and radical ions.[38] This consideration is under further investigation.

Experimental Section

Trifluoromethylnitrobenzene derivatives were obtained from Pierce Chemical Company and recrystallized or distilled before use. *p*-Trifluoromethylnitrobenzene was received as a gift from E. I. du Pont de Nemours and Company. 3-Methyl-4-nitrophenol was obtained from Aldrich Chemical Company. Acetonitrile was distilled from calcium hydride before use. Tetraethylammonium perchlorate was obtained from Eastman Organic Chemicals or made by a metathesis reaction in water from tetraethylammonium bromide and ammonium perchlorate.

Nitrobenzene radical anions were generated electrolytically *in situ* in a Varian flat cell in the cavity of a Varian 4502 epr spectrometer. This system includes a 12-in. magnet with Fieldial control. The coupling constants were calculated from the scan rates specified on the Fieldial control and scanning unit. High-resolution spectra were obtained by using 100-min scans.

Electrolytic reduction was carried out in a system very similar to that originally described by Geske and Maki.[5a] Although the mercury–calomel electrode system was adequate for stable radicals it was found that for unstable radicals such as 4-methoxy- and 4-hydroxy-2-trifluoromethylnitrobenzene the rate of production of radicals was too slow to maintain a high enough steady concentration of radicals for long scanning periods. This result seem to be related to concentration polarization of the electrode. Multistranded wire, *e.g.*, Belden 20AWG 10 × 30, gave excellent results when the electrode was separated from the bulk of the solution by a fritted glass disk. This arrangement was used for most reductions. No attempt was made to measure the reduction potential simultaneously with free-radical production. Typical values for nitrobenzene derivatives can be found in ref 5. In every experiment the applied voltage was slowly increased in small increments until the first radical was detected. This voltage was approximately the same as required to obtain the well-known spectrum of nitrobenzene radical anion.

(38) J. P. Colpa and J. R. Bolton, *Mol. Phys.*, **5**, 273 (1962).

Acknowledgment. We thank W. A. Sheppard of E. I. du Pont de Nemours and Company for providing us with a sample of *p*-trifluoromethylnitrobenzene and E. T. Strom for helpful discussions regarding this work. We also appreciate receiving a copy of Professor Watson's paper, prior to publication, describing similar work on trifluoromethylnitrobenzene anion radicals.

Chemical Shift Nonequivalence of Diastereotopic Protons Due to Restricted Rotation around Aryl–Nitrogen Bonds in Substituted Amides

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Abstract: Chemical shift nonequivalence of diastereotopic protons in cyclic and acyclic amides and several related systems is interpreted within the framework of the conformational analysis of mobile systems. An approach to a critical discussion of kinetic and thermodynamic restrictions on ring flipping, torsional, and inversional modes of conformational interchange is developed. The chemical shift nonequivalence of the diastereotopic benzyl methylene protons in N-benzyl-N-(*o*-tolyl)acetamide has been reinvestigated within this general framework. Analysis of the nmr spectra of a variety of cyclic and acyclic amides indicates that a previous interpretation which viewed this phenomenon as arising from slow inversion of pyramidal amide nitrogen is in error. A more reasonable alternative is presented, that the source of the nonequivalence lies in restricted rotation about the aryl–nitrogen bond. Coalescence temperatures indicate free energies of activation for this process of 20.0 and 17.3 kcal/mole for N-benzyl-N-(*o*-tolyl)acetamide and N-*o*-tolyl-1,4-dihydro-3(2*H*)-isoquinolinone, respectively. The possibility of cisoid–transoid isomerism about the nitrogen–carbonyl bond is also discussed, and assignments of configuration of the *s-cis* and *s-trans* isomers of N-benzyl-N-(*o*-tolyl)formamide have been made, using aromatic solvent-induced shifts.

The work described in this paper was prompted by the appearance of a recent claim by Siddall and Prohaska[2] that the chemical shift nonequivalence, at ordinary temperatures, of the methylene protons in N-benzyl-N-(*o*-tolyl)acetamide (**2**, Table I) constituted evidence for "slow inversion at the nitrogen atom" in this amide. However, it has been known for some time[3] that the pyramidal H_2NC group in formamide suffers *rapid* inversion, similar to the wagging motion in ammonia, with an activation energy barrier of only about 1 kcal/mole. The low barrier for pyramidal inversion in this and similar amides[4] is inconsistent with the conclusion[2] that the inversion in **2** "must be less rapid than the mean lifetime of something like 1–10 msec." Further, the observed[2] chemical shift equivalence of the methylene protons in N-benzyl-N-(2,6-dimethylphenyl)acetamide and in N-benzylacetanilide, assuming that the appearance of a singlet is not the result of accidental chemical shift coincidence, would be difficult to understand if slow inversion at

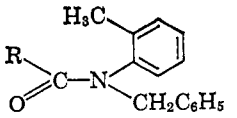
(1) (a) Institute of Chemistry, Tel-Aviv University, Ramat-Aviv, Israel. (b) Supported by a grant (CA-02551) to Princeton University from the National Cancer Institute, National Institutes of Health. (c) Supported by the Air Force Office of Scientific Research under Grant No. AF-AFOSR-1188-67.

(2) T. H. Siddall and C. A. Prohaska, *Nature*, **208**, 582 (1965).

(3) C. C. Costain and J. M. Dowling, *J. Chem. Phys.*, **32**, 158 (1960).

(4) In nitramide and cyanamide, the corresponding barriers are 2.7 and 2.0 kcal/mole, respectively [J. K. Tyler, J. Sheridan, and C. C. Costain, unpublished work, cited by P. G. Lister and J. K. Tyler, *Chem. Commun.*, 152 (1966)]. In the crystalline state, amides are said to be planar or nearly so (S. C. Nyburg, "X-Ray Analysis of Organic Structures," Academic Press Inc., New York, N. Y., 1961, p 191 ff).

