In Situ Studies of Chemical Reactions by ^{13}C Fourier Transform Nuclear Magnetic Resonance. Application to the Fischer Indole Synthesis

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Carbon-13 Fourier transform NMR has been used to follow, in situ, the course of a Fischer indole reaction. Relaxation times and nuclear Overhauser effect enhancements upon ^{13}C spectral intensities have been examined both experimentally and theoretically. Intensities obtained by rapidly pulsed ^{13}C FT NMR have yielded a semiquantitative kinetic picture whose accuracy was justified for the case that carbon atoms having identical protonic environments are compared. Imine intermediates corresponding to the stage of the Fischer indole reaction after the benzidine-type rearrangement but before closure of the five-membered heterocycle have been observed and characterized spectroscopically for the first time.

Introduction

One convenient route to 1-(4′-chlorobenzoyl)-2-methyl-5-methoxyindole-3-acetic acid, or indomethacin (**1**), a potent anti-inflammatory compound, is the Fischer indole reaction of levulinic acid and the acyl hydrazine **2** (Scheme I) discovered by Yamamoto.[1,2] ^{13}C NMR has been used to investigate the mechanism of the reaction and, as in the case of other work reported from our laboratories,[3-5] has provided insight not accessible by other means. An imine intermediate, heretofore only hypothetically involved in the reaction, has been characterized for the first time, by ^{13}C NMR spectroscopy. The Fischer indole synthesis is considered to proceed through several distinct steps, as illustrated in Scheme I[6-8] for the reaction leading to indomethacin. A few examples of isolation or trapping of intermediates in the Fischer synthesis have been reported[9-11] and Yamamoto[2] isolated **7** in low yield. Compound **7** could have been formed from either the imine corresponding to **5** or the analogous carbonyl compound. An unsaturated lactam, **8**, was isolated and characterized several years ago in our laboratories.[12] An earlier reported isolation of an imine-type intermediate[13] was corrected later.[14] As will be shown below, ^{13}C NMR spectra of reaction mixtures of **2** and levulinic acid in HCl–acetic acid clearly demonstrate the intermediacy of imine **5** per se, although it was not isolated. The analogous intermediate derived from cyclohexanone and **2** has also been visualized.

^{13}C NMR Intensities

The use of ^{13}C NMR spectroscopy for the qualitative visualization of reaction progress or stable reaction participants has required no special care[3-5,15-18] when lifetimes of species to be visualized were sufficient. But since ^{13}C FT NMR intensities, in the most general case, can be quite different for carbon atoms in different environments,[19,20] their application to quantitative measurements might be invalid or inaccurate. Even in the absence of possibly variable nuclear Overhauser (NOE) enhancements in ^{13}C spectra observed with proton decoupling, relative degrees of saturation in repetitively pulsed FT NMR signal accumulation may be unequal for ^{13}C nuclei in different environments. If pulse nutation angle and repetition rate were such that some resonances were heavily saturated with others almost fully relaxed, NMR intensity comparisons between the two types would be meaningless. But if relaxation times and NOE enhancements are identical for selected carbon atoms in the same or different molecules, their intensities will be quantitatively equal in *any* FT NMR experiment, given adequate signal to noise ratio and line shape definition. It follows that carbon atoms in very similar or identical local structural environments in sufficiently similar molecules will display intensities proportional to the concentrations of the various chemical species they represent to a high degree of accuracy.

