REFERENCES

(1) M. B. Kreig, "Green Medicine," Rand McNally, New York, N. Y., 1964.

(2) W. LaBarre, "The Peyote Cult," Shoe String Press, Hamden, Conn., 1964.

(3) A. Marriott and C. K. Rachlin, "Peyote," Thomas Y. Crowell, New York, N. Y., 1971.

(4) A. Heffter, *Chem. Ber.*, **29**, 216(1896).

(5) G. J. Kapadia and M. B. E. Fayez, *J. Pharm. Sci.*, **59**, 1699 (1970).

(6) J. Lundstrom, *Acta Pharm. Suecica*, **8**, 485(1971).

(7) J. Poisson, *Ann. Pharm. Fr.*, **18**, 764(1960).

(8) S. Agurell, *Lloydia*, **32**, 206(1969).

(9) *Ibid.*, **34**, 183(1971).

(10) N. L. Britton and J. N. Rose, "The Cactaceae," vol. 4, Carnegie Institution, Washington, D. C., 1923.

(11) H. Bravo, "Las Cactaceas de Mexico," Universidad Nacional de Mexico, Mexico, 1937.

(12) X. A. Dominguez, S. Escarria, and C. Perez E., *Planta Med.*, **18**, 315(1970).

(13) M. J. Superweed, "Herbal Highs," Stone Kingdom Syndicate, San Francisco, Calif., 1970, p. 5.

(14) W. J. Keller and J. L. McLaughlin, *J. Pharm. Sci.*, **61**, 147 (1972).

(15) K. M. Kelley Hornemann, J. M. Neal, and J. L. McLaughlin, *J. Pharm. Sci.*, **61**, 41(1972).

(16) L. Benson, in "Flora of Texas," vol. 2, part II, C. L. Lundell, Ed., Texas Research Foundation, Renna, Tex., 1969, p. 307.

(17) J. L. McLaughlin and A. G. Paul, *Lloydia*, **29**, 315(1966).

(18) J. M. Neal, P. T. Sato, C. L. Johnson, and J. L. McLaughlin, *J. Pharm. Sci.*, **60**, 477(1971).

(19) J. M. Neal, P. T. Sato, and J. L. McLaughlin, *Econ. Bot.*, **25**, 382(1971).

(20) W. W. Speir, V. Mihranian, and J. L. McLaughlin, *Lloydia*, **33**, 15(1970).

(21) W. J. Keller and F. R. Cole, *ibid.*, **32**, 498(1969).

(22) I. Stewart, W. F. Newhall, and G. J. Edwards, *J. Biol. Chem.*, **239**, 930(1964).

(23) I. Stewart and T. Wheaton, *J. Org. Chem.*, **33**, 471(1968).

(24) W. J. Keller, J. L. McLaughlin, and L. R. Brady, *J. Pharm. Sci.*, **62**, 408(1973).

(25) J. M. Neal and J. L. McLaughlin, *Lloydia*, **33**, 395(1970).

(26) T. A. Wheaton and I. Stewart, *ibid.*, **33**, 244(1970).

(27) L. Reti, in "The Alkaloids," vol. 3, R. H. F. Manske and H. L. Holmes, Eds., Academic, New York, N. Y., 1953, p. 330.

(28) T. A. Henry, "The Plant Alkaloids," 4th ed., Blakiston, Philadelphia, Pa., 1949, p. 633.

(29) T. Sollmann, "A Manual of Pharmacology," 8th ed., W. B. Saunders, Philadelphia, Pa., 1957, pp. 507, 513, 514.

(30) R. A. Heacock, O. Hutzinger, and B. D. Scott, *Can. J. Chem.*, **43**, 2437(1965).

ACKNOWLEDGMENTS AND ADDRESSES

Received March 27, 1972, from the *Drug Plant Laboratory, College of Pharmacy, University of Washington, Seattle, WA 98105*

Accepted for publication July 12, 1972.

Supported by U. S. Public Health Service Grants MH-17128-03 and MH-21448-01 from the National Institute of Mental Health.

P. T. Sato acknowledges support as a National Science Foundation undergraduate research participant 1971 and expresses appreciation to Mr. William J. Keller, University of Washington, for valuable discussions and assistance. The authors thank Dr. L. Benson, Pomona College, for confirming the plant identification. For samples of reference compounds, gratitude is expressed to Dr. A. Brossi, Hoffmann-La Roche; Dr. S. Archer, Sterling-Winthrop Research Institute; and Dr. I. Stewart, University of Florida. Thanks are due to Dr. W. Benz, Hoffmann-La Roche, for obtaining mass spectra.

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Simplified NMR Spectra of Bifunctional Tropanes Induced by the Paramagnetic Shift Reagent Tris(dipivalomethanato)europium(III)

GARY S. CHAPPELL▲, BERNARD F. GRABOWSKI, ROBERT A. SANDMANN, and DAVID M. YOURTEE

Abstract □ Tris(dipivalomethanato)europium(III) has been used as an NMR shift reagent to obtain simplified spectra of tropine, pseudotropine, nortropine, nortropinone, and tropinone. All compounds gave spectra at 60 MHz., which could be interpreted with the aid of spin-spin decoupling. Insofar as the Karplus rule holds for the piperidine ring system, deshielded spectra clearly evidenced a distorted chair form predominating in the conformational equilibrium of α- and β-tropines and tropinones. The results demonstrate the applicability of the shift reagent used with bifunctional systems containing two different heteroatoms. The observed order of coordination was secondary amine > secondary alcohol > tertiary amine ≧ ketone.