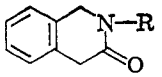
Table I. N-Benzyl-N-(*o*-tolyl)amides



Compd	R	Mp, °C	Bp °C (mm)	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Nmr of N-benzyl-methylene protons,[a] Hz from TMS[b]	$\Delta\nu_{AB}$, Hz[c]
1	H	58–59	138 (1)	$C_{15}H_{15}NO$	79.97	6.71	79.86	6.77	276, 286[d]	...
2	CH_3	...	130 (0.1)	$C_{16}H_{17}NO$	80.30	7.16	80.29	7.40	284	50.5[f]
3	C_2H_5	...	130 (0.17)	$C_{17}H_{19}NO$	80.57	7.56	80.54	7.65	284	52.7
4	$CH(CH_3)_2$	...	126 (0.2)	$C_{18}H_{21}NO$	80.86	7.92	80.86	8.20	284	57.7
5	$C(CH_3)_3$	67–69	130 (0.1)	$C_{19}H_{23}NO$	81.10	8.24	80.83	8.14	281	97.5
6	Phenyl	59–61	178 (0.2)	$C_{21}H_{19}NO$	83.69	6.35	83.47	6.54	301	35.0
7	*p*-Methoxy-phenyl	...	170 (0.2)	$C_{22}H_{21}NO_2$	79.73	6.39	79.45	6.48	297	30.8
8	*p*-Nitro-phenyl	127–129	...	$C_{21}H_{18}N_2O_3$	72.84	5.24	72.82	5.24	287	29.8[e]
9	CF_3	66.5–67.5	...	$C_{22}H_{18}NOF_3$	65.53	4.81	65.76	5.06	289	66.6
10	$CH_2C_6H_5$	...	175 (0.25)	$C_{22}H_{21}NO$	83.77	6.71	83.53	6.88	283	59.0

[a] Measured as ~15% solution in $DCCl_3$ with TMS as internal standard at 40° with a Varian A-60A nmr spectrometer. [b] Measured at the center of the AB quartet. [c] The AB coupling constants ranged from 13.8 to 14.2 Hz in the various compounds. [d] The intensity ratio of the singlets at 286:276 is 7.5:1, respectively (see text). [e] Spectrum measured in DMSO-d_6. [f] Siddall and Prohaska[2,5] reported a value of 49.8 Hz.

Table II. N-Substituted 1,4-Dihydro-3(2*H*)-isoquinolinones



Compd	R	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Nmr of 1-methylene protons[a] Hz from TMS[b]	$\Delta\nu_{AB}$, Hz[c]	*J*, Hz
11	Phenyl	96.5–98.5	90	$C_{15}H_{13}NO$	80.69	5.87	6.27	80.74	5.83	6.51	282	Singlet	...
12	*o*-Tolyl	103–105	88	$C_{16}H_{15}NO$	80.98	6.37	5.90	80.76	6.41	6.10	272	11.9	15.7
13	2,6-Dimethyl-phenyl	126–128	75	$C_{17}H_{17}NO$	81.24	6.82	5.57	81.45	7.04	5.79	270	Singlet	...
14	2-Methyl-3-chloro-phenyl	147–149	48	$C_{16}H_{14}ClNO$	70.74	5.19	5.16	70.77	5.45	5.38	278	14.4	15.5
15	α-Naphthyl	131–132.5	57	$C_{19}H_{15}NO$	83.49	5.53	5.13	83.27	5.57	5.13	285.5	16.0	15.7
16	Benzyl	91–92	94	$C_{16}H_{15}NO$	80.98	6.37	5.90	80.94	6.42	5.67	256	Singlet	...
17	1-Phenethyl	108–109.5	74	$C_{17}H_{17}NO$	81.24	6.82	5.57	81.13	6.93	5.77	244	30.3	18.0

[a] Measured as a 10% solution in $DCCl_3$ at 30–40°, relative to TMS as internal standard. [b] Measured at the center of the AB quartet. [c] Chemical shift difference between the two doublets measured at 40°.

nitrogen were to be held accountable for the nonequivalence observed in **2**.[5]

Restricted rotation around the benzene-to-nitrogen bond, long known,[6] is an alternative and more consistent rationalization of the observed results. If, as expected, the rate of rotation is slow on the nmr time scale, the methylene protons in **2** become anisochronous,[7] even though the accompanying inversion of the amide nitrogen is rapid on the nmr time scale. More recently, and while the present work was in progress, Siddall, *et al.*, recognized this alternative explanation and, though failing to repudiate their earlier conclusions,[2] have now used the restricted rotation model to account for their observations.[8]

In the present work ten acyclic amides (**1–10**, Table I) and nine cyclic amides (**11–17**, Table II; **18** and **19**) were examined. The cyclic compounds were prepared for study as prototypes of the acyclic analogs in which rotation around the N–CO amide bond is restricted and in which the conformation relative to that torsional mode is unequivocally defined. Thus one might regard

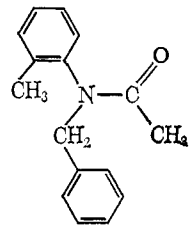
(5) Siddall and Prohaska[2] have argued that the lack of observable methylene proton nonequivalence in the two above-mentioned amides "indicates that a fairly high order of dissymmetry in the molecule is required. The requirement of a high degree of dissymmetry may be the reason that slow inversion has not been observed for acyclic trivalent nitrogen in the past." This argument is untenable.

(6) R. Adams, *Record Chem. Prog.* (Kresge-Hooker Sci. Lib.), **10**, 91 (1949).

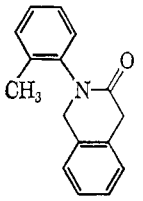
(7) This term was suggested by Dr. G. Binsch (private communication) to signify "magnetically nonequivalent in the chemical shift sense," as a counterpart to the term "isochronous," signifying "magnetically equivalent in the chemical shift sense," introduced by A. Abragam, "The Principles of Nuclear Magnetism," Oxford, 1961, p 480.

(8) (a) T. H. Siddall, III, and C. A. Prohaska, *J. Am. Chem. Soc.*, **88**, 1172 (1966); (b) T. H. Siddall, III, *Tetrahedron Letters*, 4515 (1965); (c) *ibid.*, 2027 (1966); (d) T. H. Siddall, III, and R. H. Garner, *ibid.*, 3513 (1966); (e) T. H. Siddall, III, *J. Phys. Chem.*, 70, 2249 (1966); (f) T. H. Siddall, III, and R. H. Garner, *Can. J. Chem.*, **44**, 2387 (1966); (g) T. H. Siddall, III, *J. Org. Chem.*, **31**, 3719 (1966); (h) *J. Phys. Chem.*, 70, 2050 (1966).

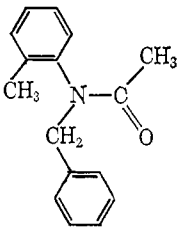
compound **12** as a conformationally locked (with respect to rotation around the amide bond) analog of *s-trans*-**2**, and **18** as a conformationally locked analog of *s-cis*-**2** (*s-trans* and *s-cis* being arbitrarily defined for purposes of the present discussion as the conformations in which the N-benzyl group is *trans* and *cis*, respectively, to the carbonyl oxygen atom in the essentially planar amide grouping).