In the viscous medium which obtains when excess levulinic acid is

Scheme I. The Fischer Indole Mechanism

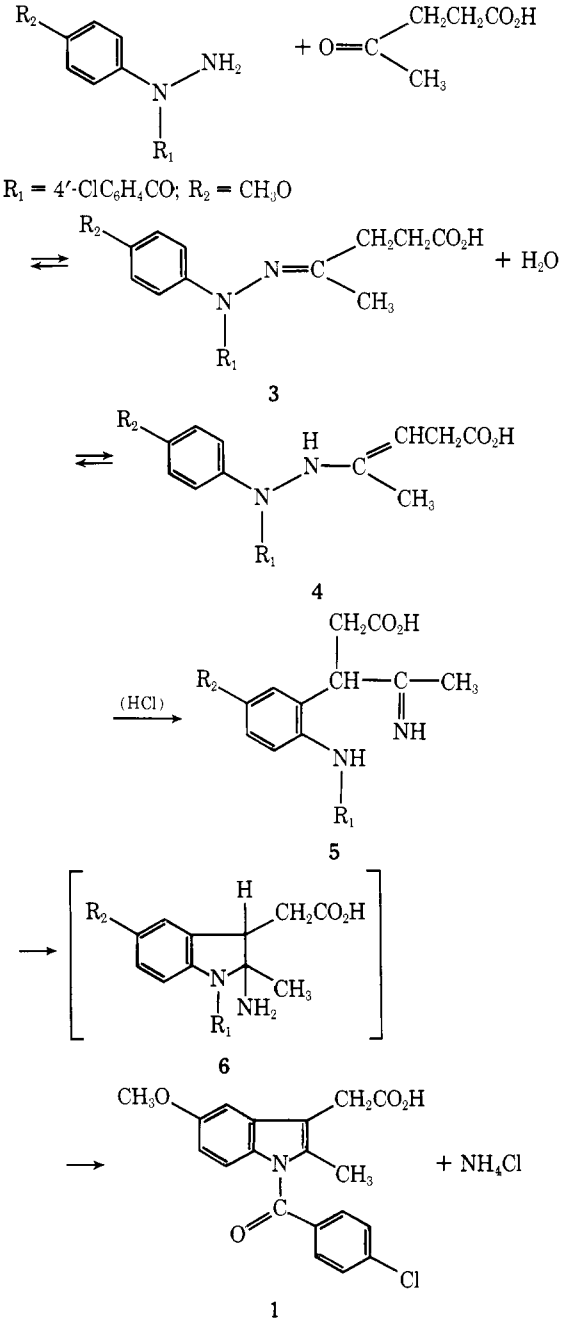

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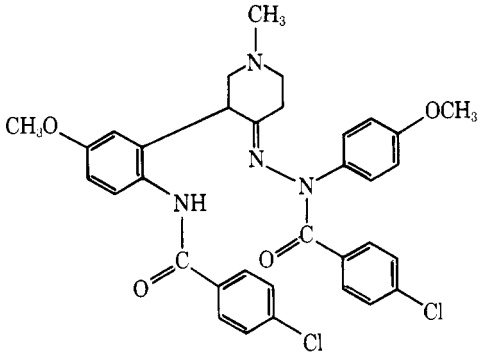
Table I. T_1 and NOE Enhancement $(1 + \eta)$ in Hydrazone 3[a] at 20 MHz

carbon position	δ_C[b]	T_1,s	T_1 limits[d]	NOE $(1 + \eta)$
4	159.9	1.09	0.96-1.25	2.0
4′	137.3	0.95	0.83-1.11	1.7
1	135.6	0.78	0.78-0.80	1.6
1′	134.6	1.05	1.03-1.07	1.6
2′,6′	131.9	0.06[c]		1.9
2,6 and 3′,5′	129.4	0.06[c]		1.9
3,5	115.4	0.04[c]		1.9
OCH_3	56.1	0.41_7	0.41_5-0.42_0	2.3

[a] Hydrazone **3** was at 1.0 M and levulinic acid at 3.0 M in acetic acid; temperature 22 °C. [b] Referenced to Me_4Si in $(CD_3)_2CO$, external solution. [c] Estimated values from only two values of recovery interval, 0.0625 and 0.125 s. [d] 95% confidence interval for five different recovery times.



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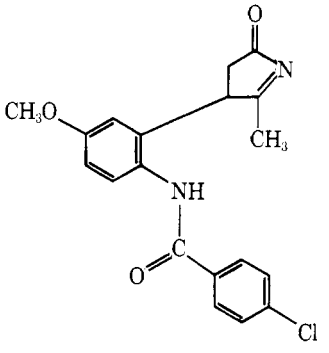

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caused to react with **2,** only the ^{13}C signals of nonprotonated sp^2 carbon atoms are of sufficiently narrow line width for easy recognition of all compounds involved in indomethacin formation. It is necessary to consider how the intensities for these atoms might change if different relaxation times and NOE enhancements accrued to molecules of different size and structure along the chemical pathway. Intensity response calculations based on the work of Allerhand and co-workers[21] have been made for several choices of effective molecular rotational correlation time, using the Fourier transform signal response formula[22,23] for repetitive pulses. Projections are made of the intensity variations which could be expected in ^{13}C FT NMR experiments if substantially different motional correlation times were applicable to structurally correspondent carbon nuclei among species observed in indomethacin synthesis. Except in special situations,[24] ^{13}C relaxation will be almost totally determined by spin dipolar interactions with protons,[25-27] at magnetic field strengths of up to 2.5 T. Even when fully substituted carbon atoms are used to follow reaction progress, results of adequate quantitative accuracy may be obtained, provided that only carbon atoms in similar "proton environments" are compared. With the use of signal intensities from appropriately chosen carbon atoms, a kinetic graph is constructed revealing a significant concentration of only a single stable intermediate between hydrazone **3** and indomethacin in this Fischer indole reaction.

In order to consider the effects of possibly variable relaxation times or NOE enhancements upon ^{13}C FT NMR intensities used to monitor indomethacin formation, an experimental measurement of these quantities is required. Hydrazone **3** is stable for several days at room

Table II. Relaxation Times, Overhauser Enhancements, and FT NMR Intensities for a Substituted Aromatic Carbon at 20 MHz at Several Effective Correlation Times

τ_R,ns	T_1, s	$(1 + \eta)$	rel FTI $\times (1 + \eta)$
0.9	1.6	2.52	1.12
1.4	1.2	2.26	1.15
2.7	0.90	1.73	(1.00)
5.5	0.73	1.32	0.82
8.0	0.73	1.21	0.75

temperature in acetic/levulinic acid mixtures without HCl, so it was subjected to T_1 and NOE determinations. The inversion-recovery method[28] was employed in T_1 measurements and a gated decoupling technique[29] was used for NOE enhancement factor evaluation. The results are presented in Table I, where recycle time between excitation pulses was 10 s. They were obtained *without* sample degassing, since it was desired to evaluate relaxation phenomena in typical reaction mixtures. For the short relaxation times obtained, any contribution due to dissolved oxygen may be safely ignored.[30,31] Accuracy is estimated at 70-80% for NOE factors, which were obtained from integrated signal intensities, and 80-90% for T_1 values (except as noted) measured using peak heights (or depths), fully adequate for the purposes for which they will be used here. The results are consistent with an analysis in terms of a single correlation time as discussed by Allerhand et al.[21a] For the proton-bearing aromatic carbons there is no reason to doubt that relaxation is fully governed by the dipolar mechanism,[25-27] but measured NOE enhancement factors fall well below the theoretical maximum of 3.0[32] for ^{13}C-{^1H} experiments. Slow rotational reorientation may, of course, cause reduced NOE enhancement even for carbons experiencing purely dipolar relaxation,[27] and one may suspect that the cause of the similarly reduced enhancements for both protic and substituted aromatic carbon atoms here is largely slow molecular reorientation, rather than sizable contributions from other relaxation mechanisms.

