratios near unity.[3] Since solvent assistance (k_s) is ruled out by severe hindrance to backside attack, di-*tert*-butylmethyl systems (**2**) were also examined as possible acyclic models for limiting (k_c) solvolysis.[4] However, the exclusive formation of rearranged products from the secondary substrate (**2a**) and the low α-methyl/hydrogen rate ratio, **2b**/**2a** = $10^{5.3}$ (vs. $10^{7.5}$ for 2-adamantyl),[3b,5] indicated that there might be a k_Δ contribution preferentially accelerating the rate of **2a** over **2b**.[4]

Would the 1,1′-diadamantylmethyl system (**3**) overcome this problem and serve as an alternative limiting (k_c) secondary system under solvolytic conditions? Solvent

(1) (a) Stable Carbocations, part 235. For part 234, see G. A. Olah, A. P. Fung, T. N. Rawdah, and G. K. S. Prakash, *J. Am. Chem. Soc.*, **103**, 4646 (1981); (b) University of Southern California; (c) Universität Erlangen Nürnberg; (d) Princeton University.

(2) For evidence that not all tertiary systems are S_N1, see, T. W. Bentley, C. T. Bowen, W. Parker, and C. I. F. Watt, *J. Am. Chem. Soc.*, **101**, 2486–2488 (1979); M. P. Jansen, K. M. Koshy, N. N. Mangru, and T. T. Tidwell, *ibid.*, **103**, 3863–3867 (1981).

(3) (a) J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **92**, 2538–2540 (1970); (b) J. L. Fry, J. M. Harris, R. C. Bingham, and P. v. R. Schleyer, *ibid.*, **92**, 2540–2542 (1970); (c) P. v. R. Schleyer, J. L. Fry, L. K. M. Lam, and C. J. Lancelot, *ibid.*, **92**, 2542–2544 (1970); (d) T. W. Bentley and P. v. R. Schleyer, *ibid.*, **98**, 7658–7666 (1976); (e) F. L. Schadt, T. W. Bentley, and P. v. R. Schleyer, *ibid.*, **98**, 7667–7674 (1976); (f) T. W. Bentley, C. T. Bowen, D. H. Merten, and P. v. R. Schleyer, *ibid.*, **103**, 5466–5475 (1981); (g) T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.*, **14**, 1 (1977).

(4) S. H. Liggero, J. J. Harper, P. v. R. Schleyer, A. P. Krapcho, and D. E. Horn, *J. Am. Chem. Soc.*, **92**, 3789–3791 (1970).

(5) (a) J. L. Fry, E. M. Engler, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **94**, 4628–4634 (1972); (b) J. S. Lomas, P. K. Luong, and J.-E. Dubois, *J. Org. Chem.*, **44**, 1647–1654 (1979).

0022-3263/82/1947-1040$01.25/0