Keyphrases □ Tropanes, bifunctional—simplified NMR spectra induced by tris(dipivalomethanato)europium(III) □ Tris(dipivalomethanato)europium(III)—used as NMR shift reagent to produce simplified spectra for bifunctional tropanes □ NMR spectroscopy—tris(dipivalomethanato)europium(III) shift reagent used to produce simplified bifunctional tropane spectra □ Paramagnetic shifts induced by tris(dipivalomethanato)europium(III)—simplified spectra of bifunctional tropanes

Tris(dipivalomethanato)europium(III) (I) has been the most extensively studied of the NMR shift reagents now available. This reagent produces paramagnetic shifts that remarkably simplify the NMR spectra of compounds containing heteroatoms for coordinative bonding with the reagent lanthanide.

The europium deshielded NMR represents a time-averaged spectrum between free substrate molecules

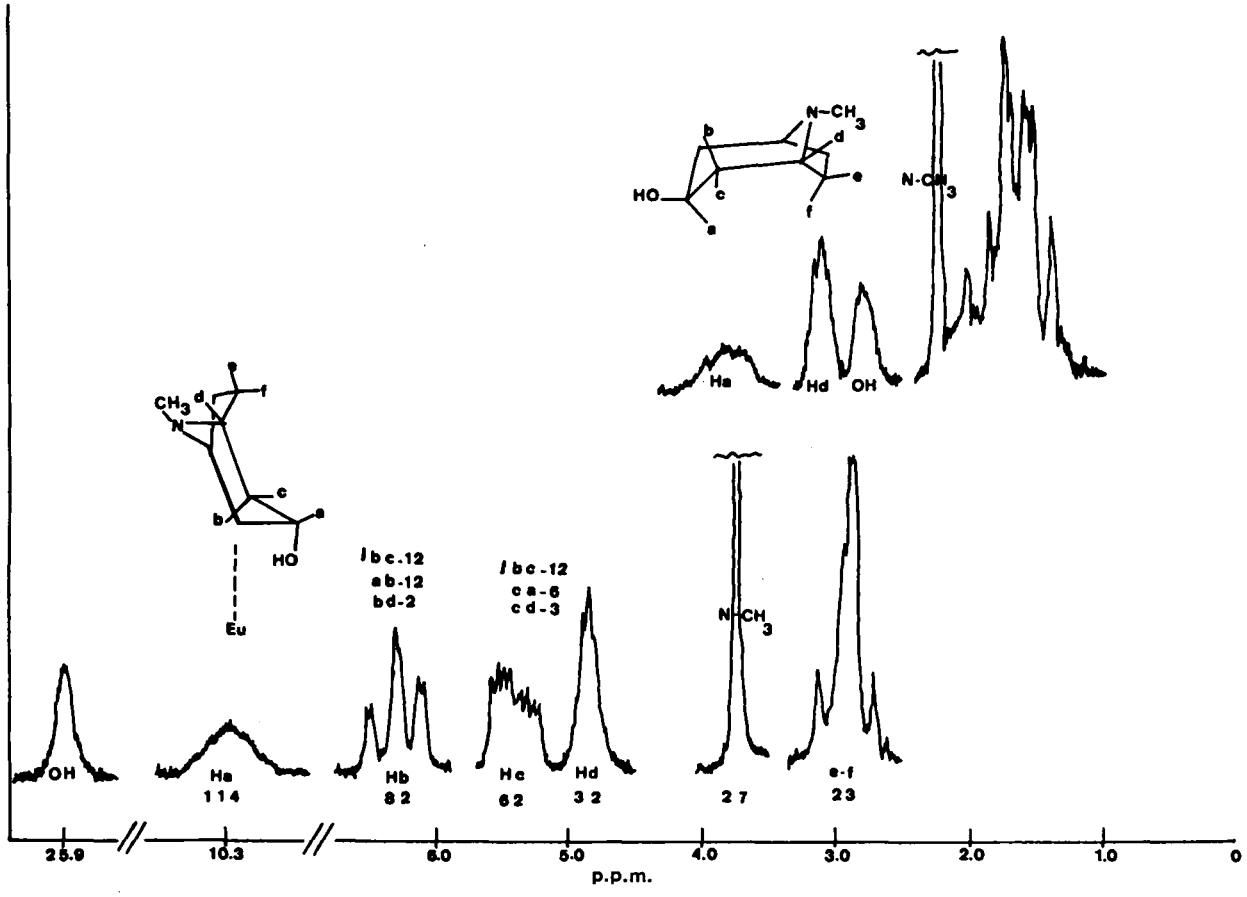


Figure 1—*Pseudotropine (II) at 60 MHz. in deuterochloroform. Key: top, without I treatment; and bottom, shifted spectra resulting at 0.35 mole ratio I/II. Numbers immediately below proton assignments represent the relative rates of proton shift between 0.2 and 0.8 mole ratio* ($\Delta\delta \times 10^1$). *The alignment with the europium complex and the conformation indicated in the molecular diagram are discussed in the text.*