If dipolar relaxation is assumed to be the only relevant mechanism for proton-bearing aromatic carbons, the NOE enhancement factor of $(1 + \eta) = 1.9$ corresponds to a correlation time for isotropic rotational reorientation, τ_R, of 2.7 ns for ^{13}C observations made at 20 MHz. The calculated T_1 of some 34 ms for $\tau_R = 2.7$ ns is close to experimentally estimated values of 40-60 ms for the protic carbons. Owing to the admittedly large errors in observed T_1's in the 50-ms range, the NOE result, where τ_R fortuitously falls in a region of strong dependence of NOE enhancement upon it, is taken as the better indicator of τ_R. Furthermore, the more accurately measured T_1 values for the substituted aromatic carbons range from 0.8 to 1.1 s while a τ_R of 2.7 ns and a chemical shift anisotropy, $\Delta\sigma$, of 200 ppm lead to a calculated T_1 of 0.90 s for two hydrogens located 2.16 Å distant[33] from the carbon nucleus. Values of $\Delta\sigma = \frac{1}{2}(2\sigma_{zz} - \sigma_{xx} - \sigma_{yy})$ for substituted aromatic carbons are typically 200 ppm or less.[34-36] The calculated NOE enhancement is $1 + \eta = 1.89$ for a protonated aromatic carbon and 1.73 for a substituted aromatic carbon flanked by two protons. The agreement with experimental averages of 1.90 and 1.74, respectively, is excellent.

Calculations of dipolar and chemical shift anisotropy contributions to T_1 for substituted carbons with two protons located 2.16 Å distant

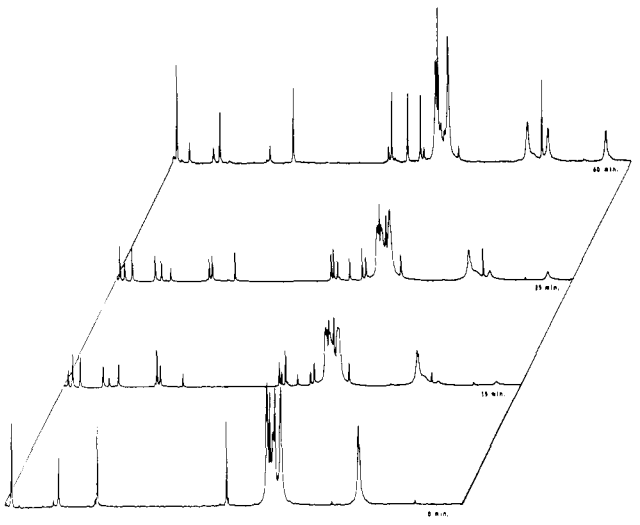


Figure 1. Time-lapse plot of partial ^{13}C spectra (approximately 97.75–177.25 ppm) obtained at 25.16 MHz and showing formation of **1** from **3.** By orienting a straightedge parallel to the slanted border lines on the figure the diminution of signals from **3,** essentially a solitary component in the lower trace, may be visualized. Growth of **1,** the dominant species in the upper trace, and the intermediacy of another species may be similarly visualized. Longer than normal 25 °C accumulation periods were employed in order to obtain the high signal to noise ratio in these illustrations.

Table III. Normal and NOE-Suppressed Ratios of Acylated Hydrazine to Its Levulinic Acid Hydrazone

run type	expt 1	expt 2
initial normal	45:55	45:56
NOE-suppressed	43:57	43:58
follow-up normal	45:55	44.56

and $\Delta\sigma = 200 \times 10^{-6}$ were also made for correlation times larger and smaller than the experimentally determined 2.7 ns for **3.** NOE enhancements were calculated and multiplied by Fourier transform intensity factors. The results for ^{13}C observation at 20 MHz appear in Table II, and are similar for 25.2 MHz. It may be seen that even a threefold change in τ_R is expected to produce only a 25% variation in ^{13}C signal intensity relative to the base value for 2.7 ns. This result supports the assumption that ^{13}C intensities may be compared directly, without loss of accuracy, among the species involved in the indolization studied. This should be particularly true for comparisons of concentrations of **3, 5,** and **1,** which differ little in molecular size. However, in order to further clarify the question of ^{13}C FT NMR intensity relationships, an experimental measurement of the significance of differences in molecular structure was made. Model mixtures containing comparable quantities of the acylated hydrazine, **2,** and its levulinic acid hydrazone, **3,** were prepared in mixed HCl–acetic–levulinic acid medium. Reaction to produce indomethacin is quite slow at 20 °C, and quantitative intensities were obtained with NOE suppression studies less protracted than would have been required to follow complete reaction sequences. Ratios of **2** to **3** based on peak heights for carbons C_4 (methoxy bearing) and C_4' (chlorine bearing) for two separate experiments appear in Table III. (cf. Experimental Section.) The results demonstrate that systematic quantitation error is insignificant in ^{13}C intensity comparisons of the type used to study the chemistry of indomethacin formation! Undoubtedly, finite signal to noise ratio is a more important source of error than any systematic cause. It may be noted that **2** and **3** represent the smallest and largest molecules involved in the present study, based on molecular weight, where one might intuitively expect the greatest disparity in tumbling mobility in solution (i.e., in τ_R). Apparently the effective correlation time for rotational reorientation is very similar in **2** and **3,** and thus, by inference, for other molecules of related size and shape in the same medium.