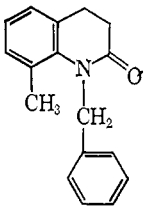
s-trans-2



12



s-cis-2



18

Results and Discussion

In all the N-benzyl-N-(*o*-tolyl)amides examined but one (*viz.*, formamide **1**), the geminal methylene protons of the N-benzyl group exhibit chemical shift nonequivalence (Table I). That the nonequivalence arises from restricted rotation around the benzene-to-nitrogen bond follows from the observations of Siddall, *et al.*, on related systems,[8] and may also be gleaned from the data on the cyclic amides presented in Table II.

1,4-Dihydro-3(2*H*)-isoquinolinone, though perhaps not a planar molecule, may safely be regarded as suffering rapid pyramidal inversion at nitrogen, and ring inversion ("flapping") at room temperature on the nmr time scale.[9] The consequence of these rapid conformational interchanges may be visualized most easily by reference to a hypothetical averaged C_s conformation which approximates the transition-state conformations for nitrogen pyramidal inversion and ring flipping and in which all of the carbon, oxygen, and nitrogen atoms lie in the symmetry plane of the (average) molecule. In analogy with biphenyl[10] we may regard the process of torsion around the benzene-to-nitrogen bond of N-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (**11**) as one in which the molecule passes through two energy minima and two energy maxima. The two energy minima correspond to conformations in which the plane of the N-phenyl ring is twisted out of the (average) plane of the 1,4-dihydroisoquinolinone ring system, with dihedral angles of tilt which have values of $0° < \phi_1 < 90°$, $90° < \phi_2 < 180°$. The conformers corresponding to ϕ_1 and ϕ_2 are enantiomeric. One of the two energy maxima corresponds to a conformation in which the N-phenyl ring is roughly perpendicular to the average plane of the 1,4-dihydroisoquinolinone ring system, with $\phi \approx 90°$, whereas the other one corresponds to a conformation in which the N-phenyl ring is coplanar with the rest of the molecule, $\phi = 0$ or 180°. However, the barrier for interconversion of the ϕ_1 and ϕ_2 enantiomers *via* the perpendicular conformation ($\phi \approx 90°$) is undoubtedly very low, *i.e.*, of the order of 1 kcal/mole,[10] and it will therefore be convenient for the purpose of the present discussion to ignore the shallow energy barrier (*i.e.*, that corresponding to $\phi \approx 90°$) between ϕ_1 and ϕ_2, and to consider the N-phenyl ring in **11** as occupying a stable average position perpendicular ($\phi = 90°$) to the average plane of the 1,4-dihydroisoquinolinone ring system. We shall refer to this as the E_{min} conformation.[11] The high-energy conformation at $\phi = 0$ or 180° is the E_{max} conformation. In both conformations the molecule has a plane of symmetry which bisects the methylene H–C–H bond angles. The geminal methylene protons are therefore enantiotopic[13] and isochronous.[7] Similar considerations apply to **16** and indeed to all N-aryl derivatives of 1,4-dihydro-3(2*H*)-isoquinolinone in which the aryl group has a local plane of symmetry which is perpendicular to the plane of the aromatic ring.

When, as in compounds **12**, **14**, and **15**, the N-aryl group does not possess a local plane of symmetry perpendicular to the aromatic ring system, two enantiomeric E_{min} conformations exist (*i.e.*, $\phi = 90°$ and $\phi = 270°$) which may interconvert (*i.e.*, racemize) *via* either one of two diastereomeric E_{max} transition-state conformations ($\phi = 0$ or 180°). The situation is entirely analogous to that encountered in the racemization of biphenyls.[14] The geminal methylene protons in either of the two enantiomeric E_{min} conformations are diastereotopic[13] and therefore anisochronous. The diastereomeric environments are exchanged by rotation around the aryl-to-nitrogen bond; in either of the two diastereomeric transition states, the molecule has a plane of symmetry which bisects the methylene H–C–H bond angles and the geminal protons thus become enantiotopic and isochronous.

In this and subsequent discussions it is important to distinguish between two different kinds of restriction on rotation about a bond axis, on pyramidal inversion, or on other simple conformational changes, which may give rise to effects in the nmr spectrum. The first sort, which may be termed a "kinetic restriction" to conformational change, involves a barrier to interchange between two conformers and is quantitatively expressed as a free energy of activation for that conformational interchange. If the kinetic barrier is high enough and the conformational change is therefore slow on the nmr time scale, the nmr spectrum shows the superimposed spectra of the two conformers, provided that the two conformers are neither identical nor enantiomeric, or it may show chemical shift nonequivalence between diastereotopic nuclei, if the two

(9) In a geometrically related molecule, 9,10-dihydroanthracene, the calculated barrier for flapping of the folded molecule is *ca.* 1 kcal/mole [F. H. Herbstein, *J. Chem. Soc.*, 2292 (1959)].

(10) F. J. Adrian, *J. Chem. Phys.*, **28**, 608 (1958).

(11) It is noteworthy that the X-ray structure[12] of N-methylacetanilide has a conformation corresponding to E_{min}, *i.e.*, with $\phi = 90°$.

(12) B. F. Pedersen and B. Pedersen, *Tetrahedron Letters*, 2995 (1965).

(13) The terms "enantiotopic" and "diastereotopic" refer to groups or atoms which reside in enantiomeric and diastereomeric environments, respectively [K. Mislow and M. Raban, in "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. L. Eliel, Ed., John Wiley and Sons, Inc., New York, N. Y., 1967, Chapter 1].

(14) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 78–79.

conformations are identical or enantiomeric. When the temperature is raised to the point where the conformational interchange becomes rapid on the nmr time scale, the signals of the anisochronous groups coalesce and an averaged signal is observed. When the two conformations are identical or enantiomeric their equilibrium populations must be the same on symmetry grounds, whether the temperature is above or below the coalescence temperature. However, this is not the case if the two conformations are diastereomeric. On the basis of symmetry arguments the energies of formation of the two conformers must be different and consequently their populations must be different. In such a case one may speak of a "thermodynamic restriction" to conformational change. Even if the conformational change is rapid enough on the nmr time scale to provide signal averaging, the conformational change is still restricted in the sense that the "conformer populations"[15] are not equal. In some cases only one conformer will be significantly populated even though the temperature is above the coalescence temperature. In such a case we must emphasize that the barrier to conformational interchange is a thermodynamic one rather than a kinetic one.