and those associated with the shift reagent through lone-pair electrons. The paramagnetic shifts induced in complexes of europium appear to be the result of a predominately pseudocontact mechanism and do not appreciably broaden peaks or affect the spin-spin coupling constants as proton signals are shifted. The pseudocontact expression given in simplified form is:

$$\frac{\Delta H_i}{H_0} = \left(\frac{3\cos^2\chi_i - 1}{r_i^3}\right)K \qquad \text{(Eq. 1)}$$

where ΔH_i is the average shift defined as the difference in resonance position for the ith substrate proton in the paramagnetic complex and in the diamagnetic ligand. K is a constant incorporating in part the g tensor anisotropy and is a characteristic of the lanthanide under consideration. K is assumed to have the same value for all protons of a substrate molecule. χ_i is the angle between the ith proton and the principal axis, and r_i is the distance from the ith proton to the europium atom[1] (1-9).

Since pseudocontact shifting of NMR spectra offers a simple approach to stereochemical problems, it is useful to assess the effect of such reagents on a wide variety of compounds of biological activity. In conjunction with our interest in the preparation of centrally acting bicyclic amine derivatives (10), investigations were begun on the effect of europium complexes on this class of compounds. Previously, Ohashi *et al.* (11) investigated the effect of small upfield and downfield contact shifts on some tropanes. The current paper reports the effect of I on 3-hydroxy- and 3-ketotropanes (II–VI). This series is attractive in that it (*a*) offers the possibility of much needed simplification while it (*b*) tests the more practical utility of the shift reagent in resolving questions of stereochemistry when the substrate contains dissimilar heterobifunctionality with some conformational mobility present.

The 60-MHz. NMR spectra of 3-substituted tropanes (*e.g.*, Fig. 1, top) show methine (*a*) and bridgehead (*d*) protons as clearly spaced absorptions. The hydroxy proton may be revealed depending on concentration. The *N*-methyl of tropane is seen as a sharp singlet; however, in simple derivatives this signal is found within an uninformative envelope of nearly coincident methylene protons (*b*, *c*, and *e*, *f*). The closely spaced methylene envelope leaves detailed spin decoupling analysis with much to be desired.

Most pseudocontact studies have shown the effect on compounds containing only one type of heteroatom. The tropane series with two different heteroatoms con-

[1] Pseudocontact is defined as the interaction arising from the combined action of an anisotropic g tensor and a through space dipolar hyperfine coupling (as opposed to a through bond spin delocalized hyperfine contact interaction). The lanthanide has a short electron spin lattice relaxation time, contributing to inefficient proton relaxation and little line broadening.

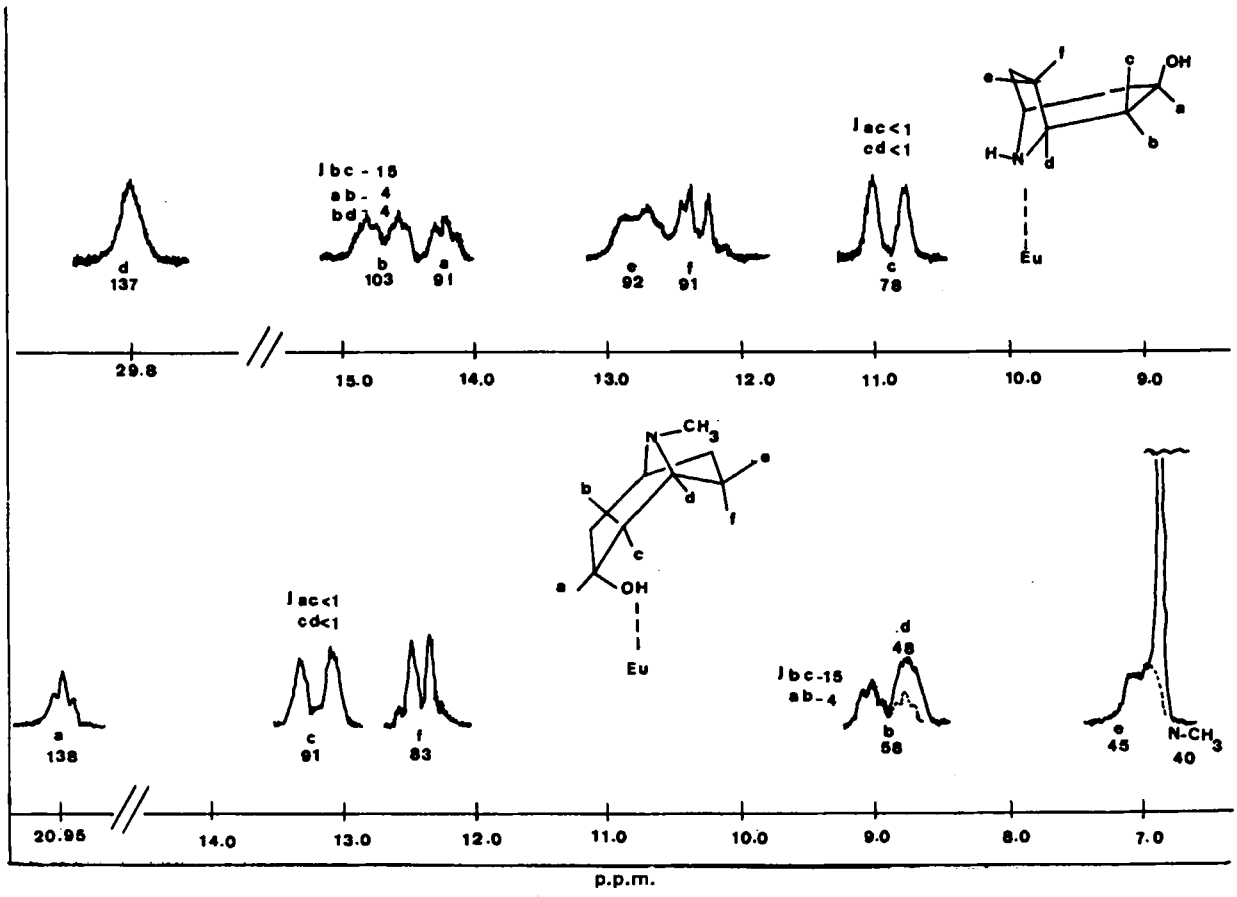
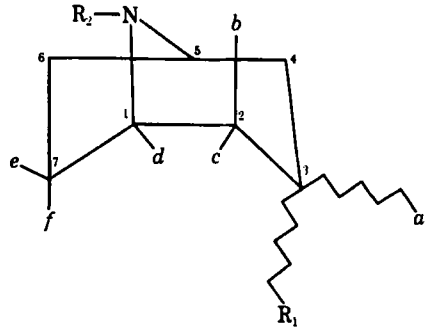