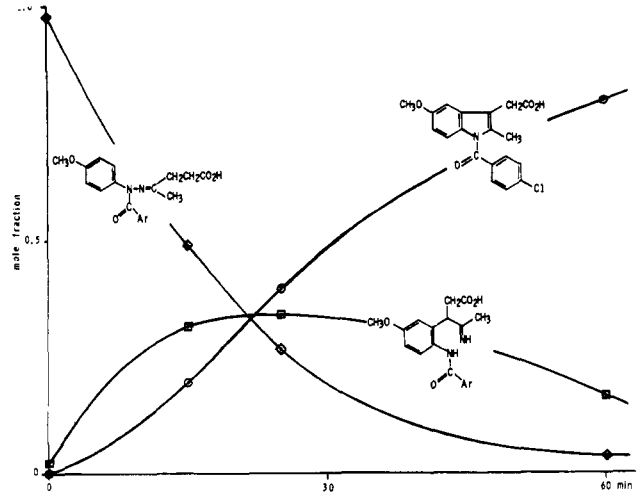


Figure 2. Kinetic plot of the course of reaction **3** → **5** → **1,** taken from the data illustrated in Figure 1. Elapsed times are accumulated heating periods at 50 °C.

Results

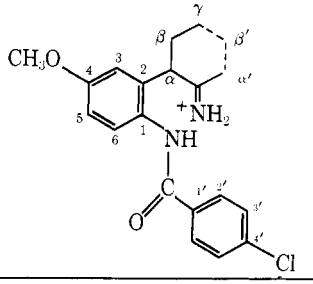
Figure 1 shows the time evolution of ^{13}C spectra when hydrazone **3** is converted to indomethacin at 50 °C. The concentration of **3** was about 1.0 M in acetic acid, saturated at room temperature with HCl, and levulinic acid was present at about 3.0 M to prevent reversal to **2.** Carbon-13 observations were made at approximately 20 °C with reaction periods at 50 °C carried out with the tightly stoppered NMR tube partially immersed in an oil bath. It is easy to visualize the gradual disappearance of the hydrazone as well as the growth of the product, indomethacin. For **3,** the stronger signals in the zero time run may be taken as its reference spectrum in the mixed acid medium. That high yields of indomethacin may be obtained[1,37] from these reaction mixtures after a few hours at moderately elevated temperatures identified the final species as **1.**

The presence of an intermediate is evident in Figure 1, since a number of peaks first rise and then fall with time. In several experimental runs similar to that illustrated the same group of peaks appeared in a comparable manner, and all are presumed to be due to a single chemical species. If this is taken to be the case, selected peaks from **3,** for the presently "unknown" intermediate, and for indomethacin (**1**) may be used to construct a kinetic plot for the reaction. Figure 2 presents such a plot based on peak heights for the same two substituted carbons in each species, the methoxyl-bearing and chlorine-bearing atoms. No evidence of significant amounts (>5%) of any other species was detected by ^{13}C NMR so the results are presented simply for a three-component mixture. When smooth freehand curves are drawn between the measured points, a classical two-step kinetic plot showing a single stable intermediate appears.

From Scheme I, any (or all) of three intermediates might have appeared, but the data support only the heretofore uncharacterized imino compound, **5,** as that observed. One might anticipate that the dihydroindole **6** would be unstable with respect to loss of ammonia (as NH_4Cl), although more complex analogues have been reported.[11] The apparent readiness of enehydrazine **4** to rearrange to **5** is indicated by the scarcity of observations or isolations of enehydrazine compounds in Fischer indole studies.[6-11]

Several spectral features of the "unknown" intermediate in Figure 1 are more clearly evident in Figure 3, obtained for a reaction time where the intermediate concentration had peaked. Despite interference from **1, 2,** and **3,** several signals for the intermediate are well resolved. There are also a low-field

Table IV. ^{13}C Assignments for Imine Products of the Benzidine Rearrangement Step in the Fischer Indole Reaction



compd HCl level	**5** normal	**5** supersaturated, 0 °C	**9** supersaturated, 0 °C
C_1	127.3	127.8	127.3
C_2	133.7	133.1	133.4
C_3	114.9 or ~115.9[a]	114.8 or ~116.3[a]	115.3 or 116.4
C_4	161.2	~161.1	161.3
C_5	114.9 or ~115.9[a]	114.8 or ~116.3[a]	115.3 or 116.4
C_6	*b*	*b*	130.9
CONH	171.7	172.2	171.9
$C_{1'}$	130.1	126.3	126.2
$C_{2',6'}$	~131.3	~131.3	131.6
$C_{3',5'}$	129.8	129.9	129.7
$C_{4'}$	140.8	141.2	141.4
C=N	198.8	198.4	202.1
C_α(CH)	45.1	44.9	47.3
C_β	~37.4	~37.3	~35.9
C_γ	175.0[c]	174.5[c]	24.7
$C_{\alpha'}$	24.0[d]	23.9[d]	27.7
$C_{\beta'}$			~35.9
OCH_3	54.5	56.3	56.3

[a] The signal near 116 ppm was partially obscured and only approximate shifts could be obtained. [b] Not observed owing to overlap. [c] Carboxyl carbon. [d] Methyl carbon.