In N-aryl-1,4-dihydro-3(2*H*)-isoquinolinones, in which the aryl substituent possesses a local plane of symmetry perpendicular to the plane of the aryl ring, as in compound **11**, inversion of pyramidal nitrogen in the E_{min} conformation ($\phi = 90°$) interconverts two enantiomeric and hence isergonic and equally populated conformers. It follows that there can be no "thermodynamic restriction" to nitrogen inversion, and since the "kinetic restriction," which cannot be much larger than a few kilocalories/mole, is too small to have any consequence on the nmr time scale at room temperature, the averaged conformation of the molecule is viewed as equivalent to a hypothetical planar (C_s) structure.

By contrast, inversion of pyramidal amide nitrogen in **12**, **14**, and **15** interconverts two diastereomeric derivatives. Here a "thermodynamic restriction" to pyramidal inversion obtains and the conformer populations or residence times will differ depending on the difference in free energy contents of the two diastereomers. Although in the previous discussion the result of rapid pyramidal inversion in the E_{min} conformation of **11** was visualized by reference to a hypothetical "average" C_s conformation in which the amide nitrogen is planar, the situation is different in **12**, **14**, and **15** where the aryl group does not possess a local plane of symmetry perpendicular to the plane of the ring. Here the conformational equilibria with respect to ring inversion and pyramidal inversion are displaced because of the lack of the symmetry plane (thermodynamic restriction), even though no kinetic restriction exists on the nmr time scale. It is such thermodynamic restriction on conformer populations which contributes in large measure to the chemical shift nonequivalence.[15] It should be noted that the occurrence of kinetic restriction to rotation about the N-aryl bond determines that the methylene hydrogens in **12**, **14**, and **15** will be diastereotopic and hence anisochronous. Thermodynamic restriction does not determine the occurrence of shift nonequivalence, but may greatly affect the magnitude of the chemical shift difference.

The occurrence of chemical shift nonequivalence observed for the geminal methylene protons in the acyclic and cyclic amides may thus be directly traced to the symmetry properties of the relevant conformations. It should be noted that restricted rotation or atropisomerism, which is the source of the molecular dissymmetry and the chemical shift nonequivalence of the methylene protons in acyclic amides (**2**–**10**) and cyclic amides (**12**, **14**, and **15**), is not exclusively the structural feature which is capable of rendering the relevant protons diastereotopic. Thus compound **17**, in which the N-substituent contains a chiral center but in which there is no restricted rotation, exhibits the AB quartet which signalizes the chemical shift nonequivalence of diastereotopic methylene protons, in contrast to the N-benzyl analog **16** where only a singlet is observed.

Further evidence for the origin of the discussed chemical shift nonequivalence is provided by the observation that the methylene protons of the N-benzyl group in **18** appear as a sharp signal which remains unchanged even at low temperatures (−30°). Compound **18** is analogous to a conformation of **2** in which the plane of the *o*-tolyl ring has been forced into the plane of the N–CO group. Thus the conformation of **18** is akin to one of the E_{max} conformations ($\phi = 0$ or 180°) of *s-cis*-**2**, and the methylene protons of the N-benzyl group are, on the average, enantiotopic and thus isochronous, in contrast to those of **2** which, because $\phi = 90°$ in the E_{min} conformation, are diastereotopic and thus anisochronous.

Rate constants, k, corresponding to the process of interchange of enantiomeric conformers at the coalescence temperature (T_c) of the AB quartet were estimated in the usual way[16] from the maximum separation of signals, $|\nu_A - \nu_B|_{max}$, and the coupling constant, J_{AB}, using the equation[16b] $k = (\pi/2)\sqrt{\Delta\nu_{max}^2 + 6J^2}$. Thus for the acyclic amide **2**, $|\nu_A - \nu_B|_{max} = 50$ Hz, $J_{AB} = 14$ Hz, $T_c = 135°$, whence $k = 95$ sec^{-1}. From the Eyring equation, $\Delta G^{\ddagger} = 20.0$ kcal/mole for the interconversion of the torsional enantiomers. Similarly, for the deuterated cyclic amide **12**-4-d_2,[17] $|\nu_A - \nu_B|_{max} = 14.6$ Hz, $J_{AB} = 11.9$ Hz, $T_c = 73°$, $k = 51$ sec^{-1}, and $\Delta G^{\ddagger} = 17.3$ kcal/mole. These values for $\Delta G^{\ddagger}$ of racemization of **2** and **12** are in good accord with the activation parameters for the epimerization of two closely related amides,[8] N-methyl-N-(2-methyl-4,6-dibromophenyl)-2-chloro-2-phenylacetamide and N-benzyl-N-(2,4,6-trimethyl-3-bromophenyl)-2-phenoxypropionamide. The choice of a value of $\Delta\nu_\infty$ ($|\nu_A - \nu_B|_{max}$) for **12** occasioned some difficulty. As shown in Figure 1, $\Delta\nu_{AB}$ does not increase to an asymptote as the temperature decreases, but instead passes through an inflection point. Undoubtedly, $\Delta\nu_\infty$ (the chemical shift nonequivalence that would be observed in the

(15) P. M. Nair and J. D. Roberts, *J. Am. Chem. Soc.*, **79**, 4565 (1957); G. M. Whitesides, D. Holtz, and J. D. Roberts, *ibid.*, **86**, 2628 (1964); M. Raban, *Tetrahedron Letters*, 3105 (1966).

(16) (a) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956); A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *J. Am. Chem. Soc.*, **88**, 3185 (1966); for some pioneering applications, see F. R. Jensen, D. S. Noyce, C. H. Sederholm, and A. J. Berlin, *ibid.*, **82**, 1256 (1960); G. Claeson, G. M. Androes, and M. Calvin, *ibid.*, **82**, 4428 (1960); L. W. Reeves and K. O. Strømme, *Can. J. Chem.*, **38**, 1241 (1960); (b) R. J. Kurland, M. B. Rubin, and W. B. Wise, *J. Chem. Phys.*, **40**, 2426 (1964).

(17) Coupling (0.5 Hz) in **12** of the protons on C-1 with those on C-4 contributed to the line width of the AB components. Exchange of the C-4 protons with deuterium considerably sharpened the signals of the C-1 protons in the resulting **12**-4-d_2.