Figure 2—*The 60-MHz. shifted spectra of IV and III as occurring at 0.75 mole ratio I/substrate. Numbers immediately below proton assignments represent* $\Delta\delta$ *as in Fig. 1. The upfield half of resonance for proton* b *(bottom) was taken from the spectrum at a mole ratio where* d *and* b *resonances were independent. Resonance for proton* e *was similarly obtained.*

stitutes a practical "intramolecular competition" experiment[2] and tests the ability of the shift reagent to be selective enough in complexation to yield interpretable NMR spectra. In this regard the tropanes are particularly good models for study. With I, only one deshielded signal would be expected for each type of proton (*e.g.*, grouping for *d* integral = 2) since a plane of symmetry exists through both heteroatoms. An additional practical test of the usefulness of the shift reagent comes about through the conformational mobility at C-2 and C-4 of tropane and the axial–equatorial orientation possible about trivalent nitrogen.

The pseudocontact deshielded spectra should lead to structural information on two levels of sophistication. First, as an "empirical approach," the deshielding process should expose spin-spin coupling constants (*J*) that would allow assignment of predominate conformers in a relative manner, *i.e.*, in comparison to Karplus' (22) interpretations. This advantage, so long as resonance lines are sharp and unperturbed by induced conformational changes, is realized whether the exact mechanism producing the shifts has been correctly understood or not. Secondly, as a "parameter approach," the europium–proton distances could, if theory is correctly interpreted, be calculated from the rate of proton shift for a refined stereochemical outline. Shift data from conformationally immobile substrates having constant average europium–proton distances have been used on numerous occasions for testing the second approach. In these cases, data demonstrate a linear relationship between the rate of proton shift and the concentration ratio



amino alcohols

II: $R_1 = \beta$-OH, $R_2 = CH_3$
III: $R_1 = \alpha$-OH, $R_2 = CH_3$
IV: $R_1 = \alpha$-OH, $R_2 = H$

amino ketones

V: R_1, a = (=O), $R_2 = CH_3$
VI: R_1, a = (=O), $R_2 = H$

[2] Hart and Love (12) pointed out the importance of accumulating information regarding preferred sites of complexation and reported effects of I on morpholine and several other polyfunctional molecules. During the time this research was underway, Fleming *et al.* (13) reported the effect of I on the spectra of hydroxy acids. Other reports that have appeared regarding polyfunctional substrates include: Hinckley *et al.* (14) on testosterones, Tjan and Visser (15) on furanones, Osashi *et al.* (16) on contact shifts in nicotine, Brederode and Huysmans (17) on bis(4-aminocyclohexyl)methane, Taylor and Walters (18) on nitrogen–phosphorus bidentate ligands, Skolik *et al.* (19) on lupanine, Tronchet *et al.* (20) on sugar oximes, and Farid *et al.* (21) on hydroxyoxetans.

of shift reagent to substrate (*e.g.*, 21, 23). Hinckley *et al.* (14) appropriately emphasized the cautions and difficulties in the latter approach for bifunctional substrates. Accordingly, it was desired to test the parameter approach in greater detail and to set the stage for further reports by offering here the results with the "empirical approach."