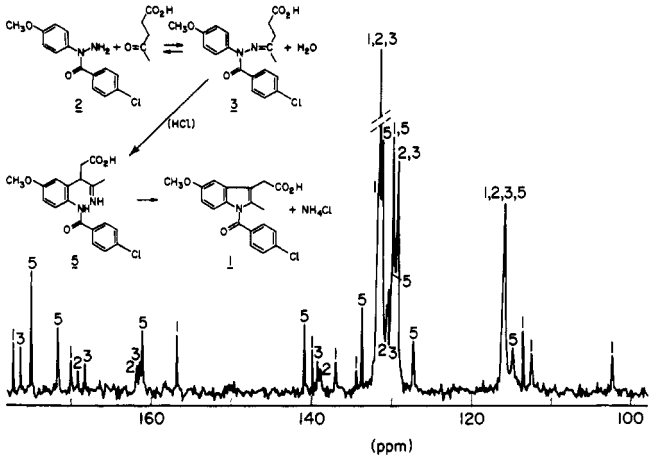


Figure 3. 25.16-MHz ^{13}C NMR spectrum of a reaction mixture containing **1, 2, 3,** and **5** illustrating distinction among chemical species. The signal to noise here is typical of the practical level at which ^{13}C information is readily obtained. Accumulation was 2250 × 0.4 s (15 min total) with the *sum* of concentrations of all species present equal to 0.9 M *in a 5-mm NMR tube.* The ^{13} C shift range presented is 98–178 ppm.

signal similar to that of the hydrazone C=N group and a somewhat broad signal at 45 ppm. The latter is a doublet under single-frequency off-resonance decoupling (sford) conditions. Several ^{13}C spectral assignments for the intermediate, as it appears in typical reaction mixtures, are made in the first column ot Table IV, where some entries must be absent due to spectral overlap. The observation of a methine carbon at 45 ppm along with a substituted one at 198 ppm would seem to allow only **5** as the correct structure for the stable intermediate among the choices of **4, 5,** and **6.** The total count of eight fully substituted sp^2 carbon atoms further attests that the reaction has passed the stage of enehydrazine **4.** However, it is possible to obtain more convincing evidence for **5,** which is certainly well advised since the intermediate was not isolated.

When the HCl level was purposely raised by supersaturation of reaction solutions higher intermediate concentrations were achieved from **3** when solutions were allowed to evolve at room temperature. Spectra of intermediate **5** could thus be produced with somewhat less interference from the starting compound **3** or indomethacin, which slowly forms even at 20–25 °C. The spectra of imine-type intermediates, as well as their further reactivity in the Fischer indole pathway, appear to be dependent upon HCl concentration. Table IV presents assigned ^{13}C chemical shifts for **5** in HCl-supersaturated medium and finally, for comparison, ^{13}C data for the analogous rearranged imine product, **9,** obtained from acylhydrazine **2** and cyclohexanone. The spectrum of just this cyclohexanone imine in acetic acid solution, supersaturated with HCl, is shown in Figure 4. This species alone is generated in situ, without heating, from equimolar amounts of **2** and cyclohexanone in glacial acetic acid, saturated at 0 °C with HCl gas. An exotherm occurs if the solution is allowed to warm directly to room temperature, but if the solution is held at 20–25 °C, conversion to the imine derivative is apparently (by ^{13}C NMR) quantitative after less than 1 h.

Assignment of ^{13}C signals for (protonated) cyclohexanone imine **9** was aided by sford experiments as well as literature data for ^{13}C chemical shifts in the cyclohexyl group.[38] Seven fully substituted sp^2 carbons were readily recognized. A doublet in the sford observation corresponding to a signal at 47.3 ppm in the fully decoupled spectrum identified this as the methine of the cyclohexyl group. By line width alone the proton-bearing aromatic carbons were easily recognized. Although

Table V. ^{13}C Shielding in Cyclohexanone Imine and Ketone Products of the Benzidine Rearrangement

carbon position	compd 9	10	2-methylcyclohexanone	2-*tert*-butylcyclohexanone
C = X	202.1	212.6	210.3	210.7
2	47.3	53.7	44.3	60.2
3	36	34.7	35.5	30.2
4	24.7	25.8	24.5	26.5
5	27.7	28.2	27.3	29.0
6	36	42.5	40.9	44.3

C_6 is almost obscured by the more intense signal due to carbons 2′ and 6′, it is clearly evident that a rearrangement involving the anisyl ring has occurred, even if only the pair of signals at 115.3 and 116.3 ppm are considered (Figure 4).

It is arguable that the intermediates **5** and **9** in fact are carbonyl compounds rather than (protonated) imine species, arising through hydrolysis of the latter, particularly since Yamamoto[2] isolated hydrazone **7** which may have arisen from the keto analogue of **9**. However, in a separate experiment where cyclohexanone was allowed to react with the hydrochloride of **2** the rearranged ketone analogue **10**, of **9** was observed, apparently as a second intermediate arising from **9** and ultimately converted to the Fischer indole product, a tetrahydrocarbazole. Carbon-13 signals assigned to the cyclohexyl moiety, in keto and imino forms, appear in Table V. The shifts of 2-methyl- and 2-*tert*-butylcyclohexanones, albeit obtained in a neutral organic solvent,[38] are presented for comparison. The correlation between these reference compounds and purported keto intermediate **10** gives strong support for the structural assignment for the latter.