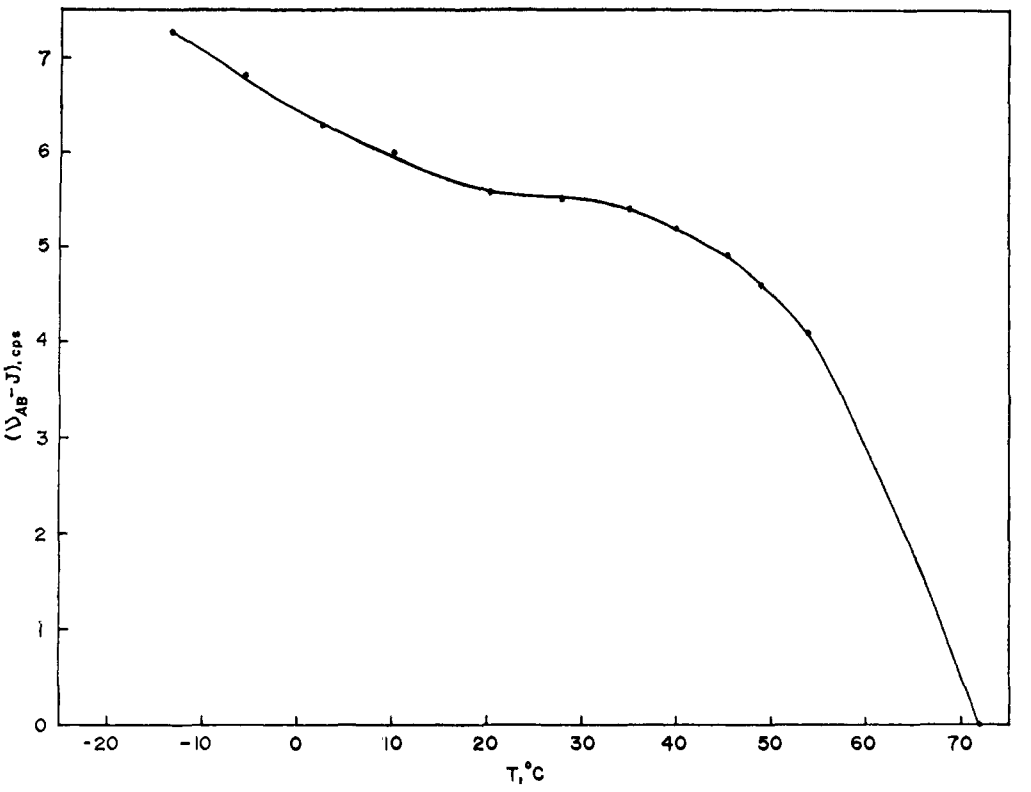


Figure 1.

absence of exchange) is not constant over this temperature range. Apparently changes in conformer populations are taking place in this temperature range in response to thermodynamic restrictions or rapid conformational changes, as discussed above. The decrease in chemical shift nonequivalence with temperature in conformationally mobile systems (in the absence of exchange) is a frequently observed phenomenon and in this system as well the chemical shift nonequivalence of **9** increased from 61.1 to 77.1 Hz on changing the temperature from 40 to $-50°$.[15] A similar anomaly was observed in the $\Delta\nu$ *vs.* temperature plot below T_c for dimethylformamide.[18] Here changes in solute–solute association were regarded as the origin of the anomaly. In the present instance, such changes in solvation and association may also be contributing to the effect although steric hindrance must limit the extent of self-association. The $\Delta\nu_\infty$ chosen for the calculation of $\Delta G^\ddagger$ was that at the inflection point. While this value may be somewhat larger than the true $\Delta\nu_\infty$ at the coalescence temperature it should be noted that the calculated $\Delta G^\ddagger$ is relatively insensitive to $\Delta\nu_\infty$ and an error of 50% in $\Delta\nu_\infty$ only produces an error of about 0.2 kcal in $\Delta G^\ddagger$.

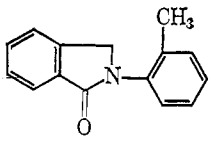
It is interesting to note that of the compounds studied in this series, a number exhibit *apparent* chemical shift equivalence for diastereotopic methylene protons. For example, the methylene protons on C-1 of the cyclic amides **12**, **14**, **15**, and **17** are clearly diastereotopic and anisochronous, as manifested by the AB quartet in the nmr spectrum. Yet the methylene protons on C-4, which must also be diastereotopic, give rise to singlets. This seeming discrepancy is resolved when one considers that increasing distance from the source of anisotropy (*i.e.*, the N-aryl group) from C-4 should lead to increasingly smaller values of $\Delta\nu_{AB}$. The C-1 methylene group is adjacent to the N-aryl group whose conformational preference (*i.e.*, above or below the approximate plane of the dihydro-3(2*H*)-isoquinolinone ring system) is determined by the thermodynamic restriction on nitrogen inversion as discussed above. In the absence of rotation around the N-aryl bond one of the diastereotopic methylene hydrogens on C-1 will spend more time *cis* to the N-aryl group than the other. On the other hand the C-4 methylene is somewhat insulated from the N-aryl group by the carbonyl carbon and a lesser influence on the two (also diastereotopic) C-4 methylene hydrogens might have been anticipated. Among the acyclic amides, the methylene protons of the C-benzyl group are also apparently isochronous. However, they are in fact diastereotopic since the methylene protons of the N-benzyl group in the same molecule give rise to an AB quartet. Here again the distance of the source of anisotropy, *i.e.*, the *o*-tolyl group, leads to very small values of $\Delta\nu_{AB}$ and the chemical shift nonequivalence is not large enough to be observed.

Similarly, in **10**, the diastereotopic methylene hydrogens in the C-benzyl group are insulated from the N-aryl moiety and appear as a singlet although the diastereotopic benzyl methylene hydrogens in the N-benzyl group are considerably chemically shifted (Table I). Benzyl hydrogens seem not to be a sufficiently sensitive probe for the observation of magnetic nonequivalence at this distance from the N-aryl moiety. However, the isopropyl group in the 2-methylpropionamide **4** is a more efficient probe since the larger distance between the diastereotopic nuclei (here the methyl hydrogens in the two diastereotopic methyl groups) permits the detection of the rather small field gradient at this distance from the source of anisotropy, the N-aryl moiety. The mag-

(18) A. G. Whittaker and S. Siegel, *J. Chem. Phys.*, 42, 3320 (1965).

nitude of the nonequivalence of the diastereotopic methyl groups in **4** is understandably small (4 Hz).