EXPERIMENTAL

Substrates—Nortropine (IV) was prepared by the method of Willstätter (24) and was found to be identical to a product prepared by the method of Perrine (25). Pseudotropine (II) was prepared by lithium aluminum hydride reduction of tropinone (V) (26) and independently from tropine (III) (27). Purification was by silica gel column chromatography and sublimation. Analysis was within accepted limits. Nortropinone (VI) was prepared from 2,5-dimethoxytetrahydrofuran and acetonedicarboxylic acid (28) and was confirmed as its *N*-benzoyl derivative.

Other compounds used were purchased as authentic[3] and then recrystallized or redistilled to literature purity as required. 1-Methyl-4-piperidone, pseudopelletierine, and 3-quinuclidinone were also treated with I or the more soluble tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione)europium (VIII), and their shifted spectra were found useful in the interpretation of results presented in this paper.

NMR Investigation—All NMR work work was performed on a 60-MHz. spectrometer[4]. Deuterochloroform, used as solvent, was dried over preheated (120°) 4-A molecular sieves to remove traces of acid which might decompose the reagent complex. Chemical shift values reported are relative to internal tetramethylsilane (VII) and are in parts per million. Coupling constants (J) are reported in hertzes.

Substrate concentrations ranged from 1.4 to 1.9 $\times$ 10^{-4} mole in 0.4 ml. deuterochloroform. Compound V and pseudopelletierine and III and II were run at the same mole concentrations of 1.46 and 1.91 $\times$ 10^{-4} mole, respectively. Study compounds were analyzed at successive additions of 5–15 mg. of I for six to 12 additions, depending on solubility and the need to separate coalescing peaks for spin decoupling dictated by each substrate. Sample tubes were warmed after each addition of I to effect solution. Solutions were allowed to equilibrate to probe temperature before recording shifted spectra. Sample solutions of tertiary amino ketones gave the lowest solubility (shift reagent/substrate mole ratio of 0.53 for V). Solutions of secondary amines and tertiary amino alcohols permitted mole ratios[5] close to 1.0.

Proton assignments were based on integration and spin decoupling of suitably shifted spectra for each compound and aided by comparisons among substrates. Resonance from the tertiary butyl absorption of the europium reagent complex appeared upfield of VII in all cases except VI and pseudopelletierine. In these cases, reagent absorption moved from just downfield of VII to upfield of VII after several additions of reagent complex. VII was easily located in all spectra. In the usual manner to aid in interpretation of results, the data generated from shifted spectra were plotted on coordinate axis, with the shift of each proton in δ (p.p.m.) units as the ordinate and I/substrate mole ratios as the abscissa. The $\Delta\delta$ values reported were abstracted from these plots.

RESULTS AND DISCUSSION

NMR work with deuterium chloride salts has shown that the *N*-substituent in tropanes is predominantly equatorial. On quaternization, the small proportion of *N*-axial conformer present reacts faster to yield a large proportion of product in which the entering group takes up the equatorial position (29). In recent years there has been considerable research regarding the conformation of the tropane piperidine ring.

Early X-ray analysis of II free base and tropine hydrobromide indicated a chair conformation for both of these compounds (26, 30). IR spectral evidence is contradictory with regard to intramolecular hydrogen bonding in II (31, 32). Dipole moment studies in conjunction with an NMR investigation of partially deuterated tropanes led to the conclusion that α-substituted tropanes (*e.g.*, III) probably exist with a major proportion in the deformed chair and a minor proportion in the boat form. 3β-Substituted derivatives such as the 3-cyano derivative were postulated to exist in the chair form. Conclusions were aided by observations of spin-spin coupling of the exposed methine proton as viewed in light of the Karplus rule. Deuteration permitted the approximate assignment of methylene protons, but the protons of the methylene envelope were not used to refine conclusions (26).

More recent X-ray analysis coupled with NMR work indicated a deformed chair for II (33). Because of the replacement of 6β- and 7β-protons by oxygen in scopolamine and scopine, C-2 and C-4 methylene protons are more evident in the NMR and determination of conformation becomes more conclusive. An elegant study of these derivatives, using spin decoupling at 60 MHz., defined J values and fortified the conclusion that α-substituted tropanes exist in the chair form with some distortion (34). Contact shift studies noted the differences in both upfield and downfield shifts induced in 1,4-dimethylpiperidine on the one hand and those occurring in tropinone and 3-tropine esters on the other. Results led to the conclusion that the tropanes exist in a nearly semiplanar form (11). Our results with the effect of I on tropanes are in general agreement with recent findings of distorted chair forms for the α-tropines and tropinones. Compound II also appears to exist predominately in a distorted chair form.

A Lewis acid–base relationship exists between a europium complex and substrate (3). Selective association between I and the two different heteroatoms would be expected (12). Work with molecular models in consideration of the rate of shift found among the protons in the substrates studied and the required relative proton–europium distance[6] indicates that tertiary amino alcohols associate with europium *via* the hydroxy function whereas secondary amino alcohols associate with the nitrogen atom. Amino ketones appear to associate with the amine function. The latter relation was more apparent in VI and 1-methyl-4-piperidone than in V. The results do not conclusively rule out bidentate behavior for the ligands of V at the low mole ratio obtained with I. However, as a result of the complexation encountered, an adequate separation of proton resonances was evident among shifted spectra. All protons were seen as unique absorption for each compound studied (Figs. 1–3), except for the *e* and *f* resonances of II and IV.