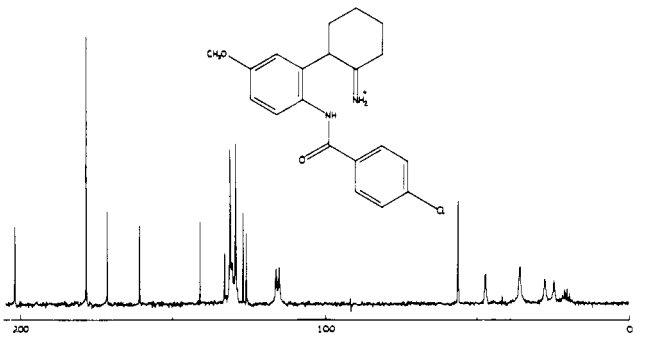


Figure 4. ^{13}C NMR spectrum at 25.16 MHz of imine intermediate, **9**, generated in situ from **2** and cyclohexanone. Run for 10 min (1500 × 0.4 s) in a 5-mm tube at approximately 1.2 M.

Discussion

Carbon-13 FT NMR has been used to visualize a Fischer indole synthesis in situ. It has allowed firm identification of benzidine-rearranged imines as stable intermediates in the formation of 1-acylindoles from acylated hydrazines or hydrazones. This work constitutes the first definite observation of such intermediates, due not only to the power of the ^{13}C method but also, of course, to natural proclivities at each reaction step. Condensation of an amide function with an unsaturated group is required in order that imine intermediates like **5** proceed to indoles. Ordinarily, a secondary amide would be unreactive toward a ketone, and, by inference, a ketimine in acid medium,[39] and only the fact that this step is intramolecular gives it a synthetically useful rate. It is not expected that an imine intermediate would be so easily visualized if a N_1-unsubstituted phenylhydrazine were converted to an indole unsubstituted at the heterocyclic nitrogen, in contrast to the relatively long lifetimes of the amide-imines studied in this work.

Sufficient stability of chemical intermediates is clearly necessary if NMR methods, expecially ^{13}C FT NMR with its naturally low sensitivity, are to be useful in their observation. But despite such problems, ^{13}C NMR remains a highly powerful tool for chemical mechanism studies owing to its great structural discriminatory power or "chemical resolution" ability. In addition, the technique may be applied to a variety of homogeneous *or* heterogeneous reactions.

If available sensitivity and total experiment time were not factors, one could use NOE suppression, requiring long recycle times between sampling pulses, and obtain fully relaxed ^{13}C FT NMR spectra with all nuclei exhibiting equivalent intensities. Signal accumulation periods would become prohibitively wasteful under such conditions, however, and only very slowly evolving chemistry could be usefully followed with ^{13}C NMR. Alternatively, one might attempt to experimentally characterize relaxation and nuclear Overhauser phenomena on individual samples of reaction products, intermediates, and starting compounds, and perform appropriate intensity corrections upon data obtained in a typical rapidly pulsed experiment. The latter approach is equivalent to characterizing motional phenomena (τ_R) and structural parameters (r_{CH}, $\Delta\sigma$) by actual measurement. This, of course, fails for "unisolatable" reaction intermediates, where experimental relaxation and NOE data would be unobtainable. However, if the structurally dependent quantities are known or may be assumed to be very similar in molecules of interest in a reaction sequence, and molecular motional factors may be assumed not to diverge greatly among them, direct comparison of ^{13}C intensities in ordinary FT NMR experiments will be at least semiquantitatively accurate.

There are doubtless many chemical reactions normally performed at sufficient concentration and which proceed sufficiently slowly that ^{13}C NMR may be applied advantageously in their mechanistic characterization. It must generally be admitted that isolated compounds might have arisen during quenching or that a trapping reagent exerted some directing influence upon a mechanistic step or equilibrium. Indeed, a trapping agent is designed to introduce another reaction pathway competitive with that under investigation, leading to the trapped product. An in situ method, by definition, purports to examine only what is already there by natural causes. The considerable ability of ^{13}C NMR to distinguish even quite subtle structural modification and to resolve signals of very similar carbon atoms in closely related structures indicates it as the tool of choice in the examination of organic reaction mechanisms, provided that time/sensitivity criteria may be met.

Experimental Section

Melting points were taken with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Mr. J. P. Gilbert and his staff. ^{13}C NMR spectra were obtained by Fourier transform at 20.0 and 25.16 MHz on either a Varian Associates CFT-20 or XL-100 spectrometer, respectively. Unless otherwise specified, observations were made at ambient probe temperature, which was approximately 36 °C for the CFT-20 but only some 25 °C

for the XL-100. Typical pulsing conditions were the use of a 45° nutation angle and 0.5-s signal acquisition time between pulses with no added pulse delays. NOE and T_1 measurements were performed at 20 MHz with full cycle times of 10 s, including appropriate delay intervals. A $\{180°-\tau-90°-AT-T_d\}_n$ sequence[28] was used to measure T_1's and NOE enhancements were obtained by a gated decoupling technique.[29] The 10-s recycle time exceeds the longest T_1 by some ninefold, in keeping with recent results.[40,41] Two separate preparations of mixtures of **2** and **3** were subjected to sequential normal, NOE-suppressed, and follow-up normal ^{13}C FT NMR observations (see Table III). Conditions were adjusted so that the solution temperature was the same for normal, full-time proton decoupled runs and NOE-suppressed runs which necessarily involve a low decoupler duty cycle, so that no temperature-dependent viscosity change could occur. All observations in both sequences correspond to 18–20 °C sample temperature. The first experiment involved initial and final accumulations of 0.25 h each for fully decoupled runs with an intervening 5-h NOE-suppressed run. The second used 0.5-h intervals for the fully decoupled runs and 3 h for the NOE suppression.