The protons on C-1 of the cyclic amide **19** also exhibit apparent chemical shift equivalence (*i.e.*, appear as a singlet) down to −40°. In this connection we may note that the chemical shift nonequivalence decreases from about 50 Hz in the conformationally mobile acyclic amides (Table I) to about 15 Hz in the more rigid dihydro-3(2*H*)-isoquinolinones (Table II) where possibilities for thermodynamic restrictions of conformation are more limited. It is reasonable to expect that in the isoindolin-1-one **19**, where the possibility for conformation preference is even more restricted, a comparable decrease will be observed and



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the resulting chemical shift nonequivalence may be too small to permit the detection of signal separation. Another possibility is that the decrease in the size of the amide ring system in going from a six-membered to a five-membered ring system is accompanied by a decrease in the effective bulk of the groups flanking the nitrogen atom. In consequence, the rotation of the *o*-tolyl group around the benzene-to-nitrogen bond axis is rendered more facile, and the time of residence in each enantiomeric conformation decreases. Since the coalescence temperature is a function both of $\Delta\nu_\infty$, the magnitude of the chemical shift nonequivalence, and the residence time in each of the enantiomeric conformations, either factor may lead to a lowering of the coalescence temperature and the resultant equivalence on the nmr time scale.

Among the acyclic amides studied, the formamide **1** is unique in manifesting *two* N-benzyl methylene proton signals, *both* of which appear as singlets rather than as AB quartets. The two signals correspond to *s-cis* and *s-trans* isomers with reference to torsion around the N–CO amide bond (see below). By analogy with the other acyclic amides (**2–10**), one might have supposed that in each of the two conformers, *s-cis*-**1** and *s-trans*-**1**, the N-benzyl methylene protons are diastereotopic, assuming that on the nmr time scale the plane of the *o*-tolyl group is twisted out of the plane of the amide group. However, the small size of the R group on the carbonyl carbon, *i.e.*, a hydrogen atom, may lower E_{max} and permit rapid interconversion of the enantiomeric E_{min} forms in *s-cis*-**1**. Alternatively, the size of the R group may merely affect the conformer population control resulting from thermodynamic restrictions. The decreased bulk of the R group may, for example, influence the disposition of the N-benzyl group or alternatively the average angle of twist in each E_{min} form, *i.e.*, the steric interaction of the R groups with the *o*-tolyl group may determine the angle of torsion (ϕ) by which this group is twisted out of the N–C–O plane, and ϕ in turn modifies the effect of *o*-tolyl anisotropy on the benzylic protons. Support for the view that thermodynamic restrictions related to the bulk of the R group attached to the carbonyl carbon may affect the magnitude of the chemical shift nonequivalence of the diastereotopic N-benzyl methylene hydrogens derives from a comparison of the $\Delta\nu_{AB}$ values of acyclic amides **1–5** (Table I); it would appear that $\Delta\nu_{AB}$ is roughly proportional to the *A* value of the R group. That a steric rather than an electronic effect is primarily operative is also suggested by the finding (Table I) that **2** (R = CH_3) and **9** (R = CF_3) have similar $\Delta\nu_{AB}$ values, and that the $\Delta\nu_{AB}$ values of **6** (R = C_6H_5), **7** (R = *p*-$CH_3OC_6H_4$), and **8** (R = *p*-$O_2NC_6H_4$) are quite similar.

It is well known that acyclic disubstituted amides may exist in diastereomeric *s-cis* and *s-trans* forms which are detectable by nmr spectroscopy.[19] The barrier between the diastereomeric conformers is appreciable, *i.e.*, in the range of about 10–20 kcal/mole, and may even be high enough to permit the physical isolation of the diastereomers.[20] It is therefore of interest to reiterate that all of the acyclic amides but one (*viz.*, **1**) exhibit a single set of N-benzyl methylene proton signals, *i.e.*, a single AB quartet.[21,22] Similarly, signals in other portions of the molecule in compounds **2–10**, such as the R group attached to the carbonyl and the methyl substituents in the N-aryl group, failed to exhibit the presence of isomers due to restricted rotation about the nitrogen–carbonyl bond. Three explanations suggest themselves to account for the absence of discrete signals due to cisoid and transoid isomers. (a) The signals due to *s-cis* and *s-trans* are fortuitously equal or nearly so. (b) The kinetic restriction is not sufficiently great to allow sufficient lifetimes on the nmr time scale for the observation of separate signals. (c) The thermodynamic restriction to rotation about the N-carbonyl bond is so great that one of the isomers is present in overwhelming preponderance, while the other is not present in sufficient amount to be detectable, *i.e.*, less than about 1%. The fairly large shifts observed for **1**, *viz.*, 24 Hz for the formyl proton, 8 Hz for the N-benzylmethylene protons, and 4 Hz for the tolyl methyl protons, make the eventuality of accidental equivalence highly improbable. Further (*vide infra*), change of solvent from carbon tetrachloride to benzene markedly changes the differences in chemical shift of corresponding groups in the *s-cis* and *s-trans* isomers. Thus, if accidental equivalence had in fact obtained in carbon tetrachloride, a change of solvent should have resulted in the observation of separate signals due to the two isomers. This was not the case; compounds **2–10** showed no indication of cisoid–transoid isomerism either in carbon tetrachloride or in benzene. Available evidence[19,20] also tends to render suspect explanation b, that the observed quartets in **2–10** could have been the resultant of an averaging operation; torsion around the N–CO bond is slow on the nmr time scale at room temperature. In addition, although the temperature at which the signals due to the two isomers of **1** coalesced was rather high (~100°), the nmr spectrum of one of the other amides, **9**, was taken at low temperature

(19) J. A. Pople, W. J. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 366 ff.

(20) A. Mannschreck, *Tetrahedron Letters*, 1341 (1965); H. A. Staab and D. Lauer, *ibid.*, 4593 (1966).

(21) Similar results have been reported by Siddall. Although the formyl derivative of N-(1-phenethyl)-2-chloro-6-methylaniline showed evidence of isomers which differed in configuration (*cis–trans*) about the N-carbonyl bond, "*cis–trans* isomerism was not observed in similar epimeric amides that had large carbonyl substituents."[8b,c]

(22) In N-methylacetanilide, the ratio of *cis* to *trans* isomers is 98.5 to 1.5.[12]

(−50°) and showed no indication of the presence of a second isomer.