Amino ketones exhibited linear plots of mole ratio *versus* chemical shift throughout the range of study permitted by solubility of the europium complex in deuterochloroform. Amino alcohols, however, showed slight curvature for some protons on these plots. This result could be taken as an indication of conformational change induced by the paramagnetic shift reagent or as a slight change in the predominate bonding equilibrium of the paramagnetic shift reagent between the two basic sites in the molecule. There is evidence that slight deviation from linearity is not a result of induced conformational changes. Conformationally free 1-methyl-4-piperidone gave linear results. The conformational mobility of this derivative was clearly evident in shifted spectra wherein, as a result of conformer averaging, no resolution was obtained between axial–

[3] Aldrich Chemical Co. and K & K Laboratories.

[4] Varian Associates T-60.

[5] The low solubility of I–substrate complex in deuterochloroform for the compounds in this study prevented evaluation to the limit of saturation of both functional groups. However, 3-quinuclidinone, tropine, and several other substrates were treated with the more soluble VIII, permitting evaluation through a 2-mole ratio. These results will appear in a future publication.

[6] Alignment of the tropanes with europium was immediately apparent because of variation inherent in the series. Results have usually been interpreted considering the angular factor as invarient with r estimated from $\Delta\delta$ values. The importance of the angular variable has been demonstrated (1). Although it is clear that the induced shift decreases with increasing distance between the proton and coordinating functionality, the exponent of r has been questioned (19). Briggs *et al.* (36) pointed out that, for a potentially bidentate ligand, the geometric factor requires two angular variables. Poly(monodentate) molecules may require weighted means of shifts expected for the various modes of coordination with the lanthanide. Dew Horrocks *et al.* (37) suggested, from X-ray crystallographic results with the eight-coordinate bis(4-picoline) adduct of 2,2,6,6-tetramethylheptane-3,5-dionatoholmium, that the assumption of axial symmetry for shift reagent adducts may not be totally valid and detailed structural inferences should be made cautiously. We have thus avoided reporting empirically derived specific r values and prefer to subject data to careful computer analysis before reporting this aspect.