A deuterium NMR signal was used for field-frequency lock, with a concentric cell containing deuterioacetone and tetramethylsilane employed on the CFT-20. The XL-100 runs were made with CD_3CO_2H solvent (Merck Sharp and Dohme) either alone or mixed with CH_3CO_2H. Reaction mixtures typically had no tetramethylsilane added and chemical shifts at 25.16 MHz were obtained by using the central peak of the CD_3 group as a secondary reference. Its shift was measured as 20.3 ppm relative to internal tetramethylsilane in one case where this was added to a reaction mixture.

N_1-4′-Chlorobenzoyl-N_1-4-methoxyphenylhydrazine (**2**)[42] was dissolved in hot 2-propanol (170 g in 3.7 L), treated with 17 g of Nuchar C100-N, stirred for 0.5 h, filtered hot, crystallized, filtered, washed with 2-propanol and petroleum ether, and dried at 60 °C under house vacuum. A white solid was obtained with mp 129–130 °C. Anal. ($C_{14}H_{13}ClN_2O_2$), C, H, N.

Hydrochloride salt of 2. To 8.5 g of **2** in 100 mL of hot benzene, HCl gas was admitted. After addition of 400 mL of ether a white solid was collected with mp 164.8 °C. Anal. ($C_{14}H_{13}ClN_2O_2$·HCl) C, H, N.

Levulinic Acid N_2-*p*-Chlorobenzoyl-N_2-*p*-methoxyphenylhydrazone (3). N_1-*p*-Chlorobenzoyl-N_1-*p*-methoxyphenylhydrazine (160 g, 0.58 mol) and 116 mL (0.9 mol) of levulinic acid were stirred 3 h at room temperature with 1.6 L of toluene. H_2O (11 mL) was then separated and the toluene was removed by vacuum evaporation. The residue was crystallized from 500 mL of ethyl acetate and 600 mL of petroleum ether, following seeding and 2 h of stirring. The solid was washed first with 800 mL of 15/85 ethyl acetate/petroleum ether and then with 500 mL of petroleum ether to give a white solid, mp 100–102 °C. Anal. ($C_{19}H_{19}ClN_2O_4$) C, H, N.

Levulinic acid and cyclohexanone were obtained from commercial sources, the former being high-vacuum distilled before use and the latter used without further purification.

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Appendix

Formulas Used in Calculating Relaxation Times, NOE Enhancements, and FT NMR Intensity Response. As a model for estimation of effects of possible variation in relaxation times or NOE enhancements in different molecules involved in the reaction sequence studied in this work, the theory of relaxation in isotropically reorienting molecules discussed by Allerhand and co-workers[21a] has been used. Their formulation for dipole–dipole spin–lattice relaxation rate and NOE enhancement is

$$1/T_1^{DD} = \frac{\hbar^2\gamma_C^2\gamma_H^2\tau_R\chi}{10r_{CH}^6} \quad (1)$$

and

$$(1+\eta_0) = 1 + \frac{\gamma_H}{2\gamma_C\chi}\left[\frac{6\tau_R}{1+(\omega_H+\omega_C)^2\tau_R^2} - \frac{\tau_R}{1+(\omega_H-\omega_C)^2\tau_R^2}\right] \quad (2)$$

where

$$\chi = \frac{\tau_R}{1+(\omega_H-\omega_C)^2\tau_R^2} + \frac{3\tau_R}{1+\omega_C^2\tau_R^2} + \frac{6\tau_R}{1+(\omega_H+\omega_C)^2\tau_R^2} \quad (3)$$

and τ_R is the effective correlation time for rotational reorientation. Following Abragam[43] and others,[44] relaxation by chemical shift anisotropy is governed by

$$1/T_1\ \text{CSA} = \frac{2}{15}\gamma_C^2H_0^2(\Delta\sigma)^2\frac{\tau_R}{1+\omega_C^2\tau_R^2} \quad (4)$$

where $\Delta\sigma = \frac{1}{2}(2\sigma_{zz} - \sigma_{xx} - \sigma_{yy})$ and the difference (if any) between σ_{xx} and σ_{yy} is ignored. When relaxation is not fully dipolar, the actual NOE enhancement parameter, η, is related to the purely dipolar quantity, η_0, by[26,45]

$$\eta = \eta_0\frac{T_1}{T_1^{DD}} \quad (5)$$

where[45]

$$1/T_1 = 1/T_1^{DD} + 1/T_1^{CSA} + 1/T_1^{other} \quad (6)$$

The intensity for repetitively pulsed Fourier transform signal accumulation is[22,23]

$$I = \frac{\sin\theta\,[\exp(T/T_1) - 1]}{\exp(T/T_1) - \cos\theta} \quad (7)$$

for pulse nutation angle θ and recycling interval T.