The most attractive interpretation of the failure to detect *s-cis* and *s-trans* isomers in compounds **2–10** is to regard this failure as an indication of the thermodynamic restriction on rotation about the nitrogen–carbonyl bond and the resulting overwhelming preponderance of one of the isomers. Even in the formyl derivative the difference in populations is marked (the ratio of isomers is about 8:1). The increase in the ratio of diastereomers (*s-cis*:*s-trans*) which is found in going from **1** to homologs **2–5** almost certainly derives from the increase in size of the R group as it is changed from hydrogen (in **1**) to alkyl (in **2–5**). This increase in size gives rise to steric interactions between R groups and other groups which change the position of the equilibrium and affect the thermodynamic control of other kinds of conformational change such as the average angle of twist of the *o*-tolyl group and the pyramidal inversion at the amide nitrogen, as has been discussed above. Of course, combinations of the three factors may equally give rise to this phenomenon in some cases.

A structurally related compound, N-*t*-butyl-N-benzyl-*o*-toluamide, displays[8f] a similar lack of signal doubling due to *s-cis* and *s-trans* isomerism, although the spectra of the N-methyl-N-benzyl and N-2-propyl-N-benzyl derivatives clearly demonstrate the presence of cisoid and transoid isomers.[8f] Although Siddall and Gardner regard this as evidence that the rotation about the N-carbonyl bond is rapid on the nmr time scale even at −40° because "the entire 360° of rotation has become crowded," [8f] we feel that the existence of thermodynamic restriction to rotation provides a more palatable alternative. More recently Siddall[8g] has recognized that thermodynamic restrictions may be implicated in the failure to detect *cis–trans* isomerism in related amides, although he has not revised his interpretation of the behavior of N-*t*-butyl-N-benzyl-*o*-toluamide.

The configuration of the preponderant, to all appearances exclusive, isomer of compounds **2–10** may be elucidated by comparison with the cyclic analogs in which the configuration around the N–CO bond is known and invariable, *i.e.*, compounds **11–17** for the *s-trans* configuration and compound **18** for the *s-cis* configuration. From previous work[23] it seems reasonable to expect that a change of solvent from carbon tetrachloride to benzene or other aromatic solvents (aromatic-solvent-induced shift, ASIS[23d]) would shift the various signals of amide solutions to different extents, depending on the position (*s-cis vs. s-trans*) of the nuclei, *i.e.*, in a manner characteristic of geometry. As seen from Table III, our expectations were not disappointed. The first entry (**18**) characterizes *s-cis* amide geometry: a large upfield shift (17 Hz) of the aromatic methyl protons and a small downfield shift (2 Hz) of the N-benzyl methylene protons. The next three entries in Table III (**11–13**) characterize *s-trans* amide geometry: a large upfield shift (*ca.* 30 Hz) of the N-benzyl methylene protons and a small upfield shift (*ca.* 3 Hz) of the aromatic methyl protons. Inspection of the chemical shift solvent displacement suffered by the acyclic amides **2–10** (Table III) clearly reveals that all exhibit a pattern characteristic of *s-cis* geometry.[24] The substantial upfield shift of both sets of protons in the trifluoro compound **9** renders an assignment of the configuration ambiguous in this instance.

In the formamide **1**, all signals are doubled, and in the intensity ratio 7.5:1.0, corresponding to a difference in free energy of the two diastereomers of about 1 kcal/mole. The composition of the mixture of conformers was only slightly sensitive to variations in temperature, and the two signals for each kind of proton coalesced to singlets at about 100°. The major diastereomer was assigned the *s-cis* conformation and the minor diastereomer the *s-trans* conformation on the basis of the solvent dependence of the chemical shifts (Table III); the two compounds of the mixture of **1** showed clearcut differences which were characteristic of the two configurations, as discussed above.

Table III. Chemical Shift Differences (ASIS), CCl_4–Benzene[a]

Compd	Δ, Hz	
	CH_2N[b]	Me (aromatic)
18	−2	+17
11	+27	0
12	+28	+3
13	+31	+4
2	−3	+15
3	−3	+15
4	−3	+10
5	−5	+13
6	−2	+6
10	−4	+10
9	+11	+20
1 (*s-cis*)[c,d]	0	+11
1 (*s-trans*)[c,e]	+20	−2

[a] Difference are in hertz units. Plus sign denotes upfield shift upon changing the solvent from carbon tetrachloride to benzene. [b] Reference is made to the center of the AB quartet. [c] See text for definition of geometry. [d] This conformer is the major component (see text). [e] This conformer is the minor component (see text).

The above assignments are supported by the following arguments. The signal for the benzylic methylene protons of the major component of **1** is at lower field (τ 5.23) relative to that of the minor component (τ 5.40). The reverse situation exists for the signal of the aldehydic proton; the strong signal occurs at higher field (τ 1.90), the weak signal at lower (τ 1.50). This result is easily rationalized if it is assumed that the major form is the *s-cis* diastereomer, in which the benzylic methylene protons are *cis* to the carbonyl group and because of the anisotropy of the carbonyl function are expected to be deshielded with respect to the same kind of protons in the *s-trans* isomer. Similarly, the aldehydic proton in the major (*s-cis*) form is *cis* to the *o*-tolyl group and if the plane of the *o*-tolyl group is twisted out of the plane of the N–CO group, the aldehydic proton will experience a diamagnetic component perpendicular to the plane of the *o*-tolyl group and will consequently be shielded relative to the corresponding proton in the *s-trans* isomer.

(23) (a) J. V. Hatton and R. E. Richards, *Mol. Phys.*, 5, 139, 153 (1962). (b) R. M. Moriarty, *J. Org. Chem.*, 28, 1296 (1963). (c) R. M. Moriarty and J. M. Kliegman, *Tetrahedron Letters*, 891 (1966). (d) For a recent comprehensive review of the use of nmr solvent shifts, see P. Laszlo in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. 3, J. W. Emsley, J. Feeney, and L. M. Sutcliffe, Ed., Pergamon Press, Oxford, 1967.