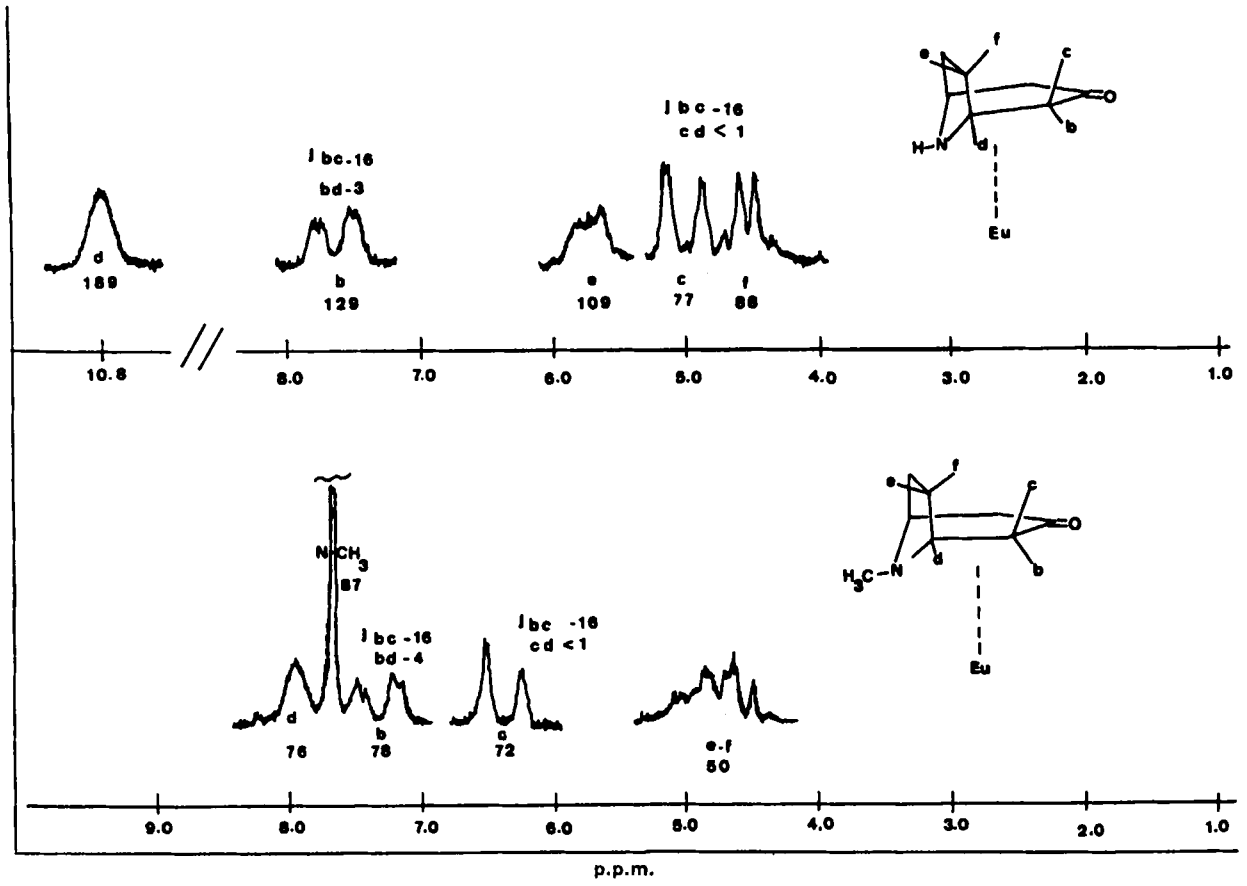


Figure 3—*Protons of VI and V as occurring at 60 MHz. in deuterochloroform solution containing 0.40 mole ratio I/substrate. Numerical data have the same meaning as in Figs. 1 and 2.*

equatorial protons of a methylene set. Moreover, no conformational change was found for the tropanes, as best evidenced by the failure of exposed protons to change significantly[7] in peak width or coupling constant from the normal deuterochloroform spectrum to the final addition of reagent. It has been shown that contact shifts are more important near the point of complex–substrate association (9). Results with the methine protons of III and II, which are geminal to the associating heteroatom, show that contact contribution was insufficient to alter J values significantly. Detailed results in line with empirical approach to data interpretation are presented below.

Amino Alcohols—The NMR of II (Fig. 1) without I revealed the methine resonance as a broad multiplet (W 1/2 = 24 Hz.). On addition of I, the methine remained as a broad multiplet (W 1/2 = 24 Hz.). The coupling constants were found to be $J_{bc} = 12$, $J_{ac} = 6$, $J_{ab} = 12$, $J_{bd} = 2$, and $J_{cd} = 3$. These data suggest a slightly distorted chair conformation. The coupling constant $J_{ac} = 6$ is somewhat larger than is normally observed for axial–equatorial coupling (2–4 Hz.) in chair cyclohexane. This can be explained by a closing of the dihedral angle between Ha and Hc from 60 to 40° which, according to the Karplus rule, would give a larger coupling constant. This closing of the angle leads one to describe the conformation as a slightly distorted chair. The data of the present study are in agreement with crystallography studies (33). Shifts are in the order OH ≫ Ha ≫ Hb > Hc ≫ Hd > N—CH_3 > Hef. A study of molecular models shows that these shift rates require europium–proton distances as indicated in the molecular diagram and evidence association *via* the hydroxy function (Fig. 1).

Both IV and III (Fig. 2) presented the methine proton in deuterochloroform as a simple triplet, $J_{ab} = 4$, $J_{ac} < 1$. These values remained constant in shifted spectra. On deshielding, the following additional J values were determined for the resulting AMXY system of the piperidine ring of the deshielded tropines: $J_{bc} = 15$, J_{ac} and $J_{cd} < 1$, and $J_{bd} = 4$ (J_{bd} was not measurable in III). According to the Karplus curve, J_{ab} and J_{bd} on the order of four or five dictate a 40° dihedral angle between these proton sets. J_{ac} and $J_{cd} < 2.0$ would indicate a dihedral angle on the order of 80° for the two α-substituted derivatives III and IV. For IV, the relative rates of shift found were Hd > Hb > Ha ≃ Hef > Hc, suggesting predominant alignment with the europium ion *via* the nitrogen function during the first mole of reagent addition. A distorted chair form is at least in concert with the observation that the shift rate of Hb is greater than Ha, while the rates for He and Hf are nearly equal and greater than Hc.

The relative rates of shift for tropine suggest the alignment in Fig. 2. The comparative shift rate for tropine protons was found to be Ha > Hc > Hf > Hb > Hd > He > N—CH_3. A boat form for III would require Hc > Ha, while a chair requires Hd > He. Thus, an empirical evaluation of the rate of shift is in relative agreement with the conformation indicated by exposed coupling constants. Measurement of the europium–proton distance and the angle factor would really be required to discriminate further.

Amino Ketones—Spectra of VI and V (Fig. 3) may be interpretated in light of the deshielded ABX coupling revealed on addition of the shift reagent. The following J values were determined: $J_{bc} = 16$, J_{bd} (IV) = 4, J_{bd} (V) = 3, and $J_{cd} < 1$ for both derivatives. These data are consistent with dihedral angles Hd–Hb of 40° and Hd–Hc of 80°, the conditions for a distorted chair form. The rates listed in Fig. 3 appear to be in line with a distorted chair conformation for the amino ketones. The rates for VI evidence alignment of europium ion with the secondary amine function. Rates for V suggest association with the tertiary amine, although both ligands could be simultaneously involved during the first mole ratio of I addition (from the crude data).