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Stereochemistry of Allylic Rearrangements. 16. Ion-Pair Return Associated with Solvolysis of *exo*- and *endo*-Bicyclo[3.2.1]oct-3-en-2-yl *p*-Nitrobenzoate in Aqueous Acetone

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Abstract: Ion-pair return associated with solvolysis of *exo*- and *endo*-bicyclo[3.2.1]oct-3-en-2-yl *p*-nitrobenzoate (**4**-OPNB and **6**-OPNB) in aqueous acetone results in racemization of optically active ester (reaction 3), equilibration of the carboxyl oxygen atoms (reaction 4), and exo ⇄ endo isomerization (reaction 5). All processes are first order and intramolecular. Rate constants for solvolysis (k_t), loss of optical activity (k_α), racemization corrected for geometric isomerization (k_{rac}), and oxygen equilibration (k_{eq}) have been determined for solvolysis of both isomers in 80 and 90% acetone. In all cases $k_\alpha > k_t$ and the initially formed solvolysis product, >99% exo alcohol (**4**-OH), is racemic. For **6**-OPNB, k_{rac} and k_{eq} are similar if not the same. This indicates that ionization gives an intermediate with equivalent carboxyl oxygen atoms and allylic carbon atoms. However, for **4**-OPNB, k_{eq} is three to five times larger than k_{rac}. In this case there is a path for randomizing the carboxyl oxygen atoms without loss of optical or geometric configuration. This shows that, although the unperturbed cation (**3**) is symmetrical, the initially formed ion-pair intermediate is not, i.e., the enantiomeric allylic *p*-nitrobenzoates give enantiomeric intermediates.

In earlier work we investigated the solvolysis of α,γ-dimethylallyl[1] and *cis*- (**1a**)[2b] and *trans*-5-methyl-2-cyclohexenyl *p*-nitrobenzoates (**1b**)[2a] in aqueous acetone (eq 1). These systems are related to symmetrical cations and thus solvolysis of optically active substrates results in loss of optical activity (eq 2). In each case, ion-pair return results in racemization of optically active substrate (eq 3) and randomization of the carboxyl oxygen atoms of ^{18}O-labeled ester (eq 4). These transformations are intramolecular, i.e., no exchange with added *p*-nitrobenzoic acid.[1,2]

$$\mathrm{ROCOAr} \xrightarrow{k_t} \mathrm{ROH} + \mathrm{ArCO_2H} \qquad (1)$$

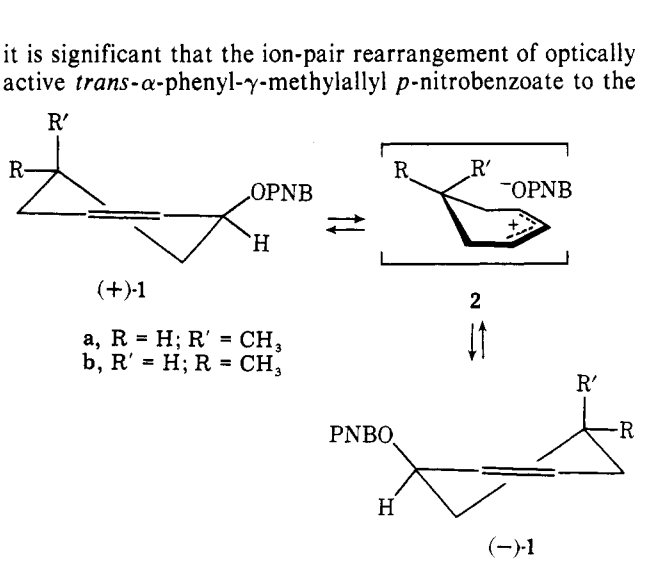
$$(d \text{ or } l)\text{-ROCOAr} \xrightarrow{k_\alpha} \text{inactive products} \qquad (2)$$

$$(d \text{ or } l)\text{-ROCOAr} \xrightarrow{k_{rac}} dl\text{-ROCOAr} \qquad (3)$$

$$\mathrm{R\text{-}OC^{18}OAr} \xrightarrow{k_{eq}} \mathrm{R\text{-}{}^{18}OC^{18}OAr} \qquad (4)$$

$$\textit{exo}\text{-R-OCOAr} \underset{k_t^{en}}{\overset{k_t^{ex}}{\rightleftharpoons}} \textit{endo}\text{-ROCOAr} \qquad (5)$$

Ion-pair return associated with solvolysis of the isomeric 5-methyl-2-cyclohexenyl *p*-nitrobenzoates (**1**) is completely stereospecific, i.e., there is no detectable geometric isomerization.[2] Presumably in this case a conformational factor, rather than inherent structural properties of allylic ion-pair intermediates, controls the stereochemistry.[3] In this connection it is significant that the ion-pair rearrangement of optically active *trans*-α-phenyl-γ-methylallyl *p*-nitrobenzoate to the



trans-γ-phenyl-α-methylallyl isomer involves substantial (~70%) loss of optical configuration.[4]

Evidently, in flexible cyclohexenyl systems such as **1**, the quasi-axial conformation is related to the best transition state for cleavage or formation of the allyl bond.[3] This means that the isomeric 5-methyl-2-cyclohexenyl *p*-nitrobenzoates give symmetrical cations that differ conformationally as illustrated by the **1** → **2** transformation. The anion is generated on the side of the out of plane C-5 carbon atom and this side is also favored for capture of the cation (microscopic reversibility). Thus the

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