(24) This geometry has been assigned to N-methylacetanilide both in solution and in the solid state.[12]

Experimental Section

General Procedure for the Preparation of N-Substituted 1,4-Dihydro-3(2*H*)-isoquinolinones (11–17). A mixture of 2-isocumaranone (0.05 mole) and the desired aromatic amine (0.055 mole) was heated in a steel bomb at 220–250° for 24 hr. After cooling, the reaction mixture was dissolved in ether (or chloroform), and the solution was washed with dilute hydrochloric acid, dilute sodium hydroxide, and finally water. After drying over anhydrous magnesium sulfate, the solvent was evaporated, and the residue was distilled at reduced pressure. Chromatography on Florisil, using ethyl acetate–hexane or chloroform–hexane as developing solvents, resulted in analytically pure products.

All substances gave a single spot on thin layer chromatography. Infrared and nmr spectra were consistent with the assigned structures in all cases.

General Procedure for the Preparation of N-Benzyl-N-(*o*-tolyl)-amides 1–10. A solution of N-benzyl-*o*-toluidine (0.05 mole) and triethylamine (0.05 mole) in 50 ml of ether was cooled in an ice bath, and a solution of the desired acid chloride (0.05 mole) in 50 ml of ether was added dropwise to the stirred amine solution. After being allowed to stand overnight at room temperature, the reaction mixture was poured over ice. The ethereal layer was washed with dilute hydrochloric acid, dilute sodium hydroxide, and water. After drying over anhydrous magnesium sulfate, the ether solvent was removed *in vacuo*, and the residue was distilled at reduced pressure, or crystallized from an appropriate solvent. Yields ranged from 40 to 80%.

The formamide **1** and the trifluoroacetamide **9** were prepared by refluxing N-benzyl-*o*-toluidine in formic acid and trifluoroacetic anhydride, respectively. The reaction mixtures were worked up as described above.

Deuteration of N-(*o*-Tolyl)-1,4-dihydro-3(2*H*)-isoquinolinone (12-4-d_2). A solution of sodium methoxide (4.0 g) in 35 ml of deuterium oxide was added to a solution of N-(*o*-tolyl)-1,4-dihydro-3(2*H*)-isoquinolinone (5.0 g) in 35 ml of anhydrous dimethylformamide and the mixture was stirred under nitrogen at 80° for 2.5 hr. After the reaction mixture had been cooled to 0°, 10 ml of deuterium oxide was added. The solid was filtered and washed with deuterium oxide, yield 4.1 g. Essentially complete exchange (97%) of both C-4 methylene hydrogens was indicated by the nmr spectrum. After an additional exchange, the doubly deuterated amide was purified by chromatography on Florisil (250 g). The product was eluted with 1:9 ethyl acetate–hexane and crystallized from the same ethyl acetate–hexane solvent mixture; mp 100–102°. The nmr spectrum indicated complete disappearance of the C-4 methylene signal, while the C-1 methylene signal was recorded as an AB quartet lacking the fine splitting which was observed with the nondeuterated compound.

2-(*o*-Tolyl)isoindolin-1-one (19). Phthalide (6.70 g) and *o*-toluidine (5.88 g) were heated in a steel bomb at 250° for 48 hr. The reaction mixture was dissolved in ether and extracted with 1 *N* hydrochloric acid and then shaken twice for 0.5 hr with 1 *N* sodium hydroxide in order to remove unreacted phthalide. The ethereal solution was washed with water and dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*, yield 7.2 g. The crude product was chromatographed on Florisil (250 g, ethyl acetate–hexane eluent) and recrystallized from ethyl acetate–hexane, mp 99–100°, single spot on thin layer chromatography. The nmr spectrum showed a singlet (down to a temperature of −40°) at τ 5.38 assigned to the C-3 methylene protons.

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.64; H, 6.14; N, 6.36.

1-Benzyl-8-methyl-3,4-dihydro-2(1*H*)-quinolinone (18). Sodium hydride (1.25 g) was added to a solution of 8-methyl-3,4-dihydro-2-(1*H*)-quinolinone[25,26] (4.2 g) in 35 ml of anhydrous dimethylformamide. Dissolution of the sodium hydride was facilitated by brief warming on a steam bath. The stirred solution was cooled in an ice bath, and benzyl chloride (4.15 gm) was added dropwise during 15 min. After stirring for an additional 15 min at 0°, the reaction mixture was heated briefly on a steam bath and allowed to stand overnight at room temperature. The solvent was evaporated *in vacuo*; the residue was partitioned between water and chloroform and the organic layer dried over anhydrous magnesium sulfate. Evaporation of the chloroform solvent *in vacuo* afforded 6.5 g of an oil which showed no indication of absorption at 2.5–3 μ (N–H stretch). The product was chromatographed on Florisil (300 g) using ethyl acetate–hexane mixtures for elution. Fractions were combined on the basis of analytical thin layer chromatograms. The product (5.2 g) was distilled; bp 150° (0.1 mm), single spot on thin layer chromatography. The nmr spectrum exhibited a singlet (at room temperature and down to −40°) at τ 4.91 assigned to the N-benzyl methylene protons.

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.87; N, 5.57. Found: C, 81.18; H, 6.99; N, 5.53.

(25) Using the Friedel–Crafts reaction conditions described[26] led to the formation of two additional methyl isomers from which the 8-methyl compound was separated by chromatography on Fluorisil, mp 128–130° (lit.[26] mp 112°). Reduction of this product with diborane yielded 8-methyl-1,2,3,4-tetrahydroquinoline, identical in all respects with an authentic sample which was prepared by catalytic reduction of 8-methylquinoline.

(26) F. Mayer, L. van Zütphen, and H. Philipps, *Ber.*, **60**, 858 (1927).

An *ortho* Effect in the Mass Spectra of Some Carbonyl-Substituted Phenylferrocenes

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Abstract: An unusual type of mass spectral decomposition of methyl esters, loss of formaldehyde, is found in certain *ortho*-substituted ferrocenylbenzenes. The reaction is interpreted in terms of a mass spectral *ortho* effect with different geometrical requirements from those previously noted, and suggests that there may be a general class of *ortho*-effect reactions not predictable by the six-membered ring rule. Other features of the spectra of carbonyl-substituted phenylferrocenes follow patterns typical of the compound types.

When the mass spectra of positional isomers of substituted aromatic rings are compared, there are often obvious differences between the fragmentation pattern of the *ortho* isomer and those of the *meta* and *para* isomers. Distinction between *ortho* isomers and the others may, in these cases, be made on the basis of the mass spectrum. Previous observations of this useful[2–4] type of rearrangement have been made in the

(1) DuPont Teaching Fellow, 1966–1967; Enka Summer Fellow, 1966.

(2) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, p 194.

(3) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, Inc., New York, N. Y., 1966: (a) p 133; (b) p 200.