CONCLUSIONS

Compound I was found to be a useful NMR shift reagent capable of simplifying the NMR of bifunctional substrates, thus allowing

[7] Compound I is expected to induce a broadening of at least 0.003 Hz./Hz. of shift (38).

for the solution of stereochemical problems from a purely empirical approach. In accordance with the Karplus rule, use of the shift reagent permitted an independent proof of previous indications that a distorted chair form predominates in the conformational equilibrium of α- and β-tropines and tropinones. At mole ratios of I/substrate of less than 1.0, it was possible to observe substrate ligand bonding orders of secondary amine > secondary alcohol > tertiary amine $\geq$ ketone.

REFERENCES

(1) B. L. Shapiro, J. R. Hlubucek, G. R. Sullivan, and L. F. Johnson, *J. Amer. Chem. Soc.*, **93**, 3281(1971).

(2) C. C. Hinckley, *ibid.*, **91**, 5160(1969).

(3) R. E. Rondeau and R. E. Sievers, *ibid.*, **93**, 1522(1971).

(4) T. H. Siddall, III, *Chem. Commun.*, **1971**, 452.

(5) J. Briggs, F. A. Hart, and G. P. Moss, *ibid.*, **1970**, 1506.

(6) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5735(1970).

(7) *Ibid.*, **92**, 5737(1970).

(8) J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641(1971).

(9) G. H. Wahl and M. R. Peterson, *Chem. Commun.*, **1970**, 1167.

(10) R. A. Sandmann, B. F. Grabowski, and G. Oestreich, to be published.

(11) M. Ohashi, I. Morishima, K. Okada, T. Yonezawa, and T. Nishida, *Chem. Commun.*, **1971**, 34.

(12) H. Hart and G. M. Love, *Tetrahedron Lett.*, **1971**, 625.

(13) I. Fleming, S. W. Hanson, and J. K. M. Sanders, *ibid.*, **1971**, 3733.

(14) C. C. Hinckley, M. R. Klotz, and F. Patil, *J. Amer. Chem. Soc.*, **93**, 2417(1971).

(15) S. B. Tjan and F. R. Visser, *Tetrahedron Lett.*, **1971**, 2833.

(16) M. Ohashi, I. Morishima, and T. Yonezawa, *Bull. Chem. Soc. Jap.*, **44**, 576(1971).

(17) H. van Brederode and W. G. B. Huysmans, *Tetrahedron Lett.*, **1971**, 1695.

(18) R. C. Taylor and D. B. Walters, *ibid.*, **1972**, 63.

(19) J. Skolik, J. Barciszewski, A. J. Rafalski, and M. Wiewiorowski, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **10**, 599(1971).

(20) J. M. J. Tronchet, F. Barbalet-Rey, and N. Le-Hong, *Helv. Chim. Acta*, **54**, 2615(1971).

(21) S. Farid, A. Ateya, and M. Maggio, *Chem. Commun.*, **1971**, 1285.

(22) M. Karplus, *J. Chem. Phys.*, **30**, 11(1959).

(23) M. R. Vegar and R. J. Wells, *Tetrahedron Lett.*, **1971**, 2847.

(24) R. Willstätter, *Chem. Ber.*, **29**, 1575(1896).

(25) T. D. Perrine, *J. Org. Chem.*, **16**, 1305(1951).

(26) R. J. Bishop, G. Fodor, A. R. Katritzky, F. Soti, L. E. Sutton, and F. J. Swinbourne, *J. Chem. Soc., C*, **1966**, 74.

(27) R. Willstätter, *Chem. Ber.*, **29**, 936(1896).

(28) British pat. 805,859 (1958).

(29) G. L. Closs, *J. Amer. Chem. Soc.*, **81**, 5456(1959).

(30) J. W. Visser, J. Manassen, and J. L. DeVries, *Acta Crystallogr.*, **7**, 288(1954).

(31) H. O. House, H. C. Muller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, **28**, 2407(1963).

(32) B. L. Zenitz, C. M. Martini, M. Priznar, and F. C. Nachod, *J. Amer. Chem. Soc.*, **74**, 5564(1952).

(33) H. Schenk, C. H. MacGillvary, S. Skolnik, and J. Laan, *Acta Crystallogr.*, **23**, 423(1967).

(34) N. Mandava and G. Fodor, *Can. J. Chem.*, **46**, 2761(1968).

(35) A. J. Rafalski, J. Barciszewski, and M. Wiewiorowski, *Tetrahedron Lett.*, **1971**, 2829.

(36) J. Briggs, F. A. Hart, G. P. Moss, and E. W. Randall, *Chem. Commun.*, **1971**, 364.

(37) W. Dew Horrocks, Jr., J. P. Sipe, III, and J. R. Luber, *J. Amer. Chem. Soc.*, **93**, 5258(1971).

(38) D. R. Crump, J. K. M. Sanders, and D. H. Williams, *Tetrahedron Lett.*, **1970**, 4419.

ACKNOWLEDGMENTS AND ADDRESSES

Received May 12, 1972, from the *School of Pharmacy, University Missouri-Kansas City, Kansas City, MO 64110*

Accepted for publication September 27, 1972.

Supported by a grant from the University of Missouri-Kansas City Trustees Graduate Fellowship Grants. The investigation is a portion of the research program of D. Yourtee in partial fulfillment of the Doctor of Philosophy degree requirements